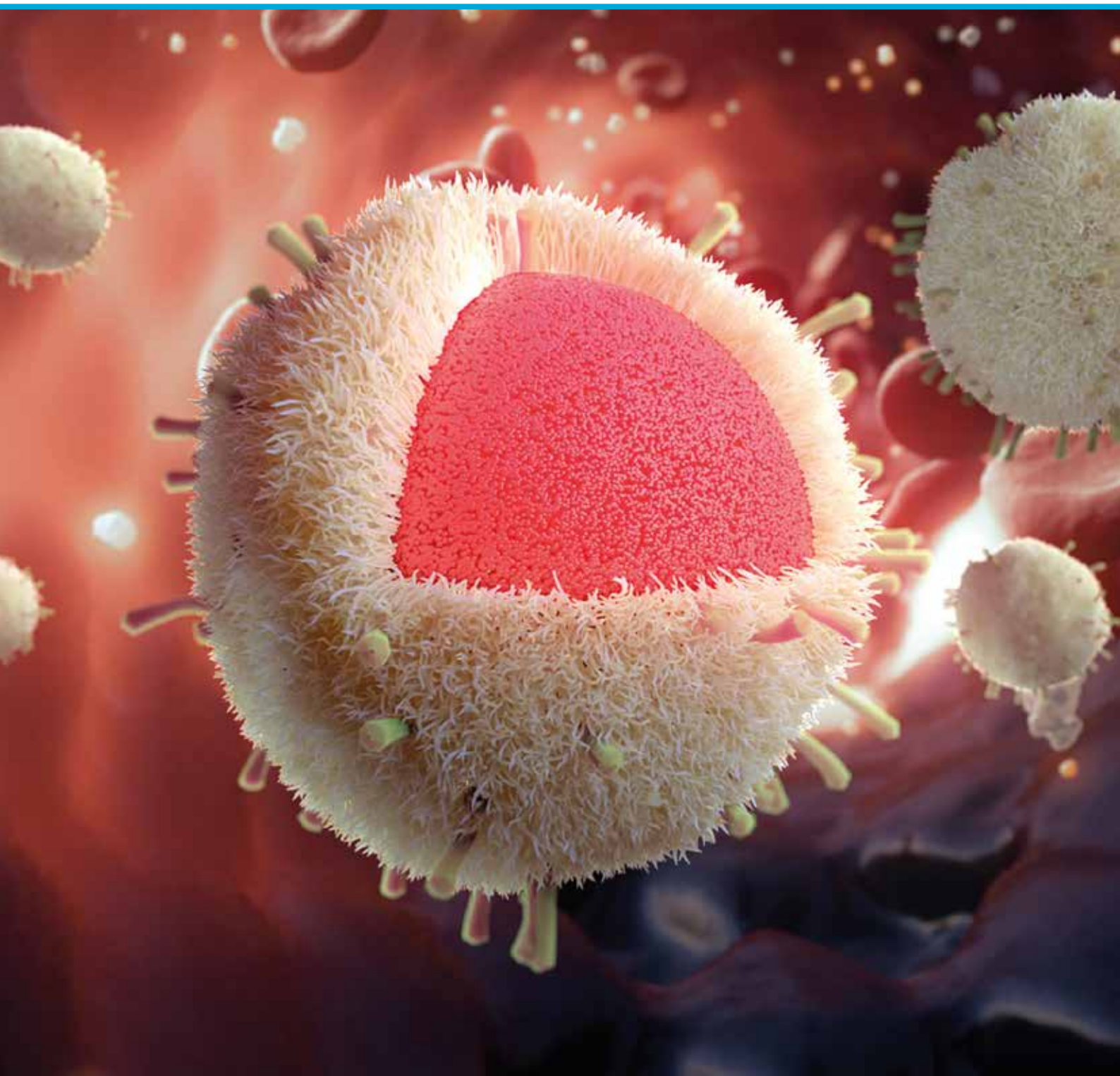


Delivering our pipeline through scientific leadership

Innovative Medicines &
Early Development Biotech Unit
2016 – A year in review

AstraZeneca 
IMED Biotech Unit





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The next wave of scientific innovation

An introduction from Mene Pangalos

In 2016 we set ourselves ambitious targets to ensure we remain fully on-track to deliver our company's bold ambition – to improve the lives of 200 million patients and be a \$45 billion company by 2023. It is clear from our flourishing pipeline that a new AstraZeneca is emerging.

As I reflect on the past six years leading Innovative Medicines & Early Development (IMED), I am immensely proud of our transformational achievements. Every year since 2010, we have met or exceeded our pipeline goals across all of our therapy areas – testament to the calibre of our scientists, their dedication and passion for science and our culture to challenge conventional thinking.

Taking a view of our pipeline delivery against industry benchmarks, we continue to make remarkable improvements in cycle times and success rates. When we compare our productivity from 2005-2010 to that of today, we can see that we have improved our success rates from first time in man and successful completion of Phase III from three and a half per cent to over 15 per cent – a clear improvement over the current industry average of four per cent. Even more importantly, this is translating into the delivery of new medicines, with drugs like olaparib, osimertinib and CAZ AVI having graduated to a successful launch.

The breadth and depth of pipeline progress made by the IMED Biotech Unit in 2016 can be highlighted by examples from across all therapy areas. In Oncology we supported the transition of five molecules into pre-clinical development, of which three – inhibitors of MCL1, Bcl2/xL and CDK9 – are all targeting pro-survival proteins in support of our goal to build an industry-leading 'tumour cell death' portfolio. Resistance to cell death is one of the hallmarks of cancer. These programmes drive cancer cells to apoptosis and look particularly exciting for research in haematological malignancies, including in combination with acalabrutinib, our best-in-class BTK inhibitor.

In Respiratory, Inflammation and Autoimmunity we refocused our efforts on lung epithelium, lung immunity and lung regeneration to allow us to better define novel disease drivers and treatment options for patients with respiratory diseases. Within lung immunity, we initiated a landmark Phase II trial with



Mene Pangalos
Executive Vice President
IMED Biotech Unit and Global
Business Development

AZD1419, our inhaled TLR9 agonist, the first ever study designed to investigate whether asthma patients can be kept in remission rather than simply treating their symptoms.

In cardiovascular disease, AZD8601 – the world's first modified RNA for VEGF-A from our Moderna partnership – received positive regulatory approvals to enter Phase I clinical development. VEGF-A is a key protein in new blood vessel formation and cardiomyocyte proliferation. AZD8601 is being investigated as a regenerative treatment option for patients with heart failure, in diabetic wound healing and other vascular diseases.

Finally, AZD3293, our BACE1 inhibitor in co-development with Lilly for Alzheimer's disease transitioned into Phase III. We now have two late stage trials running simultaneously and are poised to be one of the first to launch a disease-modifying treatment for Alzheimer's.

One of my personal highlights of 2016 was the announcement of our new genomics initiative and I was particularly delighted Professor David Goldstein joined our team in September. Professor Goldstein will play a key role in ensuring we have the right skills and people to launch our dedicated Centre for Genomics Research, as well as providing strategic guidance to integrate our genomics initiative into our research and development pipeline and into work with our partners. I would also like to call out the outstanding achievements our entrepreneurial Scientific Partnering and Alliances (SP&A) team made in 2016, creating over \$150 million in value for AstraZeneca in externalisation revenue. Working closely with groups across IMED, the SP&A team strengthened our global partnerships with leading scientists from academia, biotech and pharma.

I am also immensely proud of our scientific leadership and our ability to follow the science. At the beginning of the year, we knew it would be tough to outperform our number of high impact and high quality publications from 2015. We didn't just beat the target from last year – we smashed it. In 2016, we delivered 40 high impact and 311 high quality publications, and a total of 552 publications overall. This is truly phenomenal progress that not only reflects the quality of the research conducted in our laboratories and with our partners, but also the strength and depth of our science across the IMED Biotech Unit.

Whilst it is impossible to capture all of the achievements from across our teams in the past year, I hope the IMED Annual Review 2016 gives you a feel for the outstanding calibre of our science and our scientists and how we strive to push the boundaries of science to deliver life-changing medicines for patients around the world.

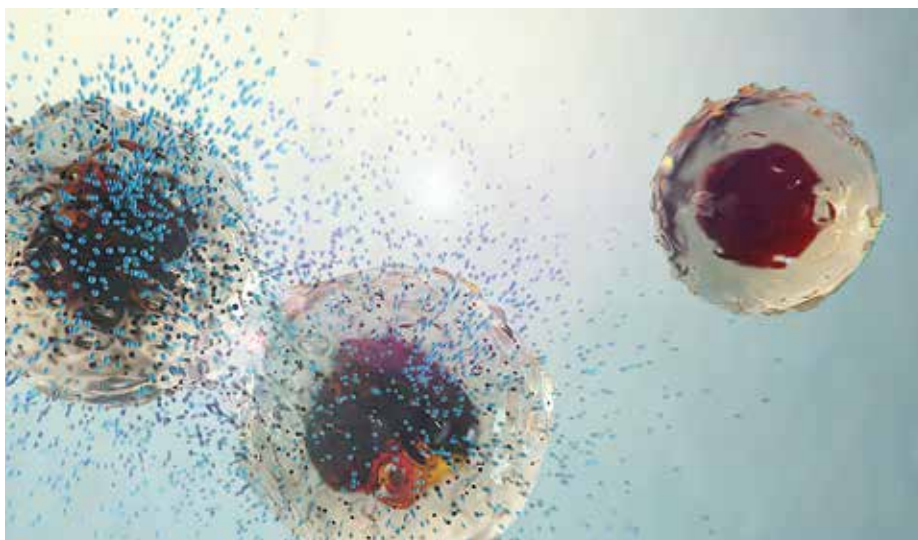
Mene Pangalos

Mene Pangalos
Executive Vice President
IMED Biotech Unit and Global
Business Development

“

2016 was an important year for AstraZeneca in which we made further significant progress on the delivery of our science-led strategy. Some of the most innovative research and development being undertaken at the moment is taking place in our IMED Biotech Unit, including transformative new platforms, such as oligonucleotides, nanoparticles and modified RNA and new technologies to advance our work in personalised healthcare, genomics and genome editing. This work is being propelled by the entrepreneurial culture that IMED has fostered, collaborations that have been established with world-leading partners and by the outstanding people who work here at AstraZeneca, whose passion for science is helping us to discover and deliver the next generation of medicines to transform the lives of patients around the world.”

Pascal Soriot, Executive Director and Chief Executive Officer



^
Pancreatic beta cells at different
stages of regeneration

IMED Biotech Unit 2016 in numbers

115

post docs

~2,300people in
IMED**>95%**of IMED projects with
a personalised
healthcare approach**23**Phase I and II
starts (New
Molecular
Entities)**6**diagnostics
launched**69**clinical project
combinations
in oncology**\$13.5M**generated
from Open
Innovation**552**peer reviewed
publications**40**high impact
publications**~1,000**current
collaborations**31**clinical projects
(New Molecular
Entities)**125**

new hires

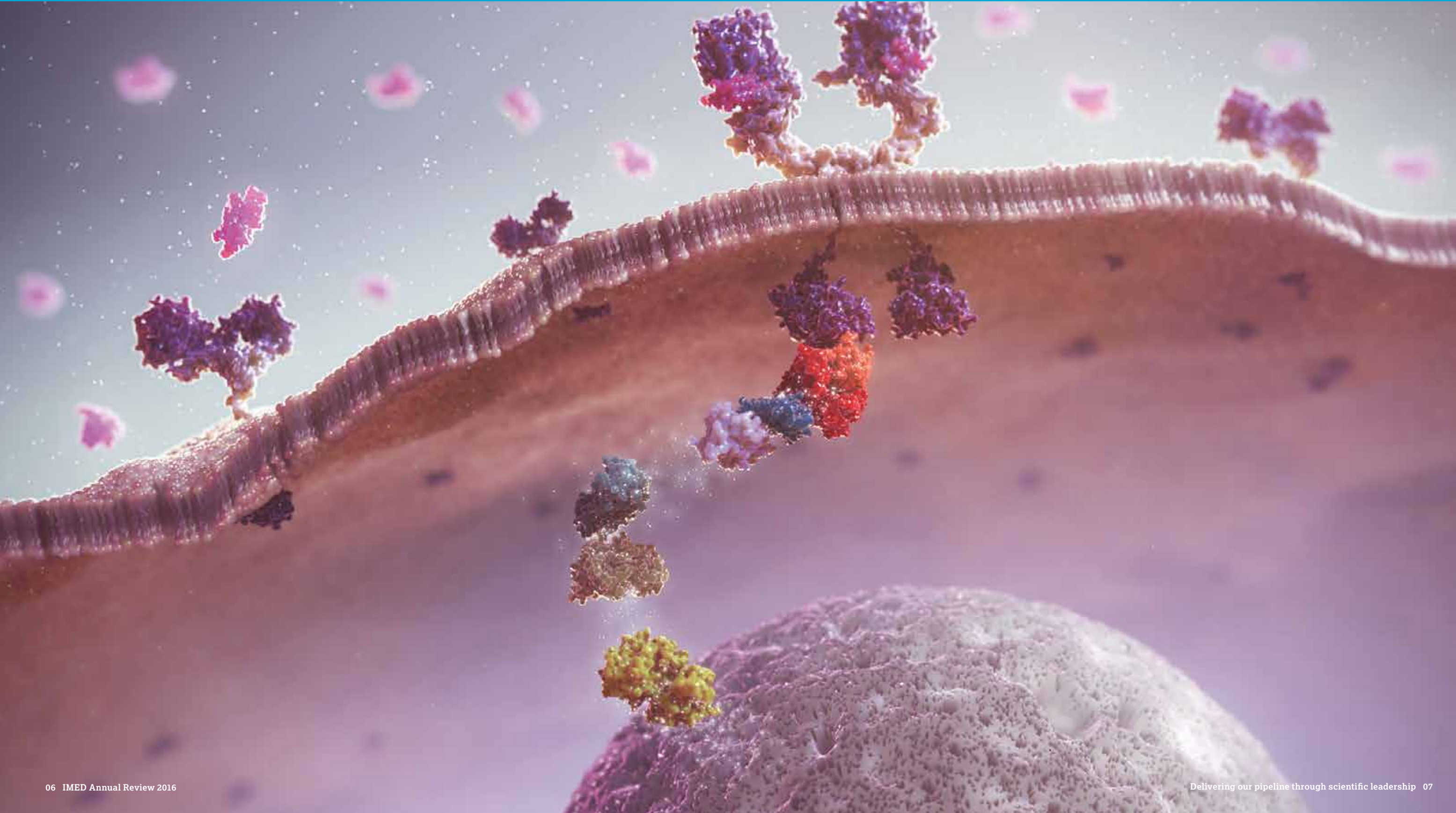
3Phase III
investment
decisions

Oncology

✓ Oncology tumour drivers – cell surface and lipid bilayer with receptor

“2016 has been an impressive year for IMED Oncology with significant developments in all areas - from Phase III progression of savolitinib to the multitude of Phase II trials, the nomination of five candidate drugs and a strong discovery portfolio. We have increased the number of external collaborations supporting the portfolio and have driven expansion of our key areas: DNA damage response, tumour drivers and resistance and small molecule immuno-oncology. Overall, we are in a great position to continue the delivery of new medicines to patients through 2017 and beyond.”

Susan Galbraith, VP IMED Oncology



Oncology

Through 2016, IMED Oncology has seen strong progress across our cancer treatment pipeline. Key data and leadership was delivered that led to achieving a Phase III investment decision for savolitinib in papillary renal cell carcinoma (PRCC), whilst the savolitinib/osimertinib combination shows great promise in cMet amplified EGFR mutant non-small cell lung cancer (NSCLC).

ATR inhibitor AZD6738 progressed to Phase II, in combination with olaparib, as part of our DNA damage response (DDR) franchise, which saw new investments for the Wee1 and ATM projects. Phase II trials also started with STAT3 inhibitor AZD9150 and CXCR2 inhibitor AZD5069 (both administered in combination with our anti-PD-L1 antibody durvalumab). The A2aR antagonist AZD4635 achieved its first Phase I dose whilst five new candidate drugs were nominated.

The practical delivery of personalised medicine remains critically important in driving clinical benefit and the great majority of our current projects are developing prospective patient selection strategies. For olaparib, significant investment in next-generation sequencing (NGS) is allowing non germ-line BRCA patients to be identified and has led to the initiation of a number of novel Phase II studies.

The high uptake of the plasma-based circulating tumour DNA (ctDNA) test for osimertinib highlights the critical value of developing minimally invasive diagnostic testing and the importance of aggressive evaluation of mechanisms of clinical resistance.

With the acquisition of a majority stake in Acerta Pharma, acalabrutinib now provides a cornerstone asset to drive our fast-developing portfolio for haematological malignancies. The Acerta Research and Early Development group will spearhead development of acalabrutinib combinations with our development portfolio and will also take forward novel agents, such as those targeting the programmed cell death mechanisms, which have a primary line-of-sight into haematological malignancies.

This year we have made a number of important new hires, bringing substantial experience and expertise to our teams and consolidating our scientific leadership in key areas; these include Wenlin Shao, Viia Valge-Archer, Charles Sinclair, Deanna Mele, Laura Prickett, Juliann Chmielecki and Kris Sachsenmeier. We have also successfully transitioned the majority of our UK group to Cambridge sites, including the establishment of a new group within the Hodgkin building in Great Chesterford.

People spotlight

Mark O'Connor

Mark O'Connor is Chief Scientist in Oncology, heading up the DDR biology area. Mark has provided scientific leadership on olaparib and was instrumental in the in-licensing of the Wee1 inhibitor AZD1775. More recently, Mark has overseen the growth of DDR within AstraZeneca to an industry leading portfolio containing seven DDR agents, and played a key role in this year's high level DDR strategy investment that led to significant additional investment in the area. In 2016, Mark published several international peer reviewed papers including a high impact publication on PARP trapping that was published in *Science Translational Medicine*, he gave a *Science* webinar and was invited by American Association for Cancer Research (AACR) to give a keynote presentation at their DDR meeting, the only non-academic faculty member at the four-day event, thus demonstrating our industry leading position in the area.

Paul Secrist

Paul Secrist is Director of Oncology Bioscience and had a significant impact on the pre-clinical portfolio this year - serving as the biology lead for two successful candidate drug investment decisions (CDIDs) for AZD5991 (MCL1) and AZD0466 (Bcl2/xL). Paul was the major driver of the overall cell death strategy and has led multiple research collaborations with prominent academic laboratories in this exciting area of drug discovery. In addition, Paul co-leads the small molecule immuno-oncology strategy within AstraZeneca and has been instrumental in building both the pre-clinical portfolio and the rapidly expanding repertoire of immunological capabilities within IMED Oncology.

Melanie Frigault

Melanie Frigault is a Principal Translational Scientist in Oncology, currently on secondment working on acalabrutinib and leading the translational science group at Acerta. Melanie is also a leader on savolitinib, where she delivered biomarker rules to automate patient inclusion/exclusion in future clinical trials of savolitinib in patients with 'MET-driven' papillary renal cell carcinoma (PRCC). This may be the first trial to use biomarker selection in renal cell. Melanie also led research from the patient to the bench resulting in discovery of novel biomarkers, leading to a new patent filing.

✓ Cross section of cells from tumour biopsy. The cells are stained to confirm presence of target receptors for AstraZeneca and MedImmune therapeutic molecules



Simon Barry

Simon Barry is a Senior Principal Scientist in Oncology Bioscience, who was awarded Senior Scientist of the Year at the IMED Science Awards 2016 for his depth and breadth of scientific achievement across the oncology portfolio. He has worked on a number of small and large molecule drug projects, from target selection through Phase III development. He has had a specific focus on the role the tumour microenvironment plays in tumour progression and resistance, working both within AstraZeneca and with external collaborators. He is currently the lead bioscientist on AZD5069 (CXCR2 inhibitor), AZD8186 (PI3Kb inhibitor) and cediranib (VEGFR inhibitor).

Simon co-leads the small molecule immuno-oncology strategy in AstraZeneca and working together with Paul Secrist is driving the pre-clinical portfolio and capabilities to develop therapeutic opportunities in this exciting area.

Alex Hird

Alex Hird led the MCL1 chemistry and early project teams to deliver the candidate drug AZD5991 in 2016. Alex co-authored three peer reviewed publications in 2016, including a high impact paper in *Nature Chemical Biology*. The paper resulted from an alternative innovative approach to covalently target a lysine residue on MCL1, carried out within the AstraZeneca post-doc programme. In addition, Alex is a Team Leader in the chemistry department in Boston.

Highlights

We set out to	We delivered
Progress savolitinib through its first Phase III investment decision	<p>We accelerated the clinical development programme for savolitinib, a potent and highly selective small molecule inhibitor of the c-Met receptor tyrosine kinase, by extending our collaboration with Hutchison MediPharma following promising Phase II results. Savolitinib achieved a positive Phase III investment decision in August 2016. The global Phase III trial of savolitinib in papillary renal cell carcinoma (PRCC) will be the first pivotal study to employ NGS methodology to prospectively select patients with c-Met-driven disease.</p> <p>In addition, the development of savolitinib in other c-Met-driven cancer types continues with a particular focus on c-Met amplified EGFR mutant NSCLC. The Phase II expansion of the ongoing TATTON trial is evaluating savolitinib in combination with osimertinib whilst another trial in China is exploring the use of savolitinib and gefitinib in a similar patient population.</p>
Demonstrate the potential of osimertinib beyond current indications	<p>We presented data from the BLOOM study at the 2016 American Society of Clinical Oncology (ASCO) meeting, which demonstrates that osimertinib is effective in reducing tumour size and improving neurological function in patients with leptomeningeal disease, a devastating form of NSCLC. The ability to access the brain by crossing the blood-brain-barrier is a key property of osimertinib which differentiates it from a number of other EGFR inhibitors.</p>
Build our portfolio of cell death agents	<p>We progressed three molecules toward the clinic following promising pre-clinical data:</p> <p>AZD5991 is a highly potent and selective MCL1 inhibitor which demonstrates tumour regression in multiple disease models <i>in vivo</i>, including acute myeloid leukaemia (AML), non-hodgkin lymphoma (NHL) and multiple myeloma (MM). Working with the ‘Beat AML’ collaboration, AZD5991 has demonstrated a highly differentiated profile compared to BCL2 and BCLxL inhibitors and has broad potential in a range of myeloid and lymphoid malignancies.</p> <p>AZD4573 is a selective CDK9 inhibitor with the appropriate PK to enable short-term target engagement. Recent pre-clinical studies have shown significant anti-cancer activity across different haematological malignancies, including AML, NHL, chronic lymphocytic leukaemia (CLL), and MM based on exciting clinical data, plus potential for combination use with acalabrutinib.</p> <p>AZD0466 is a dual BCL2/xL inhibitor with broad pre-clinical activity in a range of haematological malignancies. Delivered as a nanomedicine formulation administered intravenously, it has been designed to improve the therapeutic window for thrombocytopenia, which has prevented agents of this profile delivering their full potential previously.</p> <p>Targeting these pro-survival proteins of the BCL2 family in combination with other mechanisms, offers the potential to increase the fraction of tumour cells that are killed. All three agents were highlighted to investigators at the recent American Society of Haematology (ASH) meeting in San Diego and are being developed in combination between AstraZeneca and Acerta.</p>
Demonstrate leadership in DNA damage response (DDR)	<p>Significant investment has been made in this area in 2016, both in monotherapy and in combination. Our pre-clinical data demonstrates the potential to both broaden patient populations and deepen the level of responses compared to monotherapy. In addition, combinations with immuno-oncology agents are being prioritised with the potential to exploit the synergy between the mechanisms and drive much more durable responses in key tumours.</p> <p>Olaparib in combination with AZD1775 (Wee1 inhibitor) is being investigated in a number of Phase II trials in parallel with evaluation of AZD1775 in monotherapy and in combination with cytotoxics. At the same time, the combination of olaparib and AZD6738 (ATR inhibitor) has started Phase II efficacy studies, whilst AZD0156, a selective ATM inhibitor, is currently completing its Phase I dose-escalation study in combination with olaparib.</p> <p>To target a population of glioblastoma patients who could be responsive to an ATM inhibitor we have also nominated a second ATM inhibitor, AZD1390, which has been optimised to deliver much higher drug concentrations to the brain by improving blood-brain-barrier penetration and optimising drug transporter activity.</p> <p>Our scientific leadership was demonstrated through multiple publications, as well as significant presence at the 2016 AACR, ASCO and the European Society for Medical Oncology (ESMO) congress. In addition, Mark O’Connor was invited by AACR to give a keynote presentation at their DDR meeting, the only non-academic faculty member at the four-day event.</p>

We set out to	We delivered
Build capability in developing small molecules within immuno-oncology (IO)	<p>We developed a portfolio of small molecule inhibitors which have the potential to dramatically increase effectiveness of checkpoint inhibitors such as durvalumab; despite the progress seen with inhibitors of the immune checkpoints there remain major challenges in targeting mechanisms whereby tumour cells are able to make the local tumour micro-environment more immune-suppressive.</p> <p>AZD9150 is an antisense oligonucleotide (licensed in from Ionis Pharmaceuticals) that prevents expression of signal transducer and activator of transcription 3 (STAT3), which started Phase II trials this year in combination with durvalumab. Previously AZD9150 has shown promising responses in a small number of patients with diffuse large B cell lymphoma.</p> <p>AZD5069 is a selective CXCR2 antagonist that also entered Phase II this year in combination with durvalumab. AZD5069 inhibits the migration of CXCR2+ myeloid-derived suppressor cells to tumour microenvironments and may enhance immune-mediated tumour killing.</p> <p>AZD4635 is an adenosine 2a receptor (A2aR) antagonist that started its Phase I monotherapy dose-escalation this year and will explore combination dosing with durvalumab in a range of solid tumours. Blockade of A2aR signalling with AZD4635 has been shown to reverse adenosine-mediated immunosuppression <i>ex vivo</i>, as well as reduce tumour burden and enhance anti-tumour immunity in pre-clinical mouse models.</p>
Demonstrate scientific leadership	<p>We achieved 20 high impact and 83 high quality publications as well as showcasing our industry-leading pipeline at AACR, ASCO, ESMO and ENA, a symposium hosted by the European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) and AACR.</p> <p>A key highlight was our publication in <i>Cancer Cell</i>, which came from our collaboration with the Beatson Institute for Cancer Research, demonstrating the therapeutic potential of CXCR2 inhibition in pancreatic cancer for the first time.</p> <p>Our scientific leadership was also recognised externally through various high profile invitations; Susan Galbraith was a member of the scientific committee for the annual AACR meeting and was also asked to join the AACR genomics initiative expert panel to discuss the implementation of genomics to advance personalised medicine.</p>

Capitalising on our DNA damage response (DDR) strategy

<p>Targeting DDR deficiencies to preferentially kill cancer cells, while minimising the impact on normal cells, has the potential to be transformational in a broad range of cancers. Our portfolio has seen rapid growth in this area over the last few years, with one approved medicine and four candidate drugs now in clinical development. This pipeline is highly differentiated and targets the key molecular pathways, providing significant opportunities for innovative combinations. Ongoing work to optimise combination scheduling and increase our understanding of patient selection biomarkers is ongoing and has seen additional investment in 2016.</p> <p>At the beginning of the year, olaparib was granted breakthrough therapy designation by the US FDA for BRCA1/2 or ATM gene mutated metastatic castration resistant prostate cancer. Phase III studies are also underway in gastric cancer, pancreatic cancer and adjuvant and metastatic</p>	<p>BRCAm breast cancers. In addition, through our partnership with Foundation Medicine, we have developed a gene panel test which will allow broader patient selection for both olaparib monotherapy and combination trials.</p> <p>A key highlight this year has been the progression we have made with olaparib combinations, with three compounds now being clinically evaluated with this PARP inhibitor; AZD1775 (Wee1 inhibitor), AZD6738 (ATR inhibitor), AZD0156 (ATM inhibitor). Underpinning these combinations is our developing understanding of how the higher levels of replication stress that occur in cancer cells can be exploited: Wee1, ATR, and ATM are all activated and play complementary roles in this response. Olaparib enhances replication stress by trapping PARP onto DNA and stalling replication forks leading to an increase in the generation of DNA double-strand breaks.</p>	<p>In addition to the work on optimising dose/schedule and driving forward combinations with olaparib, combinations with immunotherapy and ionising radiation are also progressing well, with encouraging early clinical data suggesting that the effects of both these therapies can be enhanced in defined patient populations.</p>
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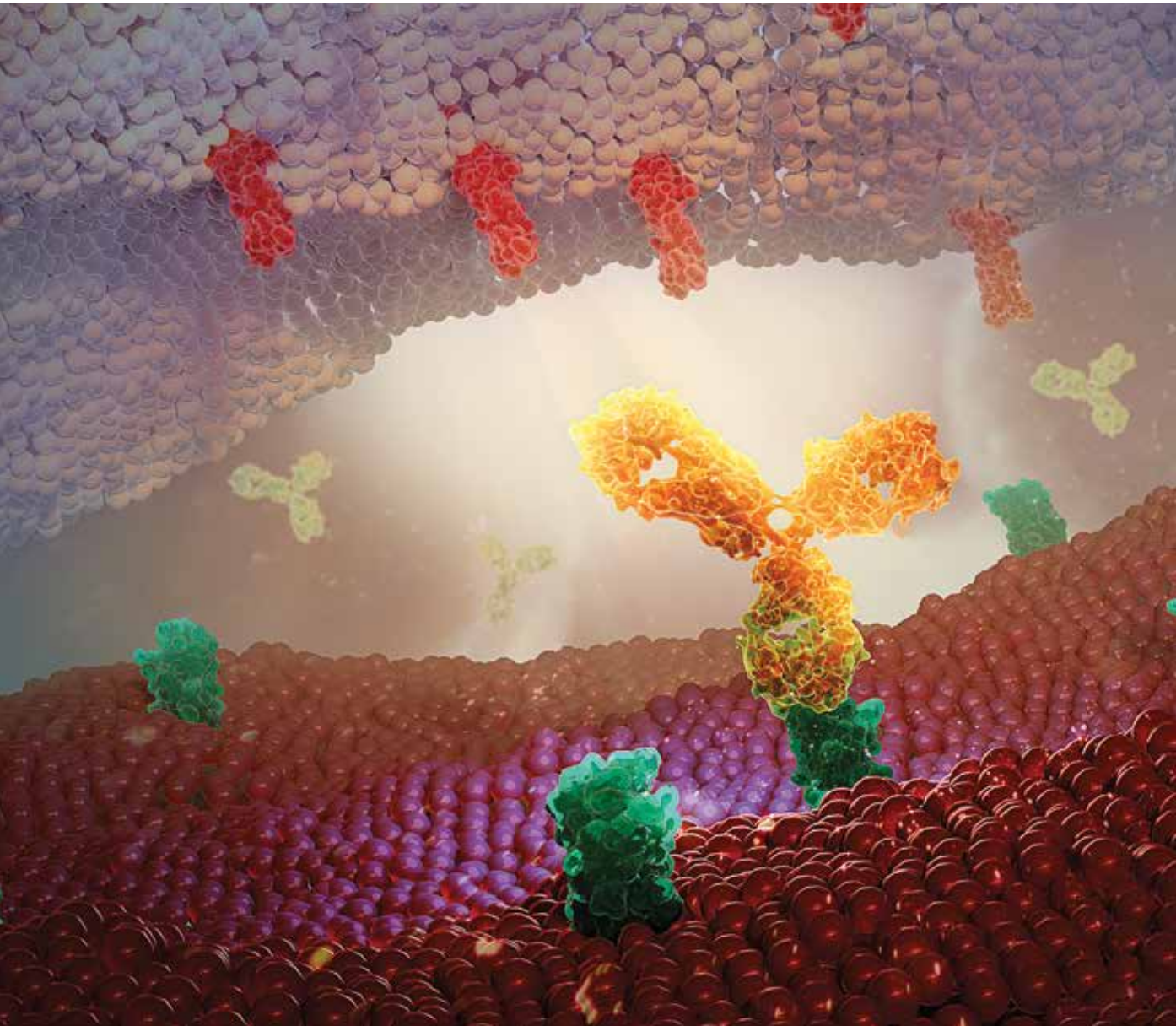
Building an industry leading cell death portfolio

The evasion of programmed cell death is one hallmark of cancer. As the balance of pro - and anti-apoptotic proteins is key to determining cellular fate, one mechanism by which cancer cells are able to overcome apoptosis is through upregulation of one or more members of the pro-survival BCL2 (B-cell lymphoma-2) family of proteins. Transient targeting of these pro-survival proteins (such as MCL1, Bcl2 or BclxL) with small molecule inhibitors blocks pro-survival signalling and will lead to increased cancer cell death. Pre-clinical data shows that synergy with other anti-cancer mechanisms can be profound and the class has enormous potential in both monotherapy and in combination.

Our goal is to deliver a best-in-class portfolio of drugs targeting the most important pro-survival proteins, together with a molecular stratification strategy that allows the treatment of each tumour with the right drug. This year we have made significant progress with the nomination of three novel candidate drugs which will advance initially in haematological malignancies. AZD5991 is a potent and selective MCL1 that induces rapid apoptosis in MCL1- dependent tumour cells. We have demonstrated tumour regression in multiple disease models *in vivo*, including acute myeloid leukaemia (AML), non-Hodgkin lymphoma and multiple myeloma.

The second candidate is AZD4573, a selective CDK9 inhibitor with the appropriate PK to enable short-term target engagement. Transient inhibition of CDK9 preferentially targets genes such as MCL1 and MYC through transcriptional inhibition thereby offering an alternative mechanism of MCL1 inhibition. Given the importance of MCL1 protein as a pro-survival signal, this complementary mechanism strengthens the cell death portfolio, while recent studies show that differences between direct and indirect inhibition of MCL1 may be exploitable in clinical studies.

✓ Antibody that blocks inhibitory signals from the tumour to cells of the immune system resulting in enhanced anti-tumour immunity



In December we nominated AZD0466 which is a dual Bcl2/xL inhibitor with broad pre-clinical activity in a range of haematologic malignancies. Bcl2 is a clinically validated target with venetoclax being approved by the FDA in 2016 for sub-types of chronic lymphocytic leukaemia (CLL). However our data suggests that venetoclax's continuous oral dosing is not ideal in maximising cell kill whilst those cells that do survive are often able to exploit Bcl2/xL as a parallel survival mechanism. Consequently AZD0466 has the potential to be a best-in-class agent in this field with a highly-optimised *i.v.* nanomedicine formulation with a broader Bcl2/xL profile. Previous attempts to develop this dual profile were seriously compromised by on-target toxicities such as thrombocytopenia.

This exciting portfolio of cell death agents and its supporting data was shared with key haematological investigators at the recent American Society of Hematology (ASH) meeting. The portfolio will be developed in collaboration with Acerta working closely with AstraZeneca as one of the three critical elements of the haematological disease strategy. A second key element is the development of the cornerstone asset acalabrutinib, a highly selective inhibitor of Bruton's tyrosine kinase (BTK) which is in a range of pivotal studies. The final component will be to maximise the value of our immuno-oncology agents, including molecules such as AZD9150 (STAT3 inhibitor), in these diseases.

“The practical delivery of personalised medicine remains critically important in driving clinical benefit and the great majority of our current projects are developing prospective patient selection strategies.”

Early clinical data suggests that the improved selectivity profile of acalabrutinib (compared to ibrutinib) has the potential to translate into greater clinical benefit for this critically important mechanism. These properties make acalabrutinib an excellent candidate for combinations across our portfolio as well as with third-party compounds. Two novel combinations are moving into the clinic in 2017 exploiting PI3K/AKT/mTOR pathway inhibitors, such as vistusertib in diffuse large B-cell lymphoma (DLBCL) and DDR inhibitors, such as AZD6738 in CLL. We have also held discussions with a number of collaborative groups and clinical centres to start planning molecularly-stratified signal searching studies (so called 'umbrella' or 'basket' trials) in diseases such as AML, (DLBCL) and mantle cell lymphoma.

Oncology pipeline

Pre-clinical

- AZD4573 / CDK9
- AZD5991 / MCL1
- AZD0466 / Bcl2/xL
- AZD1390 / ATM-BBB
- AZD4785 / KRAS
- AZD4205 / JAK1
- AZD0364 / ERK
- AZD5153 / BRD4

Phase I

- AZD0156 / ATM
- AZD4635 / A2aR
- AZD2811 / AURN
- AZD8186 / PI3Kβ
- AZD9496/ SERD

Phase II

- savolitinib / MET
- AZD1775 / Wee1
- AZD6738 / ATR
- AZD9150 / STAT3
- AZD5069 / CXCR2
- vistusertib / mTOR1/2
- AZD5363 / AKT
- AZD4547 / FGFR
- AZD3759 / EGFR-BBB

Phase III / LCM

- olaparib / PARP
- osimertinib / EGFR
- acalabrutinib / BTK
- selumetinib / MEK
- fulvestrant / ER antagonist

Pipeline correct as of Q4 2016, not including MedImmune programmes.

A selection of key collaborations in 2016

1.

MD Anderson Cancer Centre, US

We established a multi-year collaboration with MD Anderson Cancer Center to conduct clinical studies in ovarian and other gynecological cancers. A Pilot Study of Wee1 Inhibition Induction Prior to Tumour Reductive Surgery in Ovarian Cancer has been initiated as part of this collaboration, along with the clinical trial, Matched Paired Pharmacodynamics and Feasibility Study of durvalumab in Combination with Chemotherapy in Frontline Ovarian Cancer
2.

Fred Hutchinson Cancer Research Centre, US

Our collaboration with the Fred Hutchinson Cancer Research Center to evaluate multiple reaction monitoring mass spectrometry (MRMMS) to deliver Proof of Mechanism data for AstraZeneca portfolio assets has provided us with data to identify new methods by which we can evaluate the mechanistic activity of our compounds in clinical studies.
3.

Dana-Farber Cancer Institute, US

We established a collaboration with the Dana-Farber to evaluate and identify EGFR mutations from ctDNA in NSCLC patient plasma and establish patient-derived xenograft lung cancer models from tumour biopsies from patients prior to enrolment in the AZD9291 AURA trial. In 2016 results from this collaboration led to a high profile joint publication in the *Journal of Clinical Oncology*.

4.

Peter MacCallum Cancer Centre, Australia

A collaboration to perform *in vitro* and *in vivo* evaluation of MCL1 and CDK9 inhibition in genetically engineered mouse models of human lymphoma and acute myeloid leukaemia has provided key information to help inform future projects in cell death.
5.

University of Manchester, UK

Our collaboration with the University of Manchester to determine the sensitivity of small cell lung cancer (SCLC) tumour models to PARP and Wee1 inhibitors has provided pre-clinical data supporting the initiation of new clinical trials testing our Wee1 inhibitor AZD1775 and our PARP inhibitor olaparib.
6.

The Beatson Institute for Cancer Research, Scotland

We are collaborating with the Beatson Institute to test the impact of therapeutics in genetically engineered models of defined genetic subsets of colorectal and pancreatic cancer to identify potential new ways to treat these diseases. In 2016 the work led to a high profile, joint publication in the journal *Cancer Cell*.
7.

Institut Gustave Roussy, France

We established a collaboration with the Institut Gustave Roussy to implement the Immunoscore immunostaining assay and develop a more complete understanding of the tumor microenvironment and the dynamics of the immune response in multiple human cancers. In 2016 our collaboration led to two jointly published, high profile publications in the journals *Immunity* and in *Science Translational Medicine*.

8.

The Institute of Cancer Research, UK

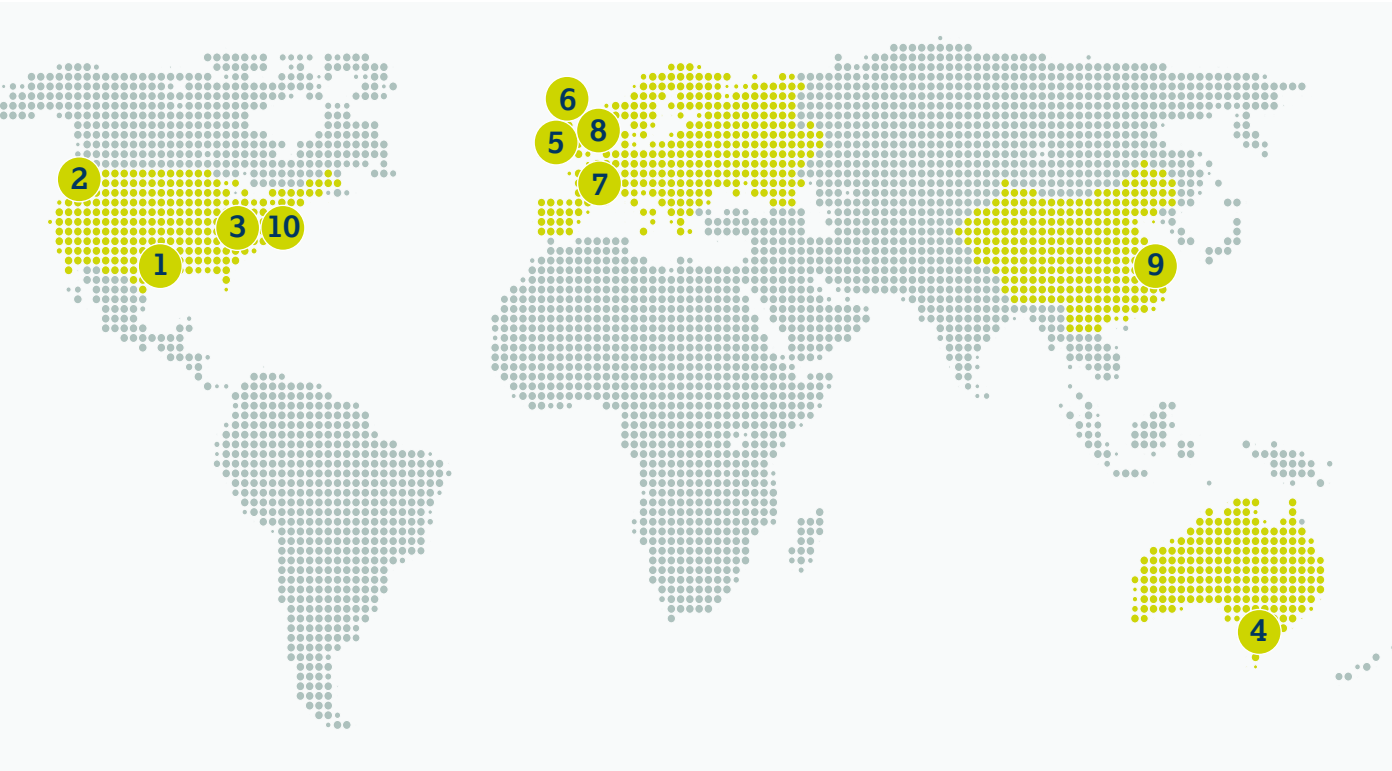
A collaboration with the Institute of Cancer Research analysed biological samples from a proof-of-concept clinical study of the FGFR kinase inhibitor AZD4547 in patients with FGFR1 and FGFR2 amplified tumors. Clinically we observed that single agent response to FGFR inhibition was only seen in high-level FGFR amplified cancers. The pre-clinical collaboration provided a mechanistic understanding for the pattern of response observed and led to a high profile, joint publication in the journal *Cancer Discovery* in 2016.
9.

Hutchison Medi Pharma, China

With Hutchison Medi Pharma we are jointly developing the highly potent and selective c-Met kinase inhibitor savolitinib in multiple diseases including c-Met amplified mutant EGFR non-small cell lung cancer (NSCLC) and papillary renal cell carcinoma (PRCC). In 2016 we made the investment decision to accelerate the PRCC clinical development program into a global Phase III trial using next generation sequencing technology to prospectively select patients with c-MET driven tumors.
10.

Memorial Sloan Kettering, US

Our collaboration with the Memorial Sloan Kettering to study models of resistance to mTOR kinase inhibitors has led to new scientific insights, a high profile joint publication in the journal *Nature* and is an example of our commitment to supporting and communicating innovative science.



Key publications in 2016

Publication	Title	Author
Nature	Overcoming mTOR resistance mutations with a new generation mTOR inhibitor	Rodrik-Outmezguine V S, Okaniwa O, Yao Z, Novotny C, McWhirter C, Banaji A, Won H, Wong W, Berger M, de Stanchina E, Barratt DG, Cosulich S, Klinowska T, Rosen N, Shokat KM
Nature Reviews Cancer	Defining Actionable Mutations for Oncology Therapeutic Development	Carr TH, McEwen R, Dougherty B, Johnson J, Dry J, Lai Z, Ghazoui Z, Laing N, Cruzalegui F, Barrett JC, Hodgson D, Hollingsworth S
Nature Medicine	Facilitating a culture of responsible and effective sharing of cancer genome data	Siu L, Lawler M, Haussler D, Knoppers BM, Lewin J, Vis DJ, Liao R, Andre F, Banks I, Barrett JC, Caldas C, Camargo AA, Fitzgerald R, Mao M, Mattison J, Pao W, Sellers W, Sullivan P, Tean TB, Ward R, ZenKlusen JC, Sawyers C, Voest E
Cell	A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds	Bruna A, Rueda OM, Greenwood W, Batra AS, Callari M, Batra RN, Pogrebniak K, Sandoval J, Cassidy JW, Tufegdzcic-Vidakovic A, Sammut S-J, Jones L, Provenzano E, Baird R, Eirew P, Hadfield J, Eldridge, M, McLaren-Douglas A, Barthorpe A, Lightfoot H, O'Connor MJ, Gray J, Cortes J, Baselga J, Marangoni E, Welm AL, Aparicio S, Serra V, Garnett MJ, Caldas C
Immunity	Integrative analyses of colorectal cancer show Immunoscore is a stronger predictor of patient survival than microsatellite instability	Mlecnik B, Bindea G, Angell HK, Maby P, Angelova M, Tougeron D, Church SE, Lafontaine L, Fischer M, Fredriksen T, Sasso M, Bilocq AM, Kirilovsky A, Obenauf AC, Hamieh M, Berger A, Bruneval P, Teuch JJ, Sabourin JC, Le Pessot F, Mauillon J, Rafii A, Laurent-Puig P, Speicher MR, Trajanoski Z, Michel P, Sesbouë R, Frebourg T, Pagès F, Valge-Archer V, Latouche JB Galon J
Cancer Cell	CXCR2 inhibition profoundly suppresses metastases and improves immunotherapy in pancreatic ductal adenocarcinoma	Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R, Rishi L, Foth M, Bryson S, McDaid K, Wilson Z, Eberlein C, Candido JB, Clarke M, Nixon C, Connelly J, Jamieson N, Carter CR, Balkwill F, Chang DK, Evans TRJ, Strathdee D, Biankin AV, Nibbs RJB, Barry ST, Sansom OJ, Morton
Journal of Clinical Oncology	Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer	Oxnard GE, Thress KS, Alden RS, Lawrance R, Paweletz CP, Cantarini M, Yang JC, Barrett JC, Jänne PA
Cancer Discovery	High-level clonal FGFR amplification and response to FGFR inhibition in a translational clinical trial	Pearson A, Smyth E, Babina I, Herrera-Abreu MT, Tarazona N, Peckitt C, Kilgour E, Smith NR, Geh C, Rooney C, Cutts R, Campbell J, Ning J, Fenwick K, Swain A, Brown G, Chua S, Thomas A, Johnston SRD, Ajaz M, Sumpter K, Gillbanks A, Watkins D, Chau I, Popat S, Cunningham D, Turner NC
Science Translational Medicine	Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index <i>in vivo</i>	Ashton S, Song YH, Nolan J, Cadogan E, Murray J, Odedra R, Foster J, Hall PA, Low S, Taylor P, Ellston R, Polanska UM, Wilson J, Howes C, Smith A, Goodwin RJ, Swales JG, Strittmatter N, Takáts Z, Nilsson A, Andren P, Trueman D, Walker M, Reimer CL, Troiano G, Parsons D, De Witt D, Ashford M, Hrkach J, Zale S, Jewsbury PJ, Barry ST
Science Translational Medicine	The tumor microenvironment and Immunoscore are critical determinants of dissemination to distant metastasis	Mlecnik B, Bindea G, Kirilovsky A, Angell HK, Obenauf AC, Tosolini M, Church SE, Maby P, Vasaturo A, Angelova M, Fredriksen T, Mauger S, Waldner M, Berger A, Speicher MR, Pagès F, Valge-Archer V, Galon J
Advanced Drug Delivery Reviews	Challenges and strategies in anti-cancer nanomedicine development: an industry perspective	Hare J, Lammers T, Ashford M, Puri S, Storm G, Barry S

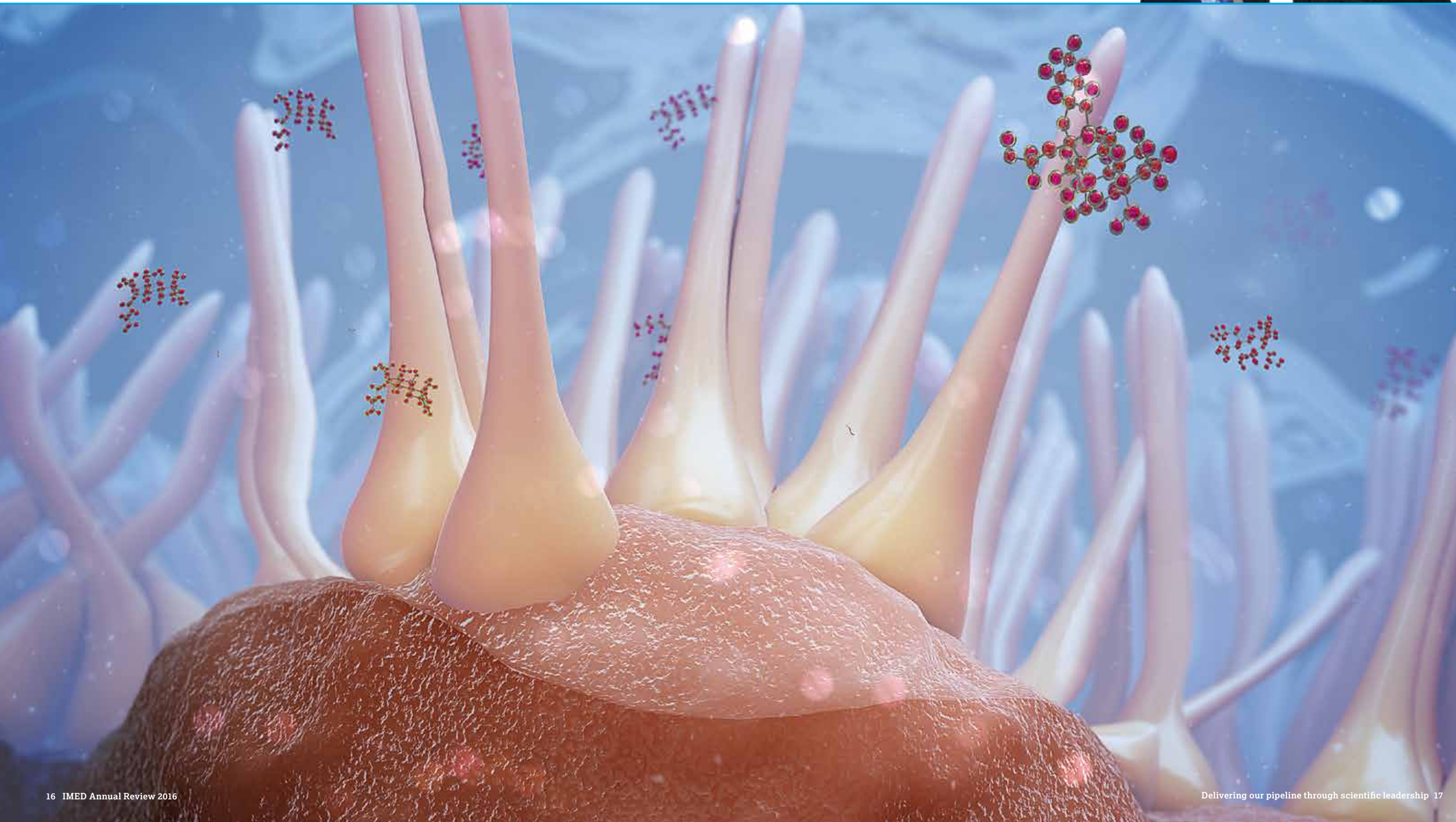
Respiratory, Inflammation and Autoimmunity

✓ Cilia in the lung

“2016 has been the start of a transition in our scientific strategy, where emphasis has shifted from symptom control and understanding respiratory disease drivers to identifying novel treatment paradigms to achieve disease modification and potentially cure patients with respiratory diseases”

Tariq Sethi, VP Respiratory, Inflammation and Autoimmunity
Translational Medicine Unit, Early Clinical Development

Outi Vaarala, VP Translational Biology, Respiratory, Inflammation and Autoimmunity



Respiratory, Inflammation and Autoimmunity (RIA)

This year we have refreshed our respiratory strategy with a focus on three core themes: **lung epithelium, lung immunity and lung regeneration**. There are over 600 million people living with asthma and chronic obstructive pulmonary disease (COPD) around the world, with therapies limited to treating or avoiding symptoms. Increasing our understanding of disease drivers forms the basis of our drug discovery programme and enables us to achieve our vision to deliver disease modifying medicines that prevent, reverse or even cure these devastating conditions.

Within lung epithelial health a key highlight has been AZD5634, our inhaled sodium channel (ENaC) inhibitor, which progressed this year through first time in man and into patients. Pre-clinical data has demonstrated the potential for AZD5634 mechanistically to improve lung function and reduce risk for infection-triggered exacerbations in patients with cystic fibrosis.

Within respiratory immunity, we have initiated a landmark Phase II trial of AZD1419, an inhaled toll-like receptor (TLR) 9 agonist, which aims to restore immune homeostasis in the airway of patients with T2 dominant asthma. This is the first ever study designed to keep asthma patients in remission rather than reduce exacerbations and AZD1419 has the potential to be the first true disease-modifying asthma treatment. In addition,

our inhaled PI3K γ inhibitor that targets asthma driven by mixed T-cell phenotype has shown promising pre-clinical results this year. As part of the programme, we are working with Ubiopred to identify gene signatures to understand and optimise patient response.

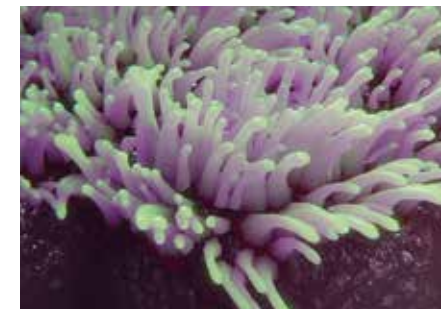
Our third focus is lung regeneration where we are investing in fundamental research to understand the mechanisms involved, including the role of epigenetic modifications, germline mutations and somatic mutations. Much of this research is being conducted through our collaborations with academic institutions including the University of Southampton, Institut national de la santé et de la recherche médicale (INSERM), and the Wallenberg Centre for Molecular and Translational Medicine, Gothenburg University.

In our journey towards disease modification and cure we are also utilising novel drug platforms beyond traditional small molecules to target protein-protein interactions and modulate protein expression. A key highlight this year has been our exciting new collaboration with Bicycle Therapeutics to explore the potential of bicyclic peptides to treat respiratory diseases.

Our robust portfolio of early targets has the potential to transform the treatment of respiratory disease. We believe our strong biology capabilities, our deep experience and capabilities in inhalation coupled with a leading scientific strategy will put us at the forefront of delivering disease modifying medicines in the future.

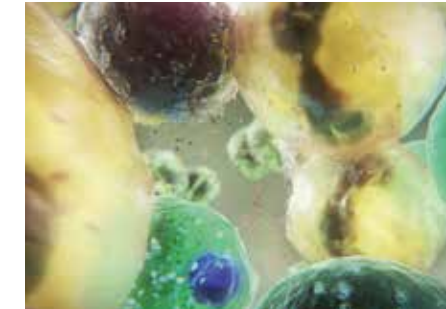
Our refreshed respiratory strategy

To realise our ambition of disease modification and cure in respiratory disease, we are renewing our research focus in IMED RIA on Lung Immunity, Lung Epithelium and Lung Regeneration. This renewed scientific focus will foster breakthrough innovation and establish world-class capabilities in respiratory disease to enable IMED RIA as scientific leaders in this field.



Lung epithelium

Disruption of the lung epithelium is a key driver of lung diseases and autoimmunity. Our goal is to identify therapies that can restore normal tissue architecture and lung epithelial integrity thereby improving patient outcome.



Lung immunity

Building on our established expertise in immunology and inflammation we aim to alter disease course by resetting immunological dysfunction in respiratory disease. We aim to identify molecules which modify disease by normalising immune homeostasis in target systems.



Lung regeneration

By understanding the key drivers of pathogenesis in the lung we aim to establish hypotheses for driving lung regeneration. We are investing in novel pre-clinical models and new technologies that will enable us to explore new biological pathways with the aim of understanding how we can restore or regenerate lung tissue to prevent, reverse and one day cure respiratory disease.

Asthma disease modification - first patient enrolled in landmark study

An estimated 300 million people worldwide suffer from asthma with prevalence increasing and despite documented awareness of asthma dating back to ancient civilisations, treatments are currently limited to symptom control.

AZD1419 is an oligonucleotide toll-like receptor TLR9 agonist originating from a collaboration with Dynavax. By stimulating Type 1 immune responses through TLR9, AZD1419 provides an opportunity to restore immune balance in patients where an excessive Type 2 inflammation underlies the disease pathology to bring patients disease free periods.

Following promising pre-clinical and Phase I studies we worked with the Karolinska Institute to develop, for the first time, a ground-breaking study in asthma designed to keep patients in remission rather than reduce exacerbations. The resulting study, INCONTROL, was initiated at the end of 2016.

In addition to clinical endpoints of asthma control, the study includes an extensive biomarker programme, which aims to understand the immunological changes associated with the loss of asthma control and the restoration of immune balance in this patient group. The outcome of the study (results November 2018) will not only determine next steps for AZD1419, but will also guide future studies to prevent asthma exacerbations.

We are very proud of this landmark study, which we believe has the potential to revolutionise the way people think about asthma management. It also demonstrates how AstraZeneca is leading in this field, delivering our ambition to re-think respiratory disease with modifying therapies to prevent, reverse or even cure these devastating conditions.

300

million people worldwide suffer from asthma.

Highlights

We set out to	We delivered
Build and progress the clinical portfolio	<p>We saw solid progression across all phases of development in 2016:</p> <p>Three candidates achieved first time in man; AZD5634 (ENaC), AZD0284 (RORγ), and inhaled SGRM/ abediterol Fixed Dose Combination.</p> <p>Two candidates demonstrated proof of mechanism; AZD9567 (oral SGRM), and AZD7986 (oral DPP1).</p> <p>Two candidates progressed into Phase II; Abediterol (LABA) and AZD1419 (TLR9).</p> <p>AZD7594 (inhaled SGRM) demonstrated Proof of Principle and our PT010 triple asthma pMDI delivered Phase IIa data enabling a Phase III investment decision.</p>
Deliver on our ambition to lead with an innovative precision medicine approach	<p>We took a personalised healthcare approach to many of our pipeline candidates. Our leukotriene C4 synthase (LTC4S) inhibitor targets cysteine leukotriene driven inflammation and bronchoconstriction in asthma patients. An activated cysteine leukotriene cascade could be used to identify patients most likely to respond to therapy in the future.</p> <p>We also have an inhaled PI3Ky6 inhibitor in pre-clinical development for patients with severe uncontrolled asthma with a mixed T-cell phenotype. We have promising pre-clinical data demonstrating the effects of our lead asset AZD8154 on mixed T2/1/17 biology in asthma cells, such as inhibition of T2/1/17 cytokine release, Type 2 innate lymphoid cells (ILC2s), eosinophil and neutrophil activation <i>in vitro</i>. Through our collaboration with Ubiopred, we are identifying gene signatures to optimise treatment through a personalised healthcare approach.</p> <p>Most respiratory patients are treated in a primary care setting with limited access to diagnostics. In 2016 we developed our first respiratory point of care diagnostic, using blood biomarkers to identify eosinophilic disease, with our diagnostic partner AgPlus.</p>
Demonstrate potential of inhaled bronchodilator candidates	<p>We demonsrated potential for once daily steroid-like anti-inflammatory and superior bronchodilator activity with improved safety in our development programme of novel inhaled bronchodilator combinations.</p> <p>AZD7594, an inhaled selective glucocorticoid receptor modulator (SGRM) has shown greater potency and selectivity than budesonide and other inhaled corticosteroids in pre-clinical models and has shown encouraging results in our asthma Phase IIa trial.</p> <p>Abediterol, a potent, selective long-acting beta2-adrenoceptor agonist (LABA), is efficacious at ultra-low doses and has shown fast onset with sustained 24 hour bronchodilation in comparison to other LABAs in asthma and COPD.</p> <p>AZD8871, an M3 antagonist-beta2-adrenergic agonist (MABA), has demonstrated fast onset and sustained 24 hour bronchodilation in patients relative to the respective monotherapy agents.</p>
Expand inhaled drug opportunities beyond small molecules	<p>We began a new collaboration with Bicycle Therapeutics, where we are excited to be working together to identify and develop bicyclic peptides to treat respiratory diseases. Highly constrained bicyclic peptides offer an exciting novel modality with high affinity, specificity and stability coupled with rapid tissue penetration and flexible routes of administration. Due to their larger size, these peptides can target protein-protein interactions, allowing us to screen targets deemed undruggable by traditional small molecule approaches.</p>
Utilise cutting edge capabilities in protein dynamics	<p>We pushed the boundaries of mass spectrometry (MS) using cutting edge hydrogen-deuterium exchange (HDX) as a tool to visualise protein dynamics in solution down to individual amino acid single residues.</p> <p>Detailed knowledge of protein dynamics upon ligand binding is key to understanding the desired pharmacological effects for drug compounds.</p> <p>HDX-MS has proved its value in the identification of allosteric binding sites, detailed understanding of the mode of action for novel ligands, studying the impact of binding on compounds in different classes of proteins to understand the biological effects, thus enabling the design of more functional selective targets.</p> <p>AstraZeneca takes an active leadership role by bringing together academic and industry experts from around the world by hosting the first ever HDX-MS conference to showcase the rapid advancement of this technology, highlighting its potential as a valuable tool in drug discovery. The conference will take place 15-17 May 2017 at the AstraZeneca site in Gothenburg.</p>
Advance modelling and prediction of inhaled pharmacodynamic (PD) and efficacy	<p>We delivered literature-unprecedented inhalation PK/PD modelling to facilitate rapid decision making and highlight possibilities of best-in-class bronchodilation of AZD8871, a dual-muscarinic antagonist/β2 agonist (MABA) for COPD patients. Proof of mechanism was demonstrated with single dose lung function results (through FEV1) and we used pre-clinical lung PK and clinical plasma PK to predict human lung PK and efficacy after single and repeat doses.</p> <p>Understanding whether inhaled drugs reach their pharmacological target in the lung is crucial and this year, for the first time ever, we quantified lung receptor occupancy using positron emission tomography (PET) imaging following inhalation. We developed a muscarinic receptor specific PET tracer to demonstrate the receptor occupancy by inhaled bronchodilator (ipratropium) in non-human primates. This exciting development raises the possibility for PET measures to be used as a surrogate for clinical efficacy in the future.</p>

People spotlight



Stefan Schiesser
Synthetic chemistry is key to our ability to discover novel, highly designed molecules that eventually may turn into clinical candidates. Over recent years, there has been a remarkable development of synthetic methodology that significantly changes the way molecules are synthesised. The recruitment of Stefan Schiesser as Senior Research Scientist, Chemistry, ensures that RIA chemistry continues to be at the forefront in the adoption and application of the most recent developments in the science of synthetic chemistry.

Stefan has a Ph.D. degree in synthetic chemistry from the Ludwig-Maximilians-University of Munich followed by post-doctoral studies with Professor Movassaghi's group at MIT in Boston. His research has included the synthesis of innovative anti-cancer compounds that helped to unravel the NPM1 regulated translesion DNA synthesis via interaction with the catalytic core of DNA polymerase-η. The quality of Stefan's research is underpinned by several publications in prominent chemistry journals such as *Journal of the American Chemical Society*, *Angewandte Chemie*, *Nature Chemical Biology* and *Journal of Organic Chemistry*.

Elin Boger
In realising our need to be world leading in predicting the local effects of inhaled drugs through applying physiologically based pharmacokinetic (PBPK) modelling, Elin Boger joined IMED RIA as Associate Principal Scientist, DMPK following completion of her PhD training at the University of Warwick. With several high quality publications and her thesis titled Lung-Targeted Receptor Occupancy by Drug Inhalation; an Experimental and Computational Evaluation, Elin embodies the scientist who is both an expert on the subject area and a mathematical modeler. With such a combination of skills Elin has taken on the task to conduct computational evaluation of inhaled drug candidates and to identify opportunities for non-small molecule inhaled therapeutics. Recently Elin's model was recognised by industry peers as the first published, non-commercial inhalation PBPK model, for which she was also awarded Breakthrough Scientist of the Year at the IMED Science Awards 2016.

Danen Cunoosamy
Danen Cunoosamy, Principal Scientist, Translational Biology became one of our new IMED RIA team leaders, with a team focused on the interaction of alveolar macrophages and epithelial cells in chronic obstructive pulmonary disease (COPD). This year Danen's team has shown that alveolar macrophages in COPD show plasticity and the phenotype of macrophages could thus be modulated by inhaled therapeutics. Furthermore, Danen, together with IMED colleagues, has demonstrated that the crosstalk between macrophages and B-cells seem to contribute to the emphysematic changes in COPD. This work has generated key publications in *American Journal of Respiratory Critical Care Medicine*.

✓ Lung bronchioles



Respiratory, Inflammation and Autoimmunity

Potentially life-changing treatment for patients with cystic fibrosis

Cystic fibrosis (CF) is a devastating genetic disorder that causes extensive lung damage and eventually, respiratory failure. While there has been progress in treating this disease, there is still no cure and life expectancy is still under 40.

AZD5634 is an inhaled sodium channel (ENaC) inhibitor that blocks the sodium channel in airway epithelial cells. AZD5634 is addressing fundamental host defence defects in CF lungs – insufficient clearance of inhaled pathogens and particles caused by dehydration of the lung epithelium, and poor mucous viscoelastic properties caused by low airway pH, leading to recurrent infections and inflammation and chronic lung damage. This concept could also be of great value in COPD patients with chronic bronchitis who have dehydrated airways, poor mucociliary clearance and recurrent exacerbations.

Building on our expertise in inhalation science, AZD5634 will be given in a single dose disposable dry powder inhaler (DPI) device: a device choice minimising risk for delivery related infections, a well-known problem with inhalation devices for chronic treatment.

We are proud of the significant progress we have made this year, successfully completing our first time in man single ascending dose study with promising safety, tolerability and pharmacokinetics. Our next step is to initiate a Phase Ib study to assess AZD5634 in CF patients and we are hopeful that AZD5634 will deliver a valuable treatment option in the future for patients suffering with this lethal disease.

“Cystic fibrosis (CF) is a devastating genetic disorder that causes extensive lung damage and eventually, respiratory failure. While there has been progress in treating this disease, there is still no cure and life expectancy is still under 40.”



Key publications in 2016

Publication	Title	Author
Nature Chemical Biology	Structural and conformational determinants of macrocycle cell permeability	Over B, Matsson P, Tyrchan C, Artursson P, Doak BC, Foley MA, Hilgendorf C, Johnston SE, Lee MD, Lewis RJ, McCarren P, Muncipinto G, Norinder U, Perry MWD, Duvall JR, Kihlberg J
Journal of Allergy and Clinical Immunology	ω-3 fatty acids contribute to the asthma-protective effect of unprocessed cow's milk	Brick T, Schober Y, Böcking C, Pekkanen J, Genuneit J, Loss G, Dalphin JC, Riedler J, Lauener R, Nockher WA, Renz H, Vaarala O, Braun-Fahrlander C, von Mutius E, Johannes Ege M, Pfefferle PI, PASTURE study group
Journal of Allergy and Clinical Immunology	U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics	Lefaudeux D, De Meulder B, Loza MJ, Peffer N, Rowe A, Baribaud F, Bansal AT, Lutter R, Sousa AR, Corfield J, Pandis I, Bakke PS, Caruso M, Chanez P, Dahlén SE, Fleming LJ, Fowler SJ, Horvath I, Krug N, Montuschi P, Sanak M, Sandstrom T, Shaw DE, Singer F, Sterk PJ, Roberts G, Adcock IM, Djukanovic R, Auffray C, Chung KF, and the U-BIOPRED Study Group
Pharmacology and Therapeutics	Patient stratification and the unmet need in asthma	Swedin L, Saarne T, Rehnberg M, Glader P, Niedzielska M, Johansson G, Hazon P, Catley M
The Lancet Respiratory Medicine	Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial	O'Byrne PM, Metev H, Puu M, Richter K, Keen C, Uddin M, Larsson B, Cullberg M, Nair P
Autoimmunity Reviews	Retinoid-related orphan receptor γ (RORγ) adult induced knockout mice develop lymphoblastic lymphoma	Liljevald M, Rehnberg M, Soderberg M, Ramnegard M, Borjesson J, Luciani D, Krutrok N, Branden L, Johansson C, Xu X, Bjursell M, Sjogren A, Hornberg J, Keeling D, Andersson U, Jirholt J
PLoS Genetics	Novel Genetic Variants for Cartilage Thickness and Hip Osteoarthritis	Castañó-Betancourt MC, Evans DS, Ramos YFM, Boer CG, Metrustry S, Liu Y, den Hollander W, van Rooij J, Kraus VB, Yau MS, Mitchell BD, Muir K, Hofman A, Doherty M, Doherty S, Zhang W, Kraaij R, Rivadeneira F, Barrett-Connor E, Maciewicz RA, Arden N, Nelissen RGHH, Kloppenburg M, Jordan JM, Nevitt MC, Slagboom EP, Hart DJ, Lafeber F, Styrkarsdottir U, Zeggini E, Evangelou E, Spector TD, Uitterlinden AG, Lane NE, Meulenbelt I, Valdes AM, van Meurs JBJ
Drug Discovery Today	Strategy for Large-Scale Isolation of Enantiomers in Drug Discovery	Leek H, Thunberg L, Jonson AC, Öhlén K, Klarqvist M
British Journal of Pharmacology	Neutrophil maturation rate determines the impact of dipeptidyl peptidase 1 inhibition on neutrophil serine protease activity	Gardiner P, Wikell C, Clifton S, Shearer J, Benjamin A, Peters S
Journal of Pharmaceutical Sciences	Development of a novel lung slice methodology for profiling of inhaled compounds	Bäckström E, Lundqvist A, Boger E, Svanberg P, Ewing P, Hammarlund-Udenaes M, Fridén M

A selection of key collaborations in 2016

1. **Wallenberg Centre for Molecular and Translational Medicine, Sweden**
In 2016 we established the Wallenberg Centre for Molecular and Translational Medicine (WCMTM) at the University of Gothenburg, in collaboration with Knut and Alice Wallenberg Foundation, Region Västra Götaland and the University of Gothenburg. Our goal is to enhance scientific collaboration in the field of respiratory and inflammatory diseases in the Gothenburg region and regain its world-leading position within medical research. This is done via recruitment of top young scientists to the University of Gothenburg where they will be able to evolve their full potential as leading independent scientists in a flourishing academic environment with unique connections to hospital infrastructures and AstraZeneca in Gothenburg.

2. **Bicycle Therapeutics, UK**
In December 2016 we signed a multi-target collaboration agreement with Bicycle Therapeutics, aimed at the identification and development of bicyclic peptides to treat respiratory, cardiovascular and metabolic diseases.

The proprietary bicyclic peptide (Bicycle®) platform provides the opportunity to screen a vast number of highly constrained macrocyclic peptides to address disease-relevant respiratory targets. Targets currently deemed difficult to target using traditional small molecule approaches, e.g. protein-protein interactions based on large and shallow binding pockets, become accessible due to improved affinity and target specificity. These attributes, usually

associated with biologics, are advantageous in a small molecule format to enable rapid tissue penetration and flexible routes of administration.

3. **Institut national de la santé et de la recherche médicale (INSERM), France**
Our collaboration with INSERM will evaluate the leukocyte subsets and cytokine profile in COPD and interstitial lung disease (ILD) in cells derived from peripheral blood, BAL and lung tissue. The primary objective is to define the phenotype and function of Treg cells subsets (natural or induced) isolated from COPD and ILD tissue and localisation of the defined subset of tissue resident Treg cells in the lung tissue from patients. The secondary objective is to define the phenotype and function of other immune cell subsets (T, B, NK, DC, alveolar macrophage, ILCs) and to determine their interaction with Treg cell subsets by analysing the immunological phenotype of COPD and ILD patients by flow cytometry and immune chemistry.

4. **Asthma UK/British Lung Foundation/ Medical Research Council Technology (MRCT), UK**
AstraZeneca, Asthma UK, British Lung Foundation and MRC Technology have joined forces to fund drug discovery collaborations to accelerate research in the field of respiratory epigenetics and develop new treatments for severe asthma and COPD. The collaboration is calling on academic researchers to submit novel epigenetic target proposals to accelerate

epigenetic respiratory research, particularly into asthma and COPD. This combines resources and expertise in drug discovery and clinical development, funding and access to research networks and patient groups to enable early stage scientific research to be translated into potential new therapies for respiratory diseases.

5. **GLAZgo Discovery Centre, UK**
Now in its third year, our collaboration with GLAZgo Discovery Centre, University of Glasgow has continued to grow from strength to strength. We are delivering decision-making translational medicine data for drug projects as well as defining new concepts, for example in immunological tolerance and cell function. It is also providing training for our current and next generation of scientists in essential scientific techniques whilst embedding concepts of academic ‘what-if’ and industrial ‘robustness’ to deliver innovation.

6. **University of Southampton, UK**
In April 2016 AstraZeneca signed a new research collaboration with leading respiratory scientists at the University of Southampton to conduct pioneering research that will reveal the pathways affecting disease modification and progression in COPD patients.

Our focus will be on how smoking-induced somatic mutations in the lung can drive the development and progression of COPD, as well as on epigenetic drivers of anti-viral responses. This strategic partnership could help us potentially identify novel targets in future areas of development for the IMED RIA.

7. **University of Alabama at Birmingham, US**
In a new collaboration with Prof. Steven Rowe, University of Alabama at Birmingham, we are investigating the importance of rehydration by ENaC inhibition with regards to mucociliary transport and clearance. By means of airway surface liquid height and mucociliary transport rates in cystic fibrosis ALI cultures (*in vitro*) we have demonstrated good efficacy and augmented clearance rates on top of other cystic fibrosis treatments and other target mechanisms in our portfolio.

8. **University of Western Australia, Australia**
We have been collaborating with Professor Le Souëf’s group in the MAVRIC study (Mechanisms of Acute Viral Respiratory Infection in Children), which aims to study the effect of rhinoviruses on the developing immune system in infants presenting to the hospital with and without pre-asthma. Learnings are currently being applied to molecular changes in nasal epithelial cells.

9. **Karolinska Institutet, Sweden**
Project ChAMP is an integrated approach to disease understanding and the development of predictive models in asthma, allergies and COPD. The goal of this collaboration with Professor Sven-Erik Dahlén at Karolinska Institutet is to identify sub-phenotypes of asthma and allied diseases through the use of a systems biology approach to model findings on all levels from gene to molecular metabolites.

10. **Tohoku University, Japan**
In human lungs, several drug metabolizing enzymes are expressed but at low levels compared to the liver. Working with Dr. Satoshi Kamata, Dr. Naoya Fujino, Dr. Mitsuhiro Yamada and Prof. Masakazu Ichinose at the Tohoku University School of Medicine, Japan, mRNA levels and activity of key enzymes of interest from healthy and diseased lungs are being quantified and compared with primary human hepatocytes. This will enable us to better predict the benefits and risks of inhaled drug administration.

RIA pipeline

Pre-clinical development

AZD9898 / LTC4s

AZD8154 / PI3Kγδ

Phase I

AZD7986 / DPP1

AZD9567 / oSGRM

AZD5634 / ENaC

AZD0284 / RORγ

AZD8871 / MABA

Phase II

AZD7594 / iSGRM

AZD9412 / IFNβ

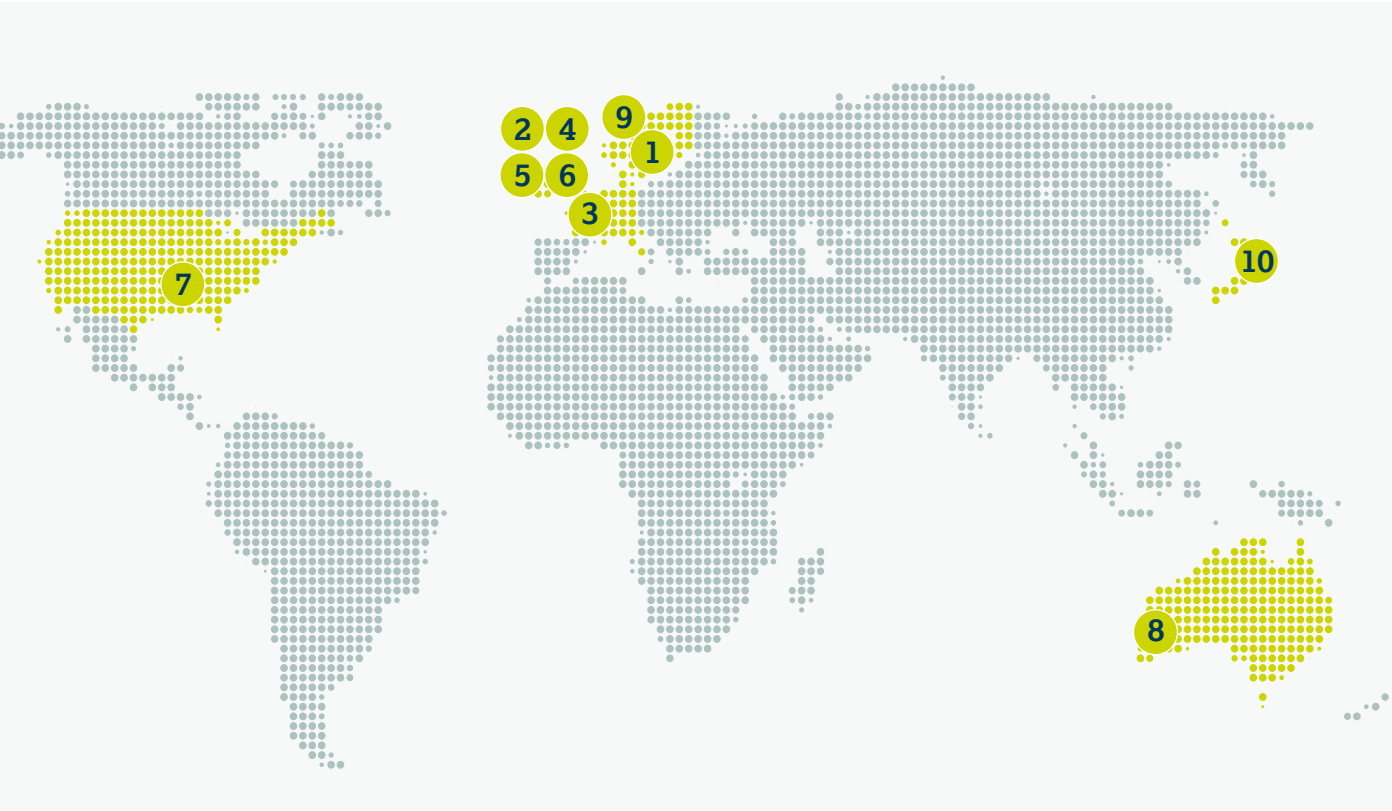
AZD1419 / TLR9

abediterol / LABA

Phase III / LCM

PT010 / Triple MDI

Pipeline correct as of Q4 2016, not including MedImmune programmes.

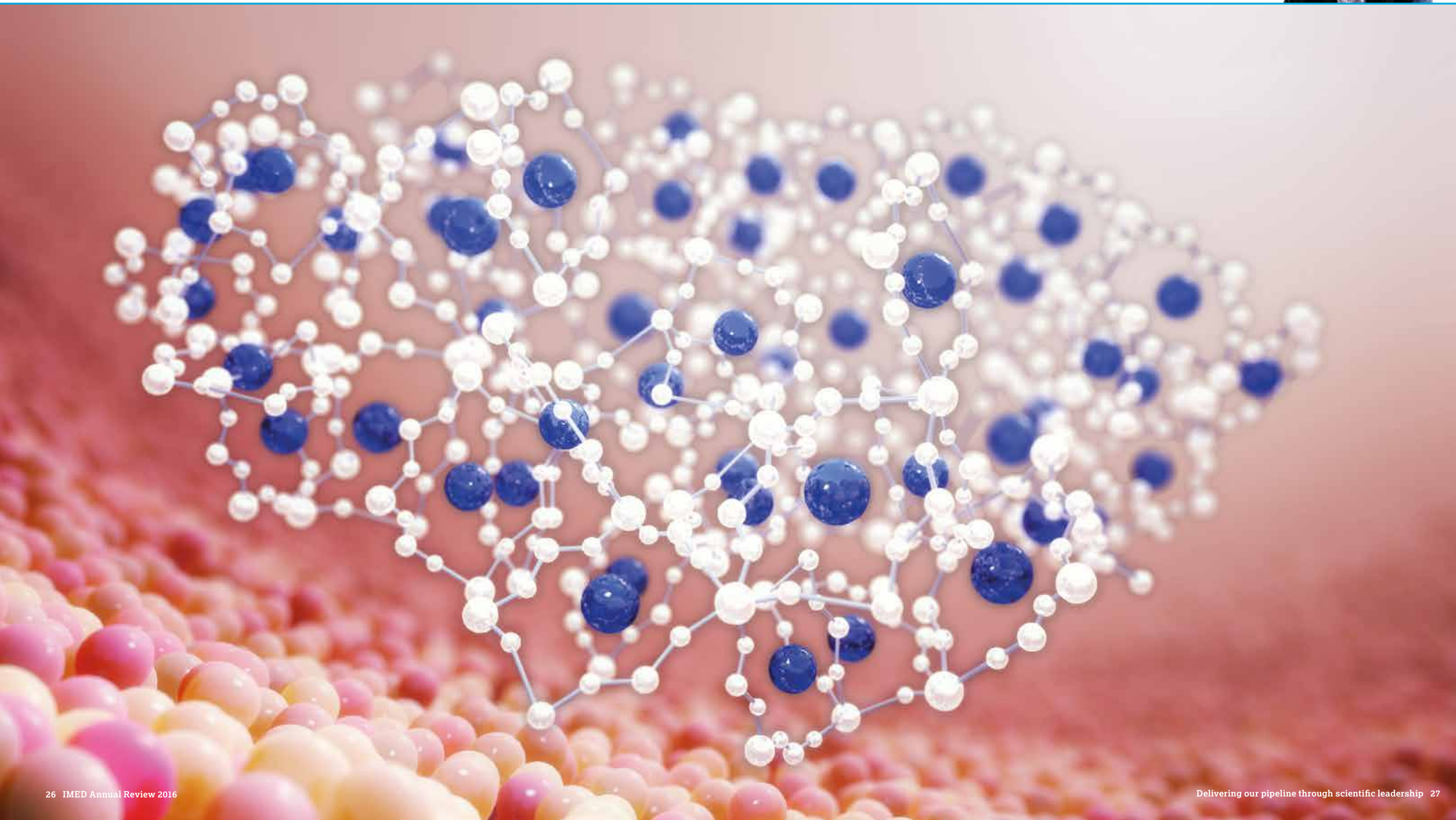


Cardiovascular and Metabolic Diseases

✓ Chronic Kidney Disease - selective crystal structure traps potassium and removes it from the body

“In the last 12 months we have made excellent progress in our pipeline and achieved many of our key milestones. We progressed the first ever modified RNA programme in Cardiovascular and Metabolic Diseases, VEGF-A messenger RNA (mRNA), into clinical development. Our clinical pipeline now consists of three drugs for heart failure/coronary artery disease plus the microRNA programme for nonalcoholic steatohepatitis (NASH)/diabetes which progressed into to Phase I/IIa this year. This is a tremendous achievement and a major step in our journey to scientific leadership.”

Marcus Schindler, VP IMED Cardiovascular and Metabolic Diseases



Cardiovascular and Metabolic Diseases

In IMED Cardiovascular and Metabolic Diseases (CVMD), we are committed to defining the new standard of care for the treatment of heart failure, diabetes and chronic kidney disease (CKD).

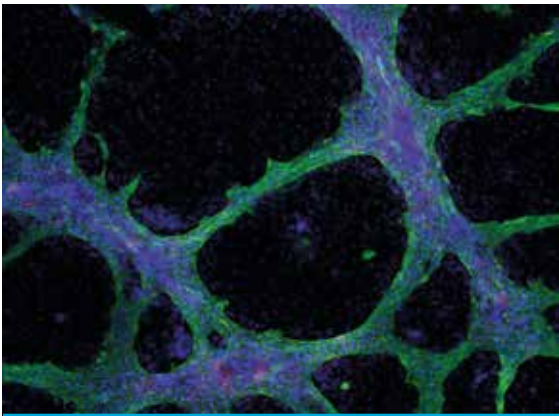
While previous years saw us build knowledge and invest in key technologies to develop both our pipeline and our level of scientific expertise, we are now strengthening a patient-centric approach aimed at better understanding the interplay and potential causal relationship between these diseases, which often present in the same patient. This is opening up unprecedented opportunities for novel treatment paradigms and will enrich our pipeline with further differentiated drugs.

In 2016, we saw significant progress in the discovery and clinical phases. During the year, we saw two programmes achieve first time in man; AZD4831 (MPO inhibitor) and AZD5718 (FLAP inhibitor). Both of these small molecule projects were invented and developed by AstraZeneca scientists and have the potential to help patients with heart failure with preserved ejection fraction (HFpEF) or coronary artery disease (CAD) respectively.

A major milestone of IMED CVMD in supporting our ambition in heart failure was the progression of AZD8601, the first ever modified RNA programme in CVMD, through regulatory approvals and further into Phase I in early January 2017. AZD8601 is a VEGF-A mRNA developed in collaboration with Moderna Therapeutics. It marks the first of hopefully many programmes to enter development through our broad partnership with Moderna in cardiovascular and metabolic diseases as well as cancer.

In metabolism, our anti-microRNA (miR 103/107) AZD4076 represents a new approach in the potential treatment of diabetic patients with non-alcoholic steatohepatitis (NASH), with the first diabetic patient with non-alcoholic fatty liver disease (NAFLD) being dosed in August 2016. To keep pushing the boundaries of science, our early pipeline was further strengthened in 2016 with projects based on human genetics

studies and characterised by strong human target validation. We believe our drive for innovation and advancing targeted drug delivery will bring life-changing medicines to patients with cardiovascular and metabolic diseases.



Cardiac regeneration

Highlights

We set out to	We delivered
Strengthen and progress our clinical stage pipeline	We successfully progressed candidates in both our small molecule and new modalities pipelines and we saw two candidates enter Phase I: AZD4831 (MPO inhibitor) and AZD5718 (FLAP inhibitor). We initiated a Phase I/IIa trial of AZD4076 (miR103/107) in diabetic patients with non-alcoholic fatty liver disease (NAFLD). We also gained full approval for our modified RNA programme, AZD8601 (VEGF-A) to progress into clinical development.
Deliver on our scientific collaborations	We identified multiple new pipeline entries through collaborative projects with representation from all three disease areas. We also achieved several publications within our strategic collaborations including several high impact publications. Two were published in collaboration with the Karolinska Institute, through our Integrated CardioMetabolic Centre (ICMC), which featured in <i>Circulation and Cell Metabolism</i> .
Drive progression within the field of chronic kidney disease	We recruited a new Head of Bioscience Chronic Kidney Disease (CKD), Professor Pernille B. Laerkegaard Hansen, to drive our early science strategy and deliver new targets to stop progression of CKD. We strengthened the science by progressing several projects aimed at CKD in our early portfolio. Furthermore, we continued to invest in our collaborations with Evotec, the ICMC and the University of Michigan.
Enhance our scientific reputation and demonstrate scientific leadership	We achieved 99 new publications in major peer-reviewed journals, of which 50 were high quality and nine high impact. The Medicinal Chemistry department in IMED CVMD, together with our collaborative partners and colleagues in IMED RIA and DSM, demonstrated they are at the forefront of chemical science with four high impact publications during 2016. In addition, significant results reflecting the impressive advancement of our discovery and clinical stage programmes were presented at key conferences in 2016 including European Society of Cardiology (ESC), European Renal Association – European Dialysis and Transplant Association Congress (ERA-EDTA), European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA), American Chemical Society (ACS), American Heart Association (AHA) and American Society of Nephrology (ASN).
Enhance our scientific exchange with local universities	We strengthened our work with the University of Gothenburg by establishing new collaborative projects. Professor Jenny Nyström joined IMED CVMD as Chief Scientist, CVMD scientist Daniel Linden was appointed Associate Professor, and Marcus Schindler, Head of IMED CVMD, was appointed Adjunct Professor in Pharmacology.

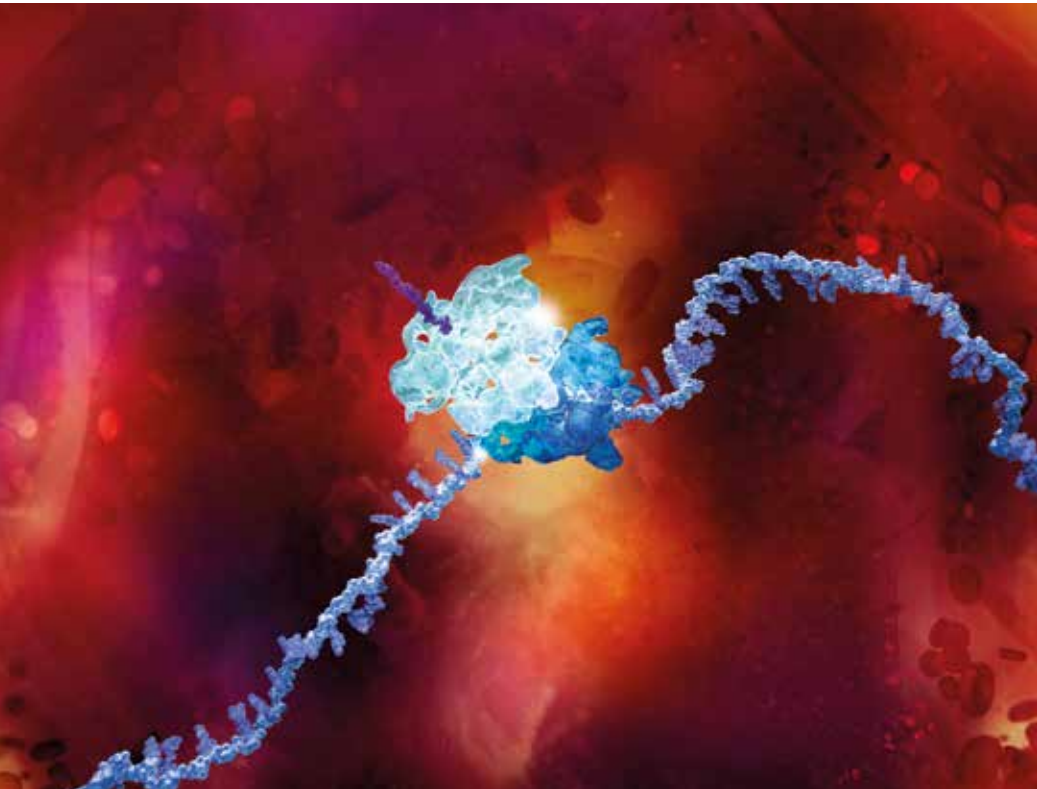
Cardiac regenerating muscle cells



Progressing the pipeline and building clinical evidence for new modalities science

In IMED CVMD, we have successfully built on our small molecule pipeline through 2016 with targets pursued using new modalities of modified mRNA and antisense oligonucleotides.

One of our promising candidates is AZD8601, our modified VEGF-A mRNA, which is designed to provide a unique regenerative treatment option for patients with heart failure or after a heart attack, as well as for diabetic wound healing and other ischaemic vascular diseases. We presented exciting data at the American Heart Association (AHA) Scientific Sessions 2016, demonstrating that at one week post Myocardial Infarction (MI) a single occasion injection of AZD8601 markedly improves cardiac function in a validate large animal model, suggesting feasibility of partially reversing cardiac dysfunction in patients post MI. This year we gained approval to progress AZD8601 into clinical trials.



People spotlight



Professor Pernille B. Lærkagaard Hansen

Professor Pernille B. Lærkagaard Hansen joined AstraZeneca in 2016 as Head of Bioscience Chronic Kidney Disease (CKD) IMED CVMD, where she is responsible for driving the early science strategy for delivering new targets to stop progression of CKD and lead the bioscience kidney discipline. She was recruited from her position as Professor and Deputy Department Head of Cardiovascular and Renal Research at the University of Southern Denmark.

Professor Hansen brings over 20 years of experience in studying the kidney and has worked in the translational, cardiovascular-renal area for almost ten years prioritising use of human material, kidney and blood vessels in experimental settings. She holds a PhD in physiology from the University of Southern Denmark and has previously held positions as post doc at the National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), USA and Associate Professor at the University of Southern Denmark. Her scientific reputation includes over 75 peer-reviewed publications including *Journal of Clinical Investigation*, *Proceedings of the National Academy of Sciences* and *Circulation Research*.

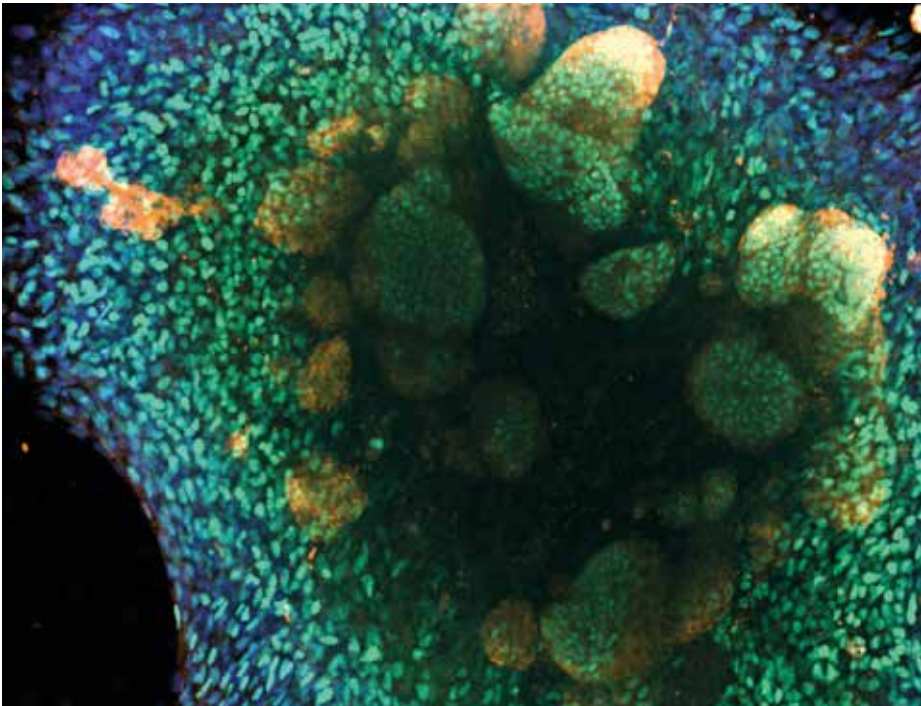
Professor Hansen’s expertise is a crucial part of the research for IMED CVMD as her capability completes the three-pronged disease area focus of IMED CVMD; heart failure, diabetes and chronic kidney disease. Furthermore her interest and focus on cardiovascular and renal diseases as well as vascular and renal effects during diabetes underlines the value she brings to IMED CVMD. This recruitment has been a major focus in 2016. Recruiting and retaining world-class talent is fundamental to the innovation, creativity, dedication and execution-focus that will enable CVMD to become industry leaders.

◀ Messenger RNA

Key publications in 2016

Publication	Title	Author
Cell Metabolism	Single-Cell Transcriptome Profiling of Human Pancreatic Islets in Health and Type 2 Diabetes	Segerstolpe Å, Palasantza A, Eliasson P, Andersson EM, Andréasson AC, Sun X, Picelli S, Sabirsh A, Clausen M, Bjursell MK, Smith DM, Kasper M, Åmmälä C, Sandberg R
Circulation	An IGF1R-Dependent Pathway Drives Epicardial Adipose Tissue Formation After Myocardial Injury	Zangi L, Oliveira MS, Ye LY, Ma Q, Sultana N, Hadas Y, Chepurko E, Später D, Zhou B, Chew WL, Ebina W, Abrial M, Wang Q-D, Pu WT, Chien KR
Advanced Drug Delivery Reviews	Cell permeability beyond the rule of 5	Matsson P, Doak BC, Over B, Kihlberg J
Nature Communications	Metal-free photochemical silylations and transfer hydrogenations of benzenoid hydrocarbons and graphene	Papadakis R, Li H, Bergman J, Lundstedt A, Jorner K, Ayub R, Haldar S, Jahn B, Denisova A, Zietz B, Lindh R, Sanyal B, Grennberg H, Leifer K, Ottosson H
Circulation	Protective Effects of Ticagrelor on Myocardial Injury After Infarction	Vilahur G, Gutierrez M, Casani L, Varela L, Capdevila A, Pons-Lladó G, Carreras F, Carlsson L, Hidalgo A, Badimon L
Chemical Reviews	Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications	Johansson, JR, Beke-Somfai T, Said Stålsmeden A, Kann N
Nature Chemical Biology	Structural and conformational determinants of macrocycle cell permeability	Over B, Matsson P, Tyrchan C, Artursson P, Doak BC, Foley MA, Hilgendorf C, Johnston S, Lee MD, Lewis RJ, McCarren P, Muncipinto G, Perry M, Duvall JR, Kihlberg J
ALTEX	Biology-inspired microphysiological system approaches to solve the prediction dilemma of substance testing	Marx U, Andersson TB, Bahinski A, Beilmann M, Beken S, Cassee FR, Cirit M, Daneshian M, Fitzpatrick S, Frey O, Gaertner C, Giese C, Griffith L, Hartung T, Heringa MB, Hoeng J, de Jong WH, Kojima H, Kuehn J, Leist M, Luch A, Maschmeyer I, Sakharov D, Sips AJ, Steger-Hartmann T, Tagle DA, Tonevitsky A, Tralau T, Tsyb S, van de Stolpe A, Vandebriel R, Vulto P, Wang J, Wiest J, Rodenburg M, Roth A
Drug Metabolism and Disposition	CYP3A specifically catalyzes 1β-hydroxylation of deoxycholic acid: Characterization and enzymatic synthesis of a potential novel urinary biomarker for CYP3A activity	Hayes MA, Li XQ, Gronberg G, Diczfalusy U, Andersson TB
Diabetes	Differential Roles of Insulin and IGF-1 Receptors in Adipose Tissue Development and Function	Boucher J, Softic S, El Ouaamari A, Krumpoch MT, Kleinridders A, Kulkarni RN, O'Neill BT, Kahn CR
Kidney International	Purinergic signaling in kidney disease	Menzies RI, Tam FW, Unwin RJ, Bailey MA
Journal of Medicinal Chemistry	Therapeutic Potential of Foldamers: From Chemical Biology Tools To Drug Candidates?	Gopalakrishnan R, Frolov AI, Knerr L, Drury WJ 3rd, Valeur E
ACS Chemical Biology	Phenotypic Screen for Cardiac Regeneration Identifies Molecules with Differential Activity in Human Epicardium-Derived Cells versus Cardiac Fibroblasts	Paunovic AI, Drowley L, Nordqvist A, Ericson E, Mouchet E, Jonebring A, Grönberg G, Kvist AJ, Engkvist O, Brown MR, Gedda K, Goumans M-J, Wang QW, Plowright AT
Hepatology	Massive rearrangements of cellular microRNA signatures are key drivers of hepatocyte dedifferentiation	Lauschke VM, Vorriink SU, Moro SM, Reyazee F, Nordling Å, Hendriks DF, Bell CC, Sison-Young R, Park BK, Goldring CE, Ellis E, Johansson I, Mkrtchian S, Andersson TB, Ingelman-Sundberg M
Heart	Contemporary risk estimates of three HbA1c variables in relation to heart failure following diagnosis of type 2 diabetes	Skrtic S, Cabrera C, Olsson M, Schnecke V, Lind M
Kidney International	Improved kinetic model for the transcutaneous measurement of glomerular filtration rate in experimental animals	Friedemann J, Heinrich R, Shulhevich Y, Raedle M, William-Olsson L, Pill J, Schock-Kusch D

Strengthening presence and commitment to fight chronic kidney disease



200

million people globally are fighting chronic kidney disease.

Stem cell-derived kidney organoid stained with kidney markers WT1 and NPHS1

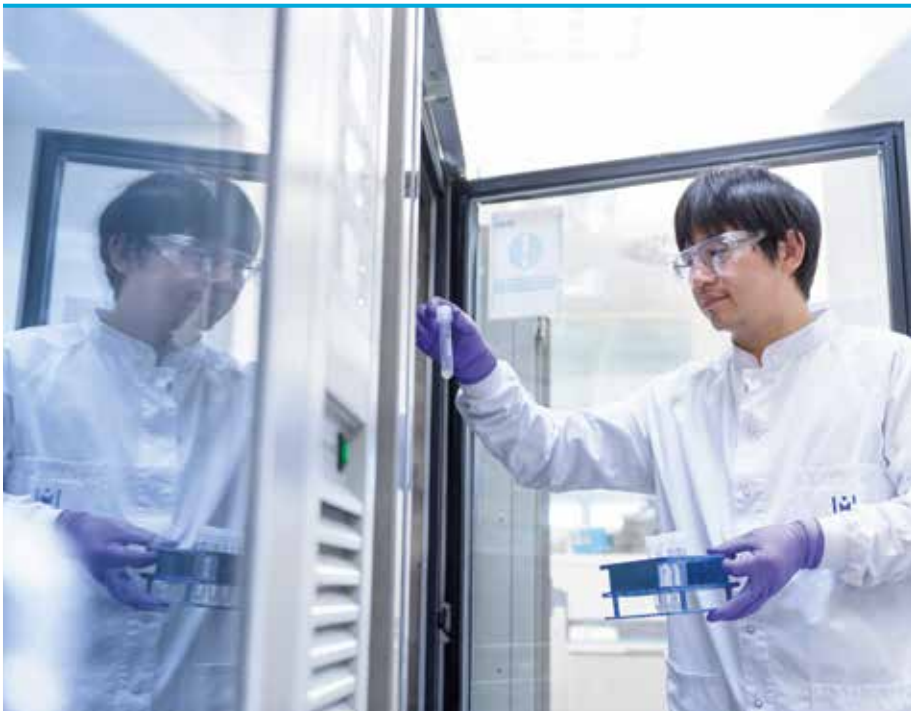
This year has been an exciting year of progress and transformation for our early CKD research. An important milestone was the recruitment of the Head of Bioscience CKD, Professor Pernille B. Lærkagaard Hansen - the experience, expertise and enthusiasm that Professor Hansen brings to the department has helped establish a new path forward to enable delivery of the medicines for tomorrow.

CKD is a critical global healthcare issue with increasing prevalence, affecting more than 200 million people worldwide. There are currently no treatments to stop or reverse deterioration without kidney transplantation, and so CKD represents a large and growing unmet medical need. In IMED CVMD we are focusing on the drugs of tomorrow aimed to slow the disease progression and further our progress towards the drugs of the future where we aim to stop or even reverse the disease. Key to realising these goals will be Professor Hansen, her team and the strong collaboration between our core functions to deliver the innovation, patient insight and technology required.

Collaborating for success

In parallel with our strong in-house science, we expanded our collaboration with the University of Michigan by joining the Renal Pre-Competitive Consortium (RPC2), giving us access to a world-leading clinical and molecular database of CKD patients. RPC2 is a unique industry-academia collaboration focusing on the use of patient-derived data to understand molecular pathways, targets and networks in CKD with diabetes complications; integrate clinical and histopathological data with large scale genomic data; and to openly share data with other consortium partners.

We believe that the knowledge generated in the consortium will lead to the strengthening of the level of human target validation in our portfolio, with potential targets already identified for our early CVMD pipeline. The first deliverable from the consortium was presented at the American Society for Nephrology (ASN) Kidney Week 2016, and showed the identification of an intrarenal transcriptomics biosignature for mesangial cells, which play a critical



role in the initiation and progression of glomerular disease and may be a novel treatment target for drug development.

Building our capabilities with cutting edge science

The development of physiologically relevant cellular models with translatability to human pathophysiology is critical for the identification and validation of novel therapeutic targets. Working closely with our colleagues in Discovery Sciences, we have pushed the boundaries of science to establish a kidney organoid model system utilising CRISPR/Cas9 in induced pluripotent stem cells (iPSCs). These organoids show expression of key markers of kidney biology, including renal cortical structures with microvilli, tight junctions and podocyte foot processes. This development of human nephron-like structures *in vitro* fills a major gap in assessing effectiveness of CKD-treatments as well as the possibility of clinical translations. Details of the model were presented at ASN Kidney Week 2016.

“We are now strengthening a patient-centric approach aimed at better understanding the interplay and potential causal relationship between these diseases.”

CVMD pipeline	
Pre-clinical	
AZD8233 / undisclosed	
Phase I	
AZD5718 / FLAP	
AZD4831 / MPO	
AZD8601 / VEGF-A	
MEDI8111 / rhFII	
Phase II	
AZD4076 / miR 103/107	
Phase III / LCM	
ticagrelor / P2Y12	
dapagliflozin / SGLT2	
saxagliptin / DPP4	
exenatide / GLP1	
ZS-9 / Potassium exchanger	
roxadustat / HIF	
epanova /omega-3-carboxylic acids	
Pipeline correct as of Q4 2016, not including MedImmune programmes.	

A selection of key collaborations in 2016

1.

Renal Pre-Competitive Consortium
(University of Michigan, Eli Lilly and
Novo Nordisk), US and Denmark

In 2016, AstraZeneca joined a two-year collaboration with the Renal Pre-Competitive Consortium (RPC2) to foster a personalised medicine approach in CKD. Through this collaboration AstraZeneca has access to a world-leading source of patient intrarenal transcriptomic data to advance the understanding of molecular drivers of CKD and identify novel therapeutic targets. Deliveries: novel targets with first-in class potential; novel approach for patient stratification and personalised medicine.

2.

Integrated Cardio Metabolic Centre (ICMC),
Sweden

In 2013 AstraZeneca with Karolinska Institute, Stockholm, Sweden established a unique joint centre for research on cardiovascular and metabolic diseases. The uniqueness of this collaboration is that the scientists from Karolinska Institute are working side-by-side with AstraZeneca scientists to identify and validate novel targets within cardiovascular and metabolic diseases.

The focus is mainly on three strategic research themes: heart failure, metabolism and CKD. Professor Christer Betsholtz, a world leading scientist with an outstanding scientific track record, has been appointed as the new director for the centre and Chief Scientist, IMED CVMD, while maintaining a position at the University of Uppsala.

3.

Harvard Stem Cell Institute, US

A collaboration with Professor Doug Melton's group to progress the novel finding that functional human beta cells can be generated from stem cells. We are aiming at better understanding how the function of beta cells declines in diabetes, and to find regenerative drugs using inducible pluripotent stem cells.

4.

IONIS Pharmaceuticals, US

A strategic collaboration to discover and develop antisense oligonucleotide (ASO) therapies for cardiovascular, metabolic and renal diseases. AstraZeneca and IONIS also continue their collaboration to discover new targeted delivery approaches to access more disease relevant tissues for oligonucleotide therapeutics.

5.

Moderna Therapeutics, US

An alliance initiated in 2013 to discover and develop mRNA therapeutics for the treatment of cardiovascular, metabolic and renal diseases as well as cancer. The first project in the alliance has entered clinical development. A Phase I safety, tolerability and pharmacodynamic study is currently enrolling patients in Europe for AZD8601, an investigational mRNA-based therapy being developed by AstraZeneca that encodes for VEGF-A.

6.

University of Michigan, US

A collaboration with Professor Matthias Kretzler that will tackle the validation of novel therapeutic targets for the treatment of CKD, the identification of biomarkers to guide clinical development and the selection of translational animal models for pre-clinical research. Through this collaboration AstraZeneca has access to a world-leading patient intrarenal transcriptomic data and animal models which allows us to better correlate our targets with molecular drivers of CKD that could ultimately lead to potential new therapies. Deliveries: human target validation data package for all portfolio projects, supporting decisions on project progression and animal models selection.

7.

Institut national de la santé et de la
recherche médicale (INSERM), France

A three year collaboration initiated in 2015. The aim of the collaboration is to advance understanding of Type 2 diabetes and CKD and develop new treatments based on this knowledge. The collaboration with Professor Frédéric Jaisser aims at better understanding the complexities of mineral corticoid receptor activity as a potential treatment for CKD. The collaboration is pursuing research to further evaluate the MR mediated pathways leading to organ damage. The collaboration with Professor Dominique Langin currently explores pharmacological ways to prevent adipose tissue release of lipid into the circulation, to normalise fat deposition and increase insulin sensitivity in peripheral tissues. The third collaboration with Dr Raphael Scharfmann is working to develop models of human β -cells which have lost their ability to produce and release insulin, to better understand the biology of this effect and how it can be corrected through treatment.

8.

National Heart Center, Singapore

A collaboration with Prof. Winston Shim on human induced pluripotent stem cell-Derived cardiomyocytes for disease modeling with the aim to characterize mutations that play a role in Heart Failure with preserved Ejection Fraction. Additionally, we will use different modalities including CRISPR methodologies to reverse deficits in this innovative "patient-in-a-dish" model.

9.

Karolinska Institutet, Sweden

Professor Berggren's group at the Karolinska Institutet (KI) has established an *in vivo* translational validation platform in which mouse or human pancreatic islets are transplanted into the anterior chamber of the eye of mice, where they become vascularized and innervated, and control blood glucose. IMED CVMD Diabetes has started a 3 year collaboration with Professor Berggren to discover and validate novel islet targets using this platform.

10.

University of Oslo, Norway

The University of Oslo has entered a five-year research agreement with AstraZeneca in the area of type 2 diabetes. As part of the agreement, four researchers from the university will work at AstraZeneca's laboratories in Sweden on joint topics of interest in adipose biology.



Neuroscience

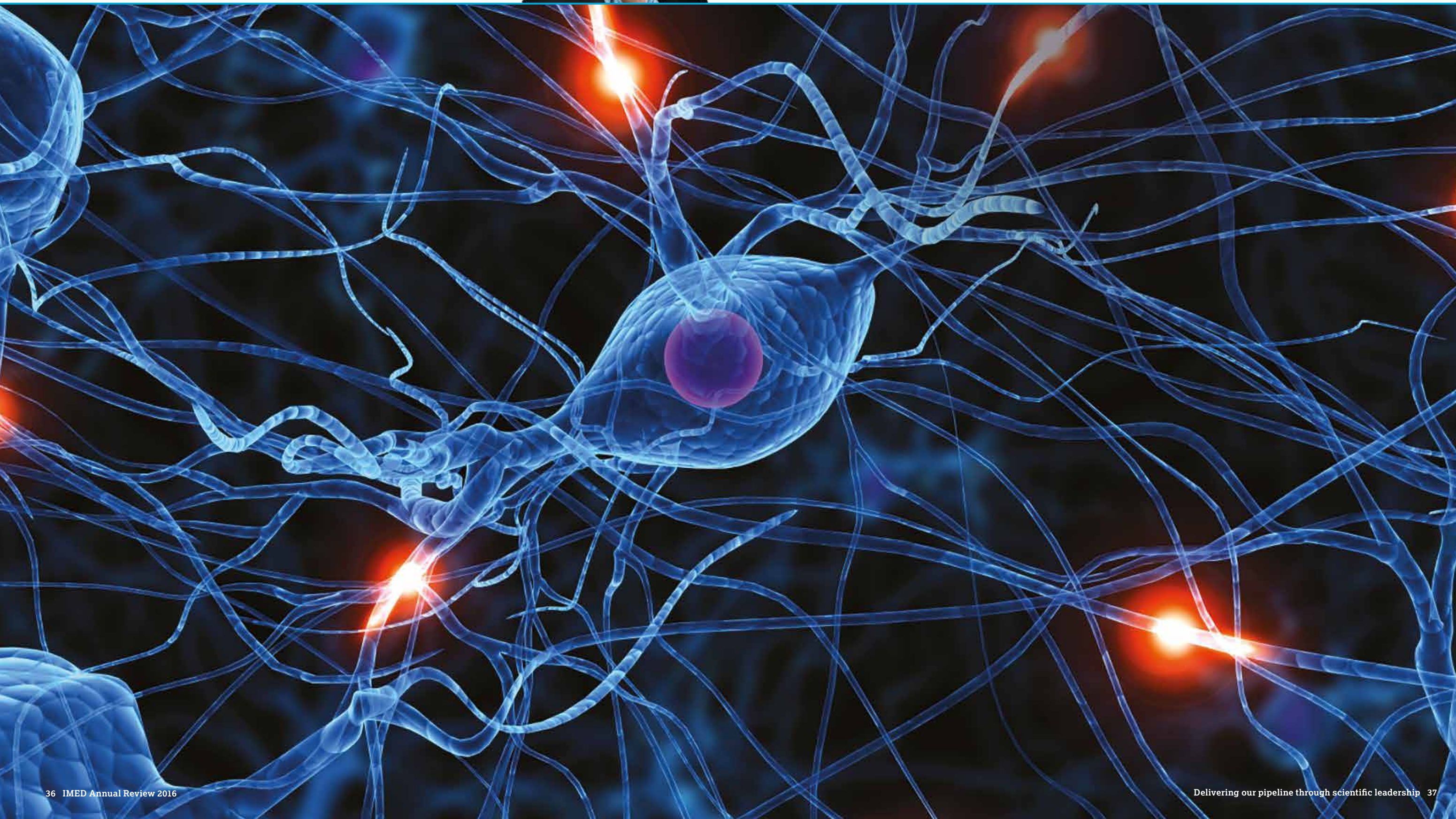
✓ Neurons in the brain



“2016 has been both challenging and rewarding – we have made great progress with our pipeline, seeing significant progression of our neurodegeneration and pain therapies, with completion of patient studies for our anti-amyloid Aβ42 antibody, continued progress of our beta secretase cleaving enzyme (BACE) compound in collaboration with Eli Lilly and Company, and the emergence of first data from our Phase I study in pain. We have also continued delivery of top-class

science, with a number of high impact and high quality papers. Our challenge in 2016 was to continue to do this amidst significant change, with a reduction in overall resources and integration of IMED and MedImmune teams into a single development unit. However, our innovative approach to this therapy area, together with a competitive portfolio and world-class talent, has meant that neuroscience continues to thrive.”

Iain Chessell, VP IMED Neuroscience



Neuroscience

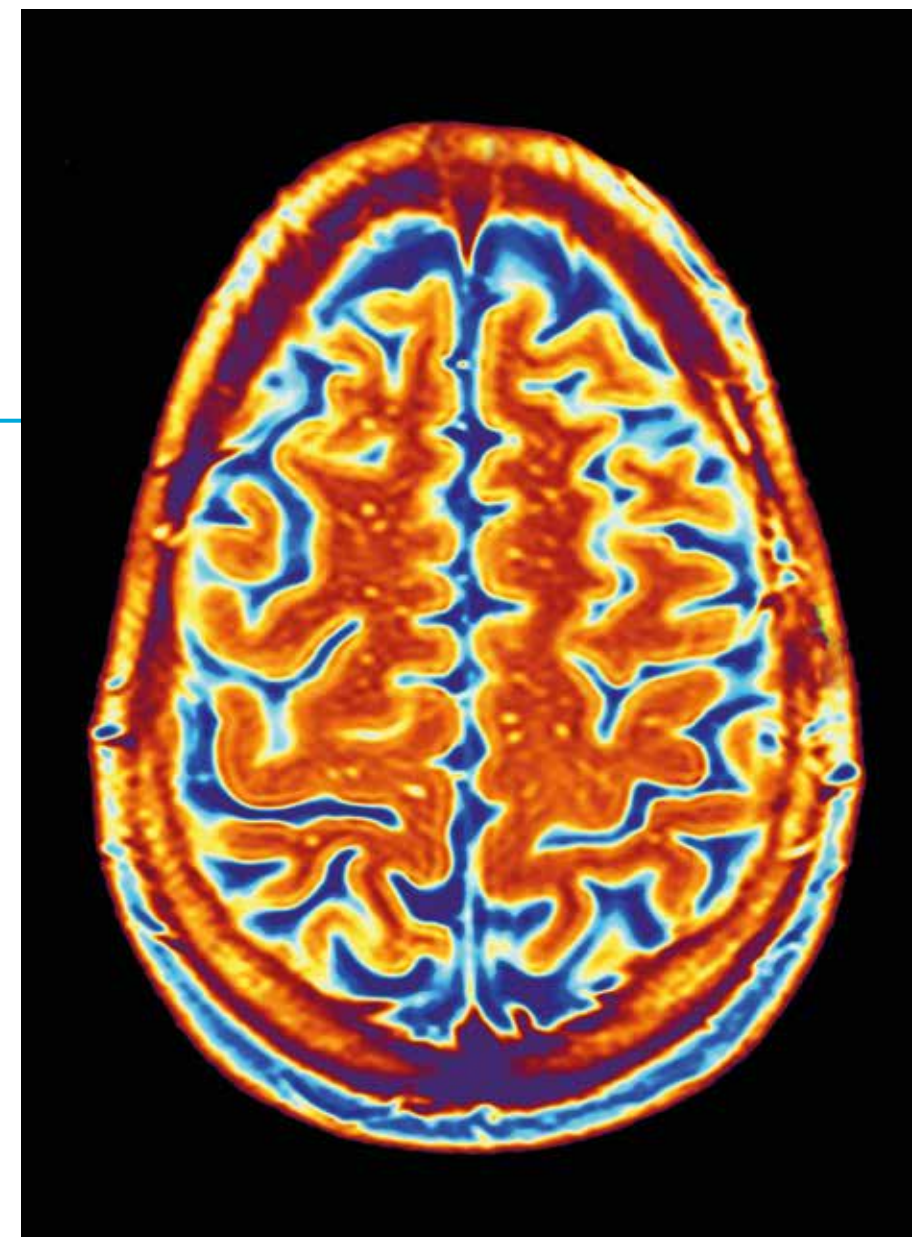
AstraZeneca has made a long-term commitment to neuroscience with ongoing investment to deliver life-changing medicines to patients with neurodegenerative diseases, chronic pain and psychiatric conditions. This year we have restructured our organisation to incorporate MedImmune Neuroscience into a single, focused function within the IMED Biotech Unit which makes us well placed to deliver first in class medicines.

Many of the team are now based at our Cambridge site and includes a concentrated organisation of world class scientists. Our approach is to build on this in the coming years by hand-picking high quality scientists to join our unique working environment both in the UK and the US, where we retain a smaller footprint.

It is an exciting time to be working in neuroscience, with more progress in basic disease mechanism research in the last 10 years than the previous 50. Being a small, focused group allows us to behave in an agile way: reacting to breaking science as it happens. As an example, as data accumulated linking alpha-synuclein spreading to Parkinson's disease we were able to react in real-time, initiating a programme to develop a monoclonal antibody targeting the protein.

Our business model thrives on being dynamic and partly externalised, with a laser-like focus driving science within our key areas of interest. Early, flexible partnering with the brightest and best in the world allows us to combine knowledge and progress clinical development as well as share the high risks and high costs associated with neuroscience research. An example is our ongoing collaboration with Eli Lilly and Company (Lilly) which led to a Phase III investment decision for AZD3293, our oral potent small molecule beta secretase clearing enzymes (BACE) inhibitor. As a result, we have two Phase III trials running simultaneously and we are poised to potentially be one of the first to launch a disease modifying treatment for Alzheimer's disease in the future.

The consistent high quality of our science has led to a strong portfolio with some highly valuable and desirable assets. These have the potential to provide the next wave of revenue generation for AstraZeneca as well as to transform the lives of patients living with devastating neurodegenerative diseases, chronic pain and psychiatric conditions.



< Brain scan

Neuroscience pipeline

Pre-clinical

MEDI1341 / α -synuclein

MEDI0168 / PAR2

Phase I

MEDI1814 / A β 42

MEDI7352 / NGF / TNF

Phase II

AZD3241 / MPO

Phase III / LCM

AZD3293 / BACE

Pipeline correct as of Q4 2016.

Promising Phase I data for MEDI1814, the only A β 42 specific antibody in development for Alzheimer's disease

Alzheimer's disease is a devastating, progressive condition that affects more than 44 million people and their families around the globe and, despite continuing efforts, there are no disease modifying therapies currently available.

Alzheimer's disease is characterised by amyloid plaques found in the brain which are made up of amyloid beta (A β) peptides; A β 40 is the most abundant, but A β 42 is more toxic. The leading hypothesis in the field is that cognitive decline in Alzheimer's disease is driven by the presence of A β 42-seeded oligomers in the brain.

MEDI1814 is a high affinity monoclonal antibody that specifically targets A β 42 in the brain without affecting A β 40. This selectivity is unique compared with other A β targeted antibodies that have been studied to date and represents an

exciting opportunity to test the amyloid hypothesis in a whole new way.

Our Phase I study completed in 2016 and promising preliminary findings demonstrate a compelling safety profile with both intravenous (IV) and subcutaneous (SC) routes of administration being well tolerated. There was linear and predictable serum pharmacokinetics and clear evidence of dose-dependent central target engagement as well as selectivity for A β 42 vs A β 40 in cerebrospinal fluid (CSF).

To best enable the progression of this exciting candidate, we are pleased to have entered a worldwide agreement with Lilly to co-develop MEDI1814. This extends our already productive collaboration on BACE which combines the expertise of our two companies but also our shared passion to bring new medicines to patients suffering from this debilitating illness.

Highlights

We set out to	We delivered
Progress our neurodegenerative diseases pipeline	<p>We began a second Phase III study of AZD3293, our oral potent small molecule BACE inhibitor, in collaboration with Lilly in patients with mild Alzheimer's disease and dementia (DAYBREAK-ALZ). AZD3293 was also awarded FDA fast track designation this year to expedite the development and review of this promising potential therapy.</p> <p>We saw exciting early results from our Phase I study of MEDI1814, our Aβ42 specific monoclonal antibody, demonstrating selective reduction of Aβ42 in the CSF of Alzheimer's disease patients. In December, we announced a co-development agreement with Lilly for this asset that complements our collaboration on AZD3293.</p> <p>Equally, we are making good progress with our antibody directed toward alpha-synuclein for Parkinson's disease, with clinical studies set to start in 2017.</p> <p>Earlier in the portfolio we have projects focused on specific disease mechanisms which should provide opportunities for Alzheimer's, Parkinson's and motor neuron disease (MND) in future years.</p>
Progress our chronic pain pipeline	<p>We commenced Phase I trials with our first in class dual action (bispecific) antibody, MEDI7352, which has potential to work in inflammatory and neuropathic pain.</p> <p>In addition, we have seen significant progression in our work understanding neuro-immune interactions and transcriptional regulation focusing on accessing the right target in the right place with exciting molecules progressing toward clinical development.</p>
Deliver on our commitment to addiction	<p>We progressed two distinct targets/neural circuits, not regulated by current addiction medicines, to address both the rewarding properties of nicotine and critically prevent relapse which is one of the biggest goals of addiction research.</p> <p>Substance abuse, in particular addiction to nicotine is the focus of IMED's psychiatric research, carried out through highly successful partnerships with the National Institutes of Health (NIH) and National Institute of Drug Abuse (NIDA).</p> <p>Clinical data on one of the mechanisms (mGluR2) is expected in early 2017.</p>
Nurture our collaborations and partnerships	<p>We continue to build world-class commercial and academic collaborations, closely aligned and focused on our areas of interest and key to our success.</p> <p>Our collaboration with Tufts University Department of Neuroscience in Boston is focused around the AstraZeneca-Tufts laboratory for Basic and Translational Neuroscience, led by Professor Stephen Moss, where a group of scientists are contributing to delivering our early portfolio. The lab works on projects where we believe neuronal plasticity and subsequent brain processes are disturbed with Motor Neuron Diseases (MND) and epilepsies being a current emphasis.</p> <p>We also enjoy a close collaboration with the University of Cambridge, working with Professor David Rubenstein and Professor Maria Spillantini looking at novel mechanisms related to our programmes in neurodegeneration, in particular Huntington's and Parkinson's disease.</p>
Demonstrate our scientific leadership	<p>We achieved many high impact and high quality publications including one published in <i>Nature Medicine</i> providing the identification of the enzyme AS3MT as a risk gene for schizophrenia. In addition, a paper on how the chaperone protein known as CCT restricts neuropathogenic protein aggregation via autophagy was published in <i>Nature Communications</i>.</p>



The consistently high quality of our science has led to a strong portfolio with some highly valuable and desirable assets.”

MEDI7352 brings new hope for chronic pain sufferers

Chronic pain affects an estimated 100 million people across Europe and despite substantial investment by the pharmaceutical industry over several decades, there has been little progress in developing new, efficacious and safe analgesic treatments.

Nerve growth factor (NGF) is a key regulator of inflammatory pain and several anti-NGF monoclonal antibody therapies in development have shown promising results at >90% suppression levels. However clinical progression has been hampered by cases of rapidly progressing osteo-arthritis (RPOA) which appears to be dose-related and exacerbated by non-steroid anti-inflammatory drug (NSAID) co-administration.

MEDI7352 is a first in class, dual action (bispecific) antibody exploiting synergy between NGF and tumour necrosis factor alpha (TNF alpha). By binding two different targets involved in chronic pain, it has the potential to work in inflammatory pain, such as in arthritis, but also neuropathic pain, such as diabetic neuropathy where there is no treatment currently available.

Pre-clinical studies using MEDI7352 have demonstrated a synergy between NGF and TNF sequestration resulting in a significant analgesic effect in models of both inflammatory and neuropathic pain at <20% sequestration of NGF. This synergistic low level sequestration means that MEDI7352 doesn't adversely interfere with other NGF actions and may have a different tolerability and safety profile, as well as a different efficacy profile as a result.

As a candidate with such potential to impact the millions of people suffering with chronic pain in the future, we were very excited to see MEDI7352 enter the clinic in a Phase I trial at the beginning of 2016.



Neurons in the brain

100
million people affected by chronic pain across Europe

People spotlight



Fraser Welsh

Fraser Welsh is a Project Director in IMED Neuroscience and is currently leading on the MEDI7352 Phase I clinical study. Fraser has been at Cambridge Antibody Technology (CAT), MedImmune and AstraZeneca for 16 years, initially in antibody engineering and latterly in research project management where he was head of the Cambridge RPM group for two years. He has significant experience in the research and pre-clinical phases of drug development projects and in portfolio management having worked in each of the therapeutic areas over the course of his career. As part of IMED Neuroscience, Fraser's role is primarily project leadership but he also contributes to the IMED Neuroscience leadership team and provides project and portfolio management support where needed.

Prior to joining CAT in July 2000 Fraser obtained a BSc in Chemistry from the University of St Andrews and a PhD in Chemistry from the University of Edinburgh. He had a brief spell as a postdoc with a Biotech company in Leeds before moving yet further south to join CAT.

A selection of key collaborations in 2016

1.

Tufts University, US

Our collaboration with Tufts University Department of Neuroscience is a true academia-industry hybrid. Formed in late 2013 we established a biotech lab to conduct research to drive our early stage portfolio, publish high quality data and deliver excellent science. By 2016 our collaboration consisted of 10 postdoctoral scientists conducting research in three main areas – neurodegeneration, psychiatric disorders and disorders with a prevalent pathology related to synaptic plasticity such as epilepsy.
2.

University of Cambridge, UK

Building on an existing strategic partnership between AstraZeneca, MedImmune and the University of Cambridge in the UK, in late 2014 we began a three year collaboration with leading scientists to advance our understanding and treatment of neurodegenerative disorders such as Parkinson's, Alzheimer's and Huntington's diseases. Working with prominent investigators the collaboration has two key aims: to drive target selection and biomarker identification through the detailed study of key mediators in the autophagy pathway, focussing in on potential project starts; to build a greater understanding of the pathological spread of alpha synuclein, working with our candidate antibody.
3.

Eli Lilly & Company (Lilly), US

In 2016 we announced a collaboration with Lilly to co-develop MEDI1814, an antibody

selective for amyloid-beta 42 (Aβ42), which is currently in Phase I trials as a potential disease-modifying treatment for Alzheimer's disease. This agreement builds on the existing collaboration related to AZD3293, a BACE inhibitor in two pivotal Phase III trials.

4.

Trinity College Dublin and Brigham and Women's Hospital, Ireland and US

Our ongoing collaboration with Trinity College Dublin and Brigham and Women's Hospital, Cambridge MA, is focussed on understanding toxic species of aggregating proteins present in Alzheimer's Disease brain samples. We are using biochemical and *in vivo* electrophysiological approaches to understand how aggregating proteins interact with neurones to disrupt synaptic communication. These data support candidate investment decisions with data that is more objective than standard cognition models in rodents

5.

King's College, UK

Our collaboration with Prof Stephen McMahon at Kings College, London aims to increase understanding of the role of inflammatory mediators like nerve growth factor and tumour necrosis factor in pathways contributing to chronic pain states. The work will investigate the potential for additive or synergistic effects as a result of interactions between these and other mediators. These studies will help elucidate the mechanism of existing clinical candidates and potentially contribute new targets to the portfolio.

6.

UK Dementia Platform, UK

AstraZeneca is a key member of the UKDP platform, whose intent is to further understanding of Alzheimer's Disease (AD) and other dementias by prosecuting experimental medicine and translational research. One example, for which AZ is the industry lead, is the deep and frequent phenotyping (DFP) platform. Here, we are studying the transition of Alzheimer's Disease from the prodromal to mild/moderate stage using biochemical biomarkers, behavioural readouts, imaging (PET and MRI) as well as a range of exploratory measures which will help us understand not only a 'biomarker fingerprint' for AD, but may also define progression endpoints which can be used in interventional studies.
7.

Eolas Therapeutics and National Institute of Health, US

We have an exciting collaboration with Eolas Therapeutics, a biotech start-up which came out of The Scripps Institute in Florida, supported by the NIH Blueprint Neurotherapeutics Network, with the aim to develop medicines for smoking cessation and other indications. The collaboration embraces the externalized and flexible model championed by the AstraZeneca Neuroscience group. The team have diligently identified and characterized a range of chemotypes in the past three years and are now focussing on a lead molecule to bring into clinical development.



Key publications in 2016

Publication	Title	Author
Nature Medicine	A human-specific isoform of AS3MT isoform and BORCS7 are molecular risk factors in the 10q24.32 schizophrenia-associated locus	Li M, Tao R, Jaffe A, Shin J, Wang Y, Chen Q, Li C, Jia Y, Ohi T, Maher B, Straub R, Brandon N, Cross A, Chenoweth J, Wei H, Hyde T, McKay R, Kleinman J, Weinberger D
Molecular Psychiatry	Early postnatal GABAA receptor modulation reverses deficits in neuronal maturation in a conditional neurodevelopmental model of DISC1	Saito A, Taniguchi Y, Rannals MD, Merfield EB, Ballinger MD, Koga M, Ohtani Y, Sedlak TW, Cross A, Moss SJ, Brandon NJ, Maher BJ, Kamiya A
Pain	Enhanced delivery of IL-1 receptor antagonist to the central nervous system (CNS) as a novel anti-TfR-IL-1RA fusion reverses neuropathic mechanical hypersensitivity	Webster CI, Hatcher J, Burrell M, Thom G, Thornton P, Gurrell I, Chessell IP
European Urology	The expression of inflammatory mediators in bladder pain syndrome	Offiah I, Didangelos A, Dawes J, Cartwright R, Khullar V, Bradbury EJ, O'Sullivan S, Williams D, Chessell IP, Pallas K, Graham G, O'Reilly BA, McMahon SB



“Our world-class commercial and academic collaborations are closely aligned and focused on our areas of interest and are key to our success.”

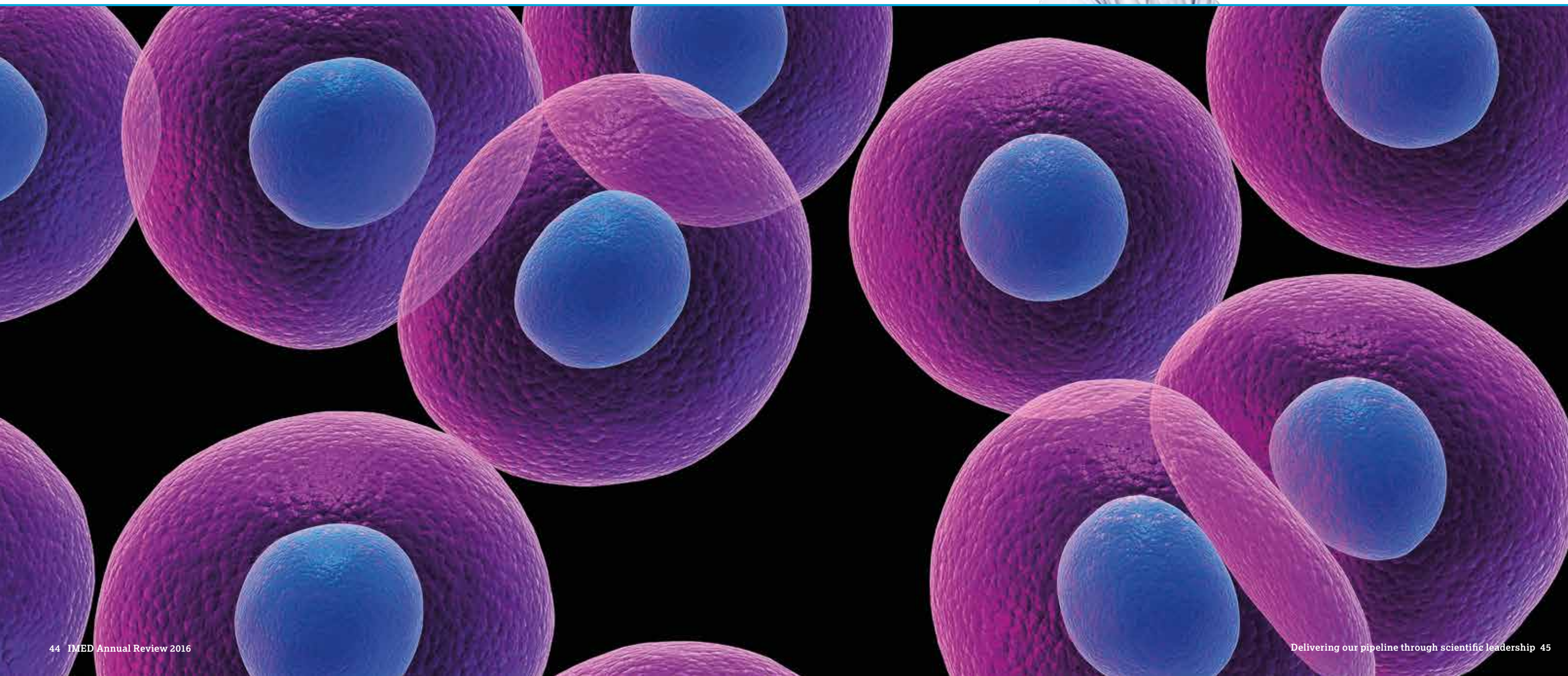
IMED Asia

“We have advanced our portfolio significantly in 2016. AZD3759, the first investigational drug out of IMED Asia, is progressing well in ongoing global BLOOM trials. AZD3759 also gained China category 1 Investigational New Drug (IND) approval, a major milestone for us. Our high impact publication in Science Translational Medicine further enhanced our scientific reputation externally.”

Xiaolin Zhang, VP IMED Asia

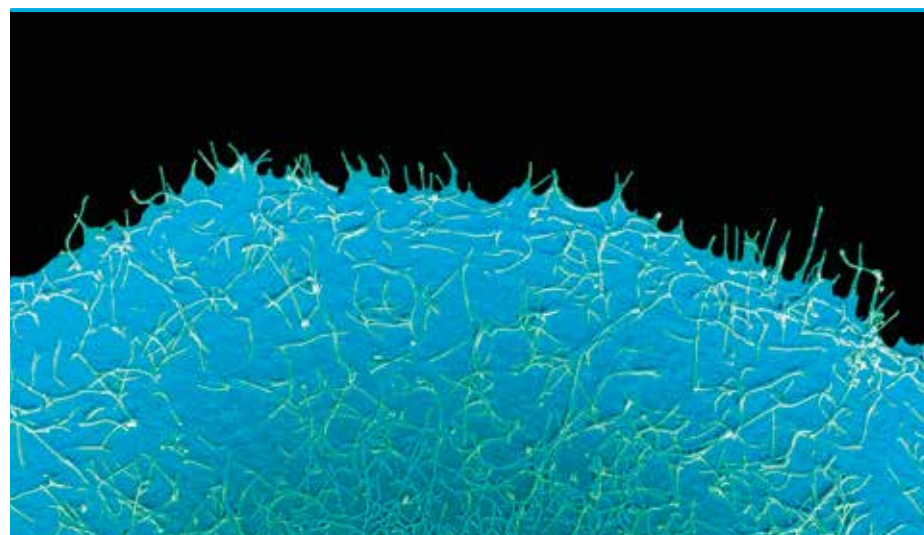


✓ Cells under a microscope



IMED Asia

The aim of IMED Asia is to accelerate patient access to innovative medicines across China and Asia. During 2016, we have continued to work closely with global teams to actively explore new potential drugs for the treatment of diseases that are most prevalent in this part of the world.



We have supported our business in China by delivering data to support New Drug Application (NDA) and Clinical Trials Permission (CTP) submissions to the China FDA (CFDA), as well as biomarker studies to support clinical trials across the portfolio. We have also continued to work with centres across Asia to drive testing uptake and thus increase patients' access to novel therapies. In addition, we have further enhanced our scientific reputation through collaboration with leading institutions globally, especially in China.

This year we have seen significant pipeline progression across AstraZeneca's three main therapy areas. In Oncology, we have continued to strengthen our scientific leadership in blood-brain-barrier (BBB) penetrant compounds with a new candidate

AZD1390, as well as high impact publications and congress activities. Currently in Phase I clinical trials, AZD1390 is an ATM inhibitor designed to treat a population of glioblastoma patients through optimised delivery of drug to the brain. Another key highlight was the promising data from BLOOM studies for AZD3759*, which was selected for oral presentation at the American Society of Clinical Oncology (ASCO) as well as the Society for Neuro-Oncology (SNO) annual meeting. AZD3759 was discovered by IMED Asia and is a novel epidermal growth factor receptor (EGFR) mutation positive inhibitor to treat non-small cell lung cancer (NSCLC) with central nervous system metastases. These preliminary findings showed encouraging intracranial and extracranial anti-tumour activity with a tolerability profile typical of the class of treatment.



We have further enhanced our scientific reputation through collaboration with leading institutions globally, especially in China."

< Cancer cell

In addition, our Chronic Kidney Disease (CKD) programme, within the Cardiovascular and Metabolic Disease (CVMD) therapy area, has progressed well this year with significant steps towards a potential candidate drug achieved by the project team.

**AZD3759 has been out-licensed to an external party for further global clinical development*

People spotlight

Renhong Tang

As the project leader of the respiratory virus team, Renhong Tang made a key contribution to the smooth transfer of the project from Infection to the Asia team. Renhong set up our virology capability from scratch within two months and helped establish our differentiation strategy for AstraZeneca's replication inhibitors from inhibitors with other modes of action. This was achieved with minimal additional headcount and investment.



Li Zheng

As one of the kidney disease project bioscience leads, Li Zheng effectively guides *in vitro* and *in vivo* bio scientists, making a significant contribution to project progression. The team successfully delivered the lead compound's dose-dependent efficacy for building up PK-coverage-efficacy relationship, verified the effect in animals at different disease severities, confirmed target engagement by Ca²⁺-image analysis on *in situ* podocytes of glomeruli, and finally understood the compound's working mechanism and differentiation from currently used drug steroid. Li also leads the bioscience team in Asia, collaboratively working with Oncology to successfully deliver the primary pharmacology data package for AZD1390 CDID.



Kan Chen

Kan Chen joined AstraZeneca in 2010 as part of the DMPK function in Asia. Kan applied his knowledge from the CNS Oncology AZD3759 programme to support compound screening and candidate selection of CNS penetrable candidates for the AZD1390 programme. AZD1390 was approved and progressed to clinical development stage in 2016. Kan established innovative assays to find the candidates to cross the CNS barrier more efficiently.



Highlights

We set out to

Progress the project pipeline across our three main therapy areas

Strengthen our scientific leadership in blood-brain-barrier (BBB) penetrant compounds

Support AstraZeneca China with our expertise

We delivered

In Oncology, we delivered preliminary data from BLOOM, our Phase I study of AZD3759, showing encouraging intracranial and extracranial anti-tumour activity with a tolerability profile typical of the class of treatment. We also delivered a new candidate AZD1390.

In CVMD we continued progression of our CKD programme, taking significant steps towards a potential candidate drug.

In Respiratory, Inflammation and Autoimmunity (RIA), we achieved a high quality publication through our ongoing collaboration with the Respiratory Division of Zhongshan Hospital, Shanghai Institute of Respiratory Disease. Our publication in the demonstrates that IL-13+ type 2 innate lymphoid cells correlate with asthma control status and treatment response.

In collaboration with IMED Oncology we delivered a new candidate AZD1390, as well as four publications relating to our BBB penetrant compounds including one published in *Science Translational Medicine*.

For the second year in a row, data on our BBB penetrant molecule AZD3759 was selected for oral presentation at ASCO, following which the Society for Neuro-Oncology invited us to present the data at their annual meeting in November.

Our study data supported the NDA submission of osimertinib and CTP filing of durvalumab to CFDA. We also significantly increased T790M and BRCA testing rates nationwide through a comprehensive educational programme. In addition, we contributed to biomarker studies in osimertinib, AZD3759, olaparib and savolitinib clinical trials, as well as boosting patient access to gefitinib across Asia.

Supporting business growth in China and across Asia

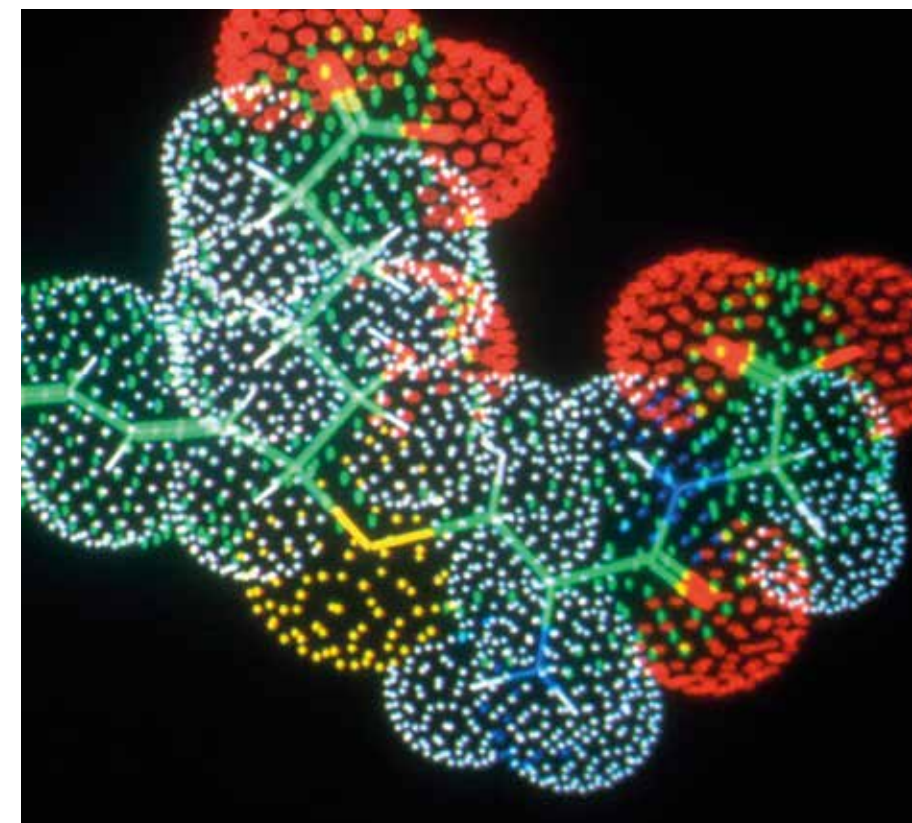
Our science unit in China is closely engaged with global study teams, the AstraZeneca China Marketing Company, Global Medical Affairs and Global Medicines Development to support business growth in China and Asia. Our remit is to provide scientific/technical support and translational science data packages to advance AstraZeneca's pipeline and portfolio in China and Asia.

This year, the team contributed to the successful NDA filing submission of osimertinib to the China Food and Drug Administration (CFDA) in August 2016 by leading a study evaluating T790M circulating tumour DNA (ctDNA) testing as a potential patient selection biomarker. We

also supported CTP filing to the CFDA for durvalumab in 1L/3L/adjuvant NSCLC by completing a PD-L1 prevalence study of NSCLC patients in China.

We contributed to the accelerated uptake of T790M and BRCA testing across China by providing technical training workshops, seminar education and lab evaluation which will increase patient access to osimertinib and olaparib in China. We also provided 30 training sessions for EGFR mutation testing, involving over 600 trainees from China, Hong Kong, Korea and Vietnam over the last seven years. This continuous effort has increased EGFRm testing rates from 0% to 60% and had a significant impact for NSCLC patients' access to gefitinib.

Our leading scientific reputation has been demonstrated by 13 high quality publications this year, including one in *Science Translational Medicine* which describes the discovery and early clinical development of AZD3759. We also continue to establish collaborations with leading institutions through expansion of our PhD and graduate programme as well as two of our senior scientists being appointed as adjunct Professors at the Tongji University School of Medicine.



600

trainees from China, Hong Kong, Korea and Vietnam market teams

< Molecular structure



We contributed to the accelerated uptake of T790M and BRCA testing across China by providing technical training workshops, seminar education and lab evaluation which will increase patient access to osimertinib and olaparib in China.”

Promising preliminary results for AZD3759 presented at American Society of Clinical Oncology (ASCO) and Society for Neuro-Oncology (SNO)

AZD3759* is the first investigational drug discovered by IMED Asia. It is a blood-brain-barrier (BBB) penetrant EGFR inhibitor evaluated for the treatment of NSCLC with brain metastasis (BM) and leptomeningeal metastasis (LM) which has shown anti-tumour activity in pre-clinical BM and LM models.

This year we were excited to present promising preliminary data from BLOOM, our ongoing Phase I study, at ASCO and subsequently at the SNO annual meeting following an invitation from the Society for Neuro-Oncology.

BLOOM is an open label, multi-centre study to assess safety and tolerability of AZD3759 in patients with EGFRm+ NSCLC who progressed with EGFR tyrosine-kinase inhibitor (TKI) and chemotherapy. This first time in man study aims to determine the maximal tolerated dose and/or recommended Phase II dose as well as preliminary efficacy.

All patients were treated with AZD3759 in escalating dose cohorts and the pharmacokinetic analysis demonstrated excellent encouraging central nervous system (CNS) penetration, with a ratio of 1:1 between cerebrospinal fluid (CSF) and free plasma concentrations. The tolerability profile was consistent with EGFR TKI class effects (primarily skin rash and diarrhoea) and no drug-related CNS adverse events were reported.

Encouraging intracranial and extracranial anti-tumour activity was observed with AZD3759 treatment. The BLOOM study has completed enrolment of BM and LM patients for AZD3759 and the majority of patients are still ongoing with median follow up time greater than six months.

**AZD3759 has been out-licensed to an external party for further global clinical development*

A selection of key collaborations in 2016

1.

Institute of Molecular Medicine, Peking University, China

Since November 2010, IMED Asia has been working together with Peking University on a number of key projects including: applying advanced imaging technologies to study calcium dynamics and their role in normal and disease pathophysiology, exploring the molecular mechanisms of phosphate transporters and their roles in human diseases and targeting an insulin signalling regulator with neutralising antibody for reverse insulin sensitivity.
2.

Shanghai Lung hospital, China

We have been working with the Shanghai Lung hospital since May 2013 to investigate: plasma testing of EGFR mutations in Chinese NSCLC patients, resistance mechanisms of first generation EGFR-TKI therapy and resistance mechanisms to osimertinib (third generation EGFR-TKI).
3.

Shanghai Chest Hospital, China

Our collaboration with the Shanghai Chest Hospital began in May 2013 and investigates plasma testing of EGFR mutations in Chinese NSCLC patients using the highly sensitive droplet digital PCR.
4.

Zhejiang Cancer Hospital, China

We have been working together to explore the underlying mechanisms of leptomeningeal metastasis (LM) in NSCLC patients. A joint paper, 'Exploration of the underlying mechanisms of leptomeningeal metastasis in NSCLC patients through next generation sequencing (NGS) of cerebrospinal fluid', was presented at the World Conference on Lung Cancer 2016.
5.

Institute Pasteur of Shanghai, Chinese Academy of Sciences, China

We collaborated to characterise the anti-viral effect of small molecule compound in animal models infected with a respiratory virus. AstraZeneca's novel compound can significantly reduce its viral load in infected mice, thus provided the first *in vivo* efficacy data for this working mechanism in respiratory virus research.
6.

Chongqing Medical University, China

We formed a collaboration with the Children's hospital of Chongqing Medical University to study the clinical characteristics of otherwise healthy infants (0-2 years old) naturally infected by a respiratory virus.
7.

Peking Union Medical College Hospital, China

We have been working together with Peking Union Medical College Hospital to explore molecular mechanism of central nervous system (CNS) metastasis, including leptomeningeal metastasis and brain metastasis, in EGFR mutation positive NSCLC patients by whole exosome sequencing.
8.

Shandong Cancer Hospital, China

Our collaboration with Shandong Cancer Hospital is to study the effect of EGFR TKI in combination with radiation on lung cancer and/or lung cancer brain metastasis and explore the potential mechanism.
9.

Respiratory Division of Zhongshan Hospital, Shanghai Institute of Respiratory Disease, China

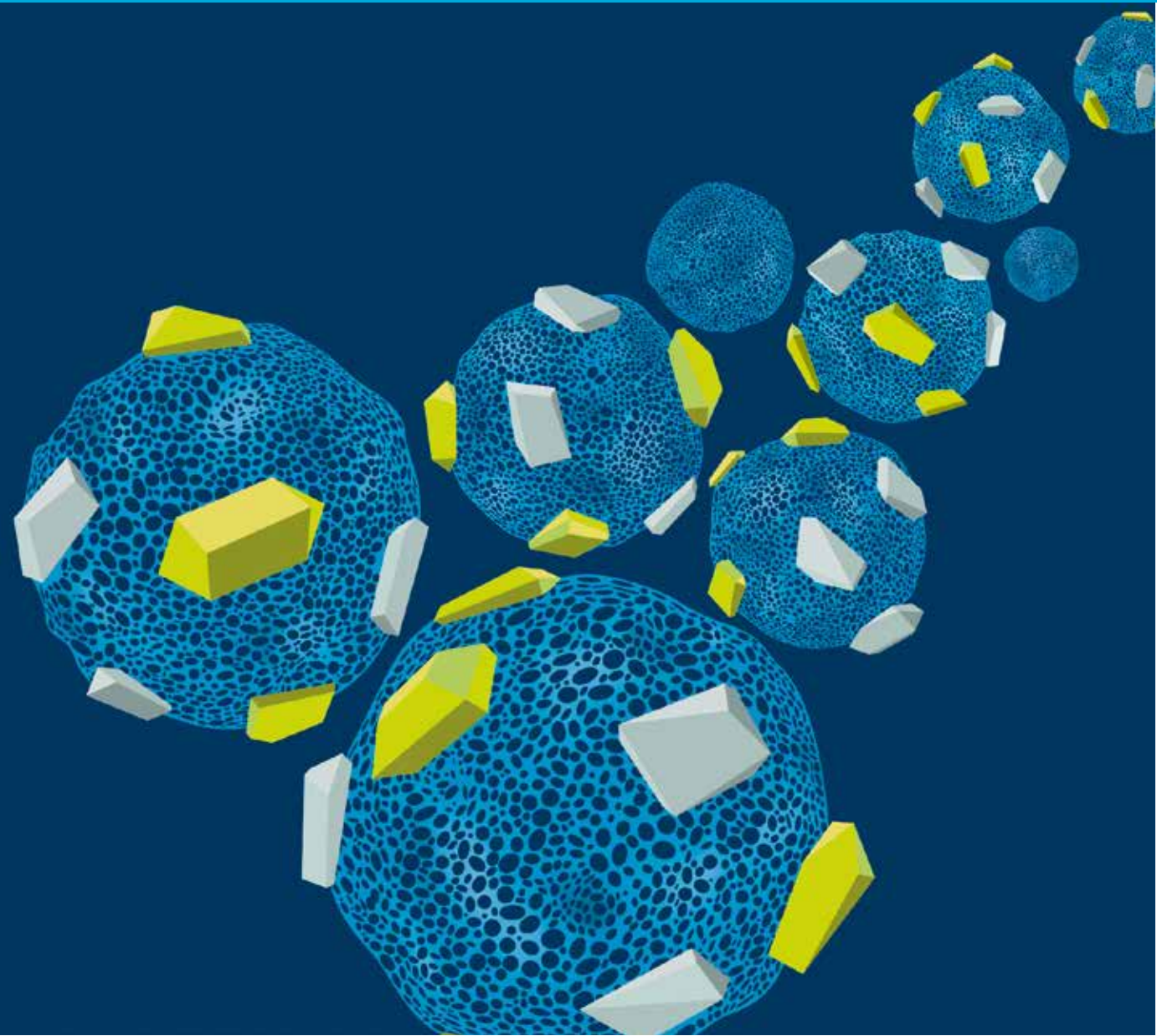
Our ongoing collaboration with the Respiratory Division of Zhongshan Hospital, Shanghai Institute of Respiratory Disease demonstrates IL-13+ type 2 innate lymphoid cells correlate with asthma control status and treatment response, which has been published in the *American Journal of Respiratory Cell and Molecular Biology*.
10.

West China Hospital, Sichuan University, China

Our collaboration with West China Hospital, Sichuan University began in June 2014, and investigates the distribution of both somatic and germline BRCA1 and BRCA2 variants in Chinese breast cancer patients.

“We also continue to establish collaborations with leading institutions through expansion of our PhD and graduate programme as well as two of our senior scientists being appointed as adjunct Professors at the Tongji University School of Medicine.”

Phospholipid particles



Key publications in 2016

Publication	Title	Author
Angewandte Chemie International Edition	Synthesis of chiral 1, 4- Benzodioxanes and chromans by enantioselective palladium - catalyzed alkene Aryloxyarylation reactions	Hu N, Li K, Wang Z, Tang W
Angewandte Chemie International Edition	Highly Enantioselective Rhodium-Catalyzed Addition of Arylboroxines to Simple Aryl Ketones: Efficient Synthesis of Escitalopram	Huang L, Wang Z
Oncotarget	Quantification of mutant alleles in circulating tumor DNA can predict survival in lung cancer	Yang X, Zhuo M, Ye X, Bai H, Wang Z, Sun Y, Zhao J, An T, Duan J, Wu M, Wang J
Oncotarget	Identifying anti-cancer drug response related genes using an integrative analysis of transcriptomic and genomic variations with cell line-based drug perturbations	Sun Y, Zhang W, Chen Y, Ma Q, Wei J, Liu Q
Bioinformatics	DTMiner: Identification of potential disease targets through biomedical literature mining	Xu D, Zhang M, Xie Y, Wang F, Chen M, Zhu KQ, Wei J
Scientific Reports	Plasma EGFR T790M circulating tumour DNA (ctDNA) status is associated with clinical outcome in advanced non-small cell lung cancer patients with acquired EGFR-TKI resistance	Zheng D, Ye X, Zhang MZ, Sun Y, Wang JY, Ni J, Zhang HP, Zhang L, Luo J, Zhang J, Tang L, Su B, Chen G, Zhu G, Gu Y, Xu JF
Acta Crystallographica Section D	Discovery of a novel allosteric inhibitor-binding site in ERK5: comparison with the canonical kinase hinge ATP-binding site	Chen H, Tucker J, Wang X, Gavine PR, Phillips C, Augustin MA, Schreiner P, Steinbacher S, Preston M, Ogg D
Oncotarget	Differences in diagnosis, treatment patterns and outcomes between rural and urban patients diagnosed from 2005 to 2009	Peng Z, Wei J, Lv X, Zheng H, Zhong X, Gao W, Chen Y, Jing J
Oncotarget	Ranking novel cancer driving synthetic lethal gene pairs using The Cancer Genome Atlas (TCGA) data	Ye H, Zhang X, Chen Y, Liu Q, Wei J
Medicine	Treatment and survival patterns of female Chinese patients diagnosed with breast cancer between 2005 and 2009 in Southwest China	Peng Z, Wei J, Lv X, Zheng H, Zhong X, Gao W, Chen Y, Jing J
PLoS One	Epidemiology and Outcomes of Complicated Skin and Soft Tissue Infections among Inpatients in Southern China from 2008 to 2013	Li X, Chen Y, Gao W, Ouyang W, Wei J, Wen Z
PLoS One	Prevalence and Prognostic Role of BRCA1/2Variants in Unselected Chinese Breast Cancer Patients	Zhong X, Dong Z, Dong H, Li J, Peng Z, Deng L, Zhu X, Sun Y, Lu X, Shen F, Su X, Zhang L, Gu Y, Zheng H
Cancer Biomarkers	Expression of potential biomarkers associated with homologous recombination repair in patients with ovarian or triple-negative breast cancer	Nomura H, Kataoka F, Aoki D, Jinno H, Kitagawa Y, Sato Y, Womack C, Wombwell H, Hodgson D, O'Connor M, Harbron C, Yin X
International Journal Of Antimicrobial Agents	Clinical characteristics and antimicrobial patterns in complicated intra-abdominal infections: a 6-year epidemiological study in southern China	Chen Y, Wei J, Gao W
American Journal of Respiratory Cell and Molecular Biology	IL-13+ Type 2 Innate Lymphoid Cells Correlate With Asthma Control Status And Treatment Response	Jia Y, Fang X, Zhu X, Bai C, Zhu L, Jin M, Wang X, Hu M, Tang R, Chen Z

Publication	Title	Author
Journal of Clinical Psychiatry	Gene expression profiling of extended major histocompatability complex (xMHC) region reveals nine candidate genes in schizophrenia	Sun L, Qing Y, Yang Z, Ding J, Tan L, He L, Wan C
Cancer Chemotherapy and Pharmacology	EGFR mutation status in cerebrospinal fluid of non-small cell lung cancer patients who developed central nervous system metastases after EGFR-TKI treatment	Zhao J, Ye X, Xu Y, Chen M, Zhong W, Sun Y, Yang Z, Zhu G, Gu Y, Wang M
Clinical Cancer Research	Pre-clinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant non-small cell lung cancer Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity.	Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, Pickup K, Jordan A, Hickey M, Grist M, Box M, Johnström P, Varnäs K, Malmquist J, Thress KS, Jänne PA, Cross D
Science Translational Medicine	AZD3759, a blood-brain-barrier-penetrating EGFR inhibitor for the treatment of EGFR mutant non-small cell lung cancer with central nervous system metastases	Yang Z, Guo Q, Wang Y, Chen K, Zhang L, Cheng Z, Xu Y, Yin X, Bai Y, Rabbie S, Jiang H, Ahn M, Kim D, Yang JC, Zhang X
Diabetes and Vascular Disease Research	Patient characteristics related to metabolic disorders and chronic complications in type 2 diabetes mellitus patients hospitalized at the Qingdao Endocrine and Diabetes Hospital from 2006 to 2012 in China	Dong Y, Gao W, Zhang L, Wei J, Hammar N, Cabrera C, Wu X, Qiao Q
Journal of Translational Science	Analysis of cancer-specific isoforms across the cancer genome atlas tumor types: potential disease linkages	Ji Y, Chen Y, Chen M, Wei J
Current Topics in Medicinal Chemistry	Drug repositioning through network pharmacology	Ye H, Wei J, Tang K, Feuers R, Hong H

NiCoLA-B: The most advanced drug discovery robot in the world



Key facts

Fast – Three times faster than previous technology, analysing 300,000 samples a day

Removing barriers – We have removed all physical barriers so scientists can directly interact with their experiment that is being performed at an industrial scale

Configurable – The robots and their controlling software are easily and quickly configurable to the requirements of the science

Modular – The automation is modular and mobile so it can be easily shared across researchers' needs

Mobile – For certain experiments the mobile robots can be relocated to specialised labs to either protect people from the biology, or the biology from the people

Intelligent correction – The intelligent robot is able to detect errors and make corrections to ensure that no science is lost

AstraZeneca is entering a new era of drug discovery by unveiling the most advanced screening robots in the world. Our scientists drew on decades of experience working with first-generation robots and, through partnership with *HighRes Biosolutions*, co-developed a bespoke system suited to the delicate manoeuvres and human interactions needed in drug discovery.

Historically, assays were moulded to what the robot could do. Now, with NiCoLA-B it is possible to configure the technology to match what the researcher wants the science to do; helping make drug discovery smarter, faster, and cheaper. Designed to work three times more quickly than previous drug discovery robots, NiCoLA-B is also more scientist-friendly, flexible and responsive.

Technology profile

The main robot system is called "CoLAB" (for collaborative laboratory) and the plug-in component carts are called "CoLAB Flex" (for collaborative and flexible deployment). The system can operate as a whole to perform highly complex biological experiments, or be separated to perform simpler experiments. This mitigates the issue with older systems where running a simple experiment on a complex robot would leave much of the equipment redundant. The modules are also mobile, allowing them to be relocated to specialised labs for certain experiments as required.

Previously robots had to be isolated but NiCoLA-B is a collaborative robot, interacting with and learning from scientists in the same space. It can also be controlled remotely via a smartphone/tablet application called "Cellario Connect" allowing scientists to interact with NiCoLA-B at any time; from labs, offices, homes, or even the other side of the world.

In addition to developing the robot, there has been significant investment in the enhancement of the controlling schedule software. This includes autonomous decision making for error recovery, and experimental progress; essentially automating some of the simpler decisions scientists would make to free their time for scientific innovation and to permit reliable out-of-hours operation.

Enabling drug discovery of the future

NiCoLA-B generates and processes large amounts of data, performing science on a scale, timeframe, complexity, precision and consistency not possible before. Each year the combined group of robots will test around 40 million chemicals, investigating 40 to 50 diseases and ultimately identifying the best potential molecules as starting points for future medicine development.

Drug discovery is changing, using more complex disease models and more disease relevant cell assays – the modularity and flexibility of NiCoLA-B allows us to align and evolve to this work.

Cultivating a porous scientific culture

NiCoLA-B will be deployed into our ground-breaking collaborative laboratory, the UK Centre for Lead Discovery, based in our new research facility in Cambridge.

We are making NiCoLA-B available to our research partners through Open Innovation – our pioneering initiative for sharing compounds, technology and expertise with academic and industry collaborators. The first research partners to work with NiCoLA-B are Cancer Research UK and the Medical Research Council. By combining our expertise, we are accelerating medicines research for the treatment of diseases with substantial unmet needs.

“NiCoLA-B delivers a new way of working, reducing costs and transforming our ability to identify new molecules that could become medicines of the future.”

Paul Harper, Associate Principal Scientist - Screening Sciences, IMED Biotech Unit

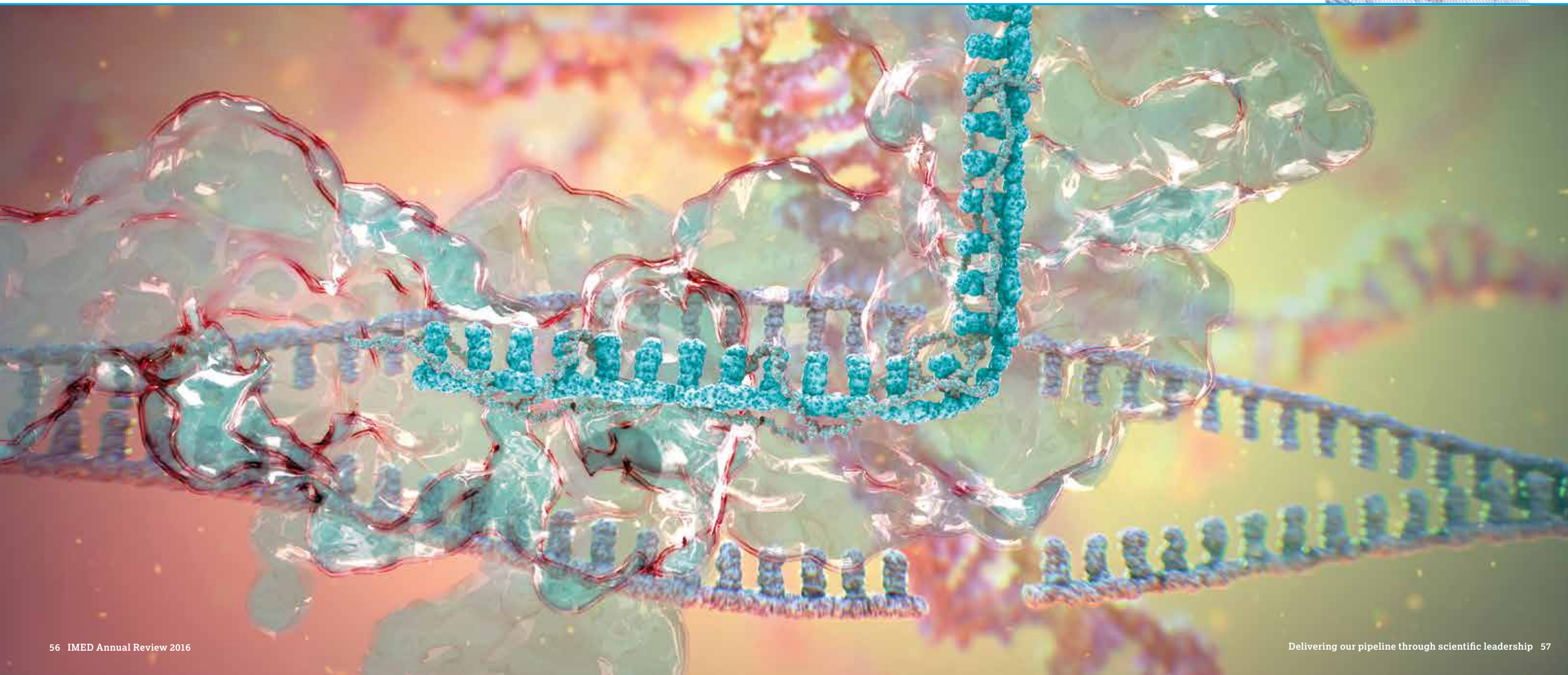
Discovery Sciences

✓ CRISPR (clustered regularly interspaced palindromic repeats) gene editing tool

“2016 was another great year for discovery at AstraZeneca. We saw substantial growth in the Discovery Sciences pipeline both through internal and external Open Innovation projects and saw exciting advances with a number of our developing technology platforms. We supported internal projects by providing more hit series, tissues, cellular/animal models, and assays than ever before, and grew the IMED early phase Open Innovation portfolio to more than 40 projects by forging screening partnerships with world-renowned institutions.

To support projects, we advanced our knowledge and use of gene-editing techniques both *in vitro* and *in vivo*, saw our first Cryo-EM protein structures and witnessed the final stages of the development of our acoustically enabled high throughput mass spectrometry machine. To cap the year off, we took delivery of our revolutionary new high throughput screening (HTS) robots that will future-proof both our own hit finding activities and those of our collaborators, who will share them in our new building in Cambridge.”

Mike Snowden, VP Discovery Sciences



Discovery Sciences

Discovery Sciences (DS) provides pre-clinical support and platform technologies to therapy areas and other teams across IMED. Divided into five core scientific disciplines we provide extensive target identification/validation, hit finding and compound optimisation expertise to therapeutic areas within IMED.



This year we sought to provide outstanding project support to the growing pipeline of IMED Discovery Science projects and to continue to develop a number of technology platforms key to our future success.

It was a record year for both internal discovery project starts and for growth in our Open Innovation discovery efforts which now include collaborations with the very best non-pharma discovery institutes including University of California, San Francisco (UCSF), Institut national de la santé et de la recherche médicale (INSERM), the Medical Research Council (MRC) and Cancer Research UK (CRUK). The programme has a very exciting pipeline of early projects and we are looking forward to translating innovative ideas into scientific breakthroughs in the future.

We saw excellent progress with a number of target identification/validation platforms including precise genome

editing (PGE) and phenotypic based screening. Our CRISPR genome editing platform delivered new reagents, including complex new cell lines and animal models for target validation and disease modelling. We have published this work widely in high impact journals.

In addition to advances in target identification technologies we made significant progress with technologies aimed at either finding or optimising the molecules of the future. We took delivery of state-of-the-art HTS robotics and saw the development of platforms that enable us to study the properties of single isolated biomolecules resulting in better data, or in some instances new data types. Of these, Cryo-Electron Microscopy (CRYO-EM) and Total Internal Reflection Fluorescence (TIRF) microscopy promise to be important techniques for the discovery scientist of the future.



It was a record year for both internal discovery project starts and for growth in our Open Innovation discovery efforts.”

< Acoustic mass spectrometry

People spotlight

Taiana Maia De Oliveira

Taiana is Senior Scientist, Structural Biology and joined AstraZeneca in April 2016 from the EMBL (European Molecular Biology Laboratory) in Grenoble, to establish our capability in Cryo-Electron Microscopy, a fast breaking technique with the possibility of transforming the field of structural biology. She has made an immediate impact within the Discovery Sciences function, establishing our infrastructure and delivering the first internal AstraZeneca protein structures by this technique. Originally from Brazil and having studied for her PhD in Norway, Taiana has joined the Structure and Biophysics group in Cambridge where she is using a number of integrated structural biology techniques to further our understanding of key molecular mechanisms driving disease.



Paul Harper

Paul is Associate Principal Scientist, High Throughput Screening. He joined AstraZeneca in 1999 to the newly formed Charnwood screening centre after specialising in high throughput screening with GlaxoSmithKline and Pfizer. With a background in the design and development of technology to fulfil scientific gaps, he has been pivotal in the evolution of AstraZeneca's automated science for Hit Identification. Moving to Discovery Sciences in 2011, he currently leads the development of the next generation of automated screening technologies through partnership with HighRes Biosolutions. Paul works closely with the HighRes team, to co-develop the world's most advanced screening robotics which will be deployed into a ground-breaking new laboratory as part of the UK Centre for Lead Discovery.



Emanuela Cuomo

Emanuela joined AstraZeneca in 2015 from the Cancer Institute, University College London, as an Associate Principal Scientist in the UK Cell Reagent team. Since joining, Emanuela has taken a leading role in development of our internal CRISPR cell line capability and driving innovative approaches using this technology. This includes the generation of novel CRISPR-based cellular models of clinically relevant mutations for targets such as EGFR and further driving our understanding of drug resistance by initiating and leading saturation mutagenesis based CRISPR approaches to prediction of drug resistance. Emanuela was also instrumental in the organisation of the first AstraZeneca-Sanger CRISPR conference in 2016.



Accelerating our drug discovery with CRISPR (clustered regularly interspaced palindromic repeats)

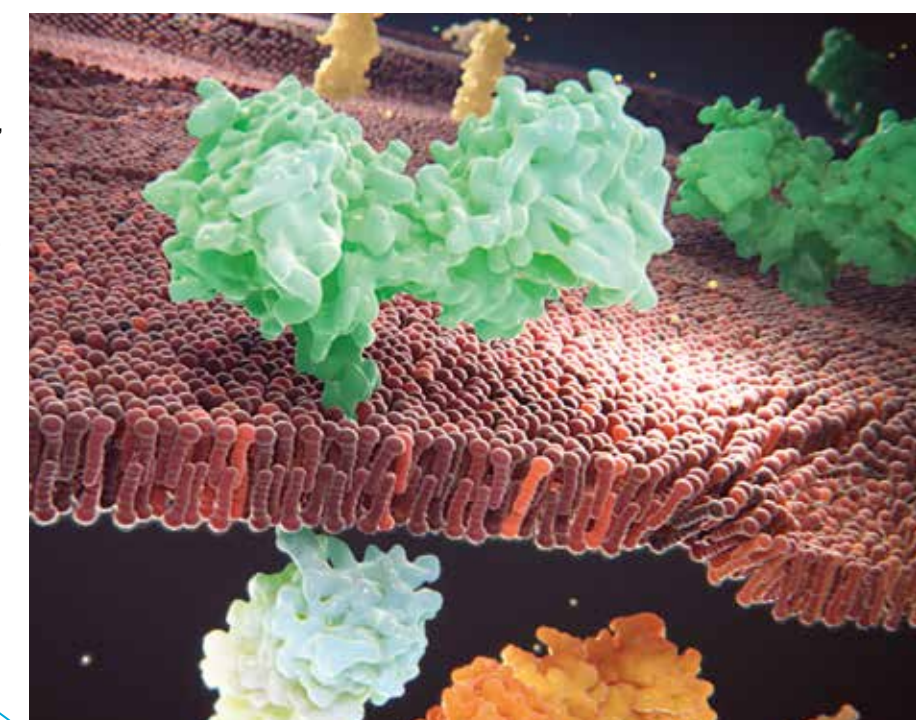
AstraZeneca was one of the first adopters of CRISPR in the industry and we continue to drive an industry-leading position, including working in collaboration with the world's best scientists from the Sanger Institute, MIT Whitehead, UC Berkeley and IGI. We use CRISPR/Cas9 technology to empower our drug discovery activities across our main therapy areas by delivering sophisticated *in vitro* and *in vivo* models which are directly translatable into human disease, enabling us to bring meaningful lead compounds into the pipeline. It also helps us reduce our use of animals by developing animal models, which are a necessary regulatory step in drug discovery, much more quickly. Previously, several generations of mice had to be bred over 12-18 months to arrive at the gene of interest in the offspring, whereas now it takes around three to four months.

A significant achievement this year was the generation of a transgenic mouse expressing a tightly controlled, inducible Cas9 protein with no detectable basal activity of the non-induced transgene. This unique and novel mouse model will have widespread impact on future *in vitro* and *in vivo* applications of genome engineering, as it allows us to avoid any potential Cas9 toxicity issues and focus on the adult phenotypes most relevant to human disease biology. This means that *in vivo* mouse human disease modelling experiments which once took years to complete can now be achieved in weeks.

Cancer cell lipid bilayer >

The first major application of this innovative Cas9 inducible mouse has been in revolutionising the speed for engineering mouse models of human lung cancers to test and validate AstraZeneca anti-cancer targets and test and optimise new drugs. Cas9 nuclease is induced and the animals' lungs infected with adeno-associated virus (AAV), engineered to delete the p53 tumour suppressor and target the cancer driving K-RasG12 mutation via

CRISPR/Cas9 actions. Within six weeks, all mice developed human-like lung adenocarcinomas. To our knowledge, this technology is the most advanced to date for the ultra-fast generation of human relevant *in vivo* tumour models in mice. We now intend to develop and apply similar technologies employing our unique Cas9 inducible mice model to enable ultra-fast target validation in other AstraZeneca therapy areas and develop novel *in vivo* disease models.



A selection of key collaborations in 2016

1.

Labcyte/Waters/AstraZenca Acoustic mass spectrometry collaboration, US/UK
A Research and Development collaboration focused on developing a world first acoustically enabled mass spectrometer. Once commercialised (through Waters) AstraZeneca will receive hardware and royalties on sales to other Pharma.
2.

Brooks/Labcyte, US
This collaboration to deliver the first acoustic dispensing (Labcyte) direct from individual sample storage tubes (Brooks) and the first entirely acoustic workflow for the generation of compound screening plates. The miniaturised, high-speed workflow will enable any compound to be supplied to any screen and will provide an unparalleled level of quality in the screening data produced from our biological assays.
3.

Pelago Bioscience, Sweden
Research collaboration focused on the application and extension of Pelago's 'CETSA' cellular target engagement technology, to directly measure *in vivo* cellular and tissue target engagement by small molecules.
4.

Massachusetts General Hospital, US
A research collaboration with Keith Joung to develop technologies to assess off target activities of genome editing techniques.
5.

Medical Research Council Technology (MRCT), UK
A research collaboration to identify new epigenetic targets/compounds for respiratory diseases
6.

Imperial/Lumicks, Netherlands
A research collaboration to investigate the combined use of optical tweezers and confocal microscopy for the study of DNA interacting proteins (initially CRISPR Cas9).
7.

Cambridge Pharmaceutical CryoEM Consortium, UK
Joining with 4 Pharma partners, the leading technology company FEI, the MRC, and the University of Cambridge, AstraZeneca have established a 'state of the art' Cryo-Electron Microscopy facility housed in the University's Nanosciences department.
8.

Royal Institute of Technology (KTH), Sweden
The objective of the Secretome collaboration is to produce and screen all human secreted proteins to unravel new biology leading to biological hypothesis and target discovery. During 2016-2018, KTH will produce all proteins in the extracellular space which will then be screened in cell-based phenotypic assays at AstraZeneca. During 2016, KTH has already delivered the first 700 proteins which have been screened in five cellular assays. Hits have been confirmed in T-regulatory cell assays and cardiac proliferation assays.
9.

Royal Holloway, University of London, UK
AstraZeneca and Royal Holloway have partnered with the EU funded collaboration ExCAPE, an initiative to transform the way machine-learning algorithms are applied within drug discovery to utilize supercomputing resources and harness vast amounts of heterogeneous data. This partnership allows us to take the lead in chemogenomics and support us in our transformative efforts to automate chemistry and hit finding.



Highlights

We set out to	We delivered
Continue to use and develop precise genome editing techniques as a tool for pre-clinical science	We developed sophisticated <i>in vitro</i> and <i>in vivo</i> models for assessing efficacy and safety of novel targets and novel chemical and biological matter. In a recent example, we generated an exquisitely controllable inducible Cas9 mouse that will accelerate the development of mouse models of human disease from months to weeks. The first major application of this mouse has been to develop a AAV mediated p53 KO, K-RasG12 mutation driven model of lung cancer. To our knowledge, this model is the most advanced to date for the ultra-fast generation of human relevant <i>in vivo</i> tumour models in mice, and is potentially game changing for the Oncology field.
Advance a suite of methodologies that would allow us to study kinetic and structural properties of single molecules	We delivered three technology platforms that enable kinetic and structural studies at the single molecule level. We visualised individual molecules using cryo-EM for a DNA damage response project. We successfully followed the kinetics of Cas9 binding to DNA using a platform that combines confocal imaging with optical tweezers to help us understand the properties of this important precise genome editing component. In addition, we have employed total internal reflection fluorescence (TIRF) single molecule microscopy to a number of projects. This has delivered detailed mode of action information with a fraction of the reagent and with unprecedented data quality for key project compounds whose properties prevented such analysis previously.
Push the boundaries of mass spectrometry (MS) for rapid analyte detection and for mapping small molecule binding sites on proteins	We achieved a world first HTS using our unique acoustically enabled mass spectrometer and developed industry-leading techniques to map small molecule binding sites in proteins to almost a single residue amino acid residue using Hydrogen-Deuterium Exchange (HDX) mass spectrometry. Our HTS acoustic MS system can sample 60 times faster than any current technology, enabling us to deploy the technology for diversity based HTS, saving time and money in screening and assay development. Together with our collaborators at the LMB we have used HDX to investigate tool compound binding to PI3Kα, an important Oncology target and to MALT1, a target for autoimmunity.
Develop a new generation of high throughput screening (HTS) robotics to future proof compound collection screening at AstraZeneca for the next 10 years	We delivered two of the most sophisticated screening robots in the world to AstraZeneca through our collaboration with HighRes Biosolutions. Both robots are three times faster than any other screening robot in Pharma and have advanced features such as autonomous decision making for error recovery and experimental progress, application control through tablets and highly advanced touch and visual recognition systems. The availability of these systems has accelerated our Open Innovation discovery pipeline and will be core assets in the Centre for Lead Discovery AstraZeneca will share with the MRC and CRUK.
Expand our use of cellular thermal shift assays to confirm drug discovery target engagement in cells	We enabled multiple forms of the thermal shift assay (CETSA) developed by Pelago to support projects needing to confirm cellular target engagement or target specificity of their compounds in complex systems. We developed a system to measure cellular binding affinities for antagonists of the Androgen Receptor and showed, for the first time, that the technology platform could be used for not only soluble proteins, but also for multi-pass transmembrane proteins (e.g. KCC2).

Key publications in 2016

Publication	Title	Author
Cell Metabolism	Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes	Segerstolpe A, Palasantza A, Eliasson P, Andersson E, Andreasson A, Sabirsh A, Clausen M, Bjursell M, Smith D, Ammala C, Sandberg
Nature	Overcoming mTOR resistance mutations with a new generation mTOR inhibitor	Rodrik-Outmezguine V S, Okaniwa O, Yao Z, Novotny C, McWhirter C, Banaji A, Won H, Wong W, Berger M, de Stanchina E, Barratt DG, Cosulich S, Klinowska T, Rosen N, Shokat KM
Nature Chemical Biology	Inhibition of Mcl-1 Through Modification of a Non-Catalytic Lysine Side Chain	Akcay G, Grimster N, Aquila B, Belmonte M, Chuaqui C, Hird A, Lamb L, Rawlins P, Tentarelli S, Su Q
Nature Chemical Biology	Potent and selective bivalent inhibitors of BET bromodomains	Waring M, Chen H, Rabow A, Walker G, Bobby R, Boiko S, Bradbury H, Callis R, Dale I, Daniels D, Flavell L, Holdgate G, Jowitt T, Kikhney A, McAlister M, Ogg D, Patel J, Robb G, Robers M, Stratton N, Svergun D, Wang W, Whittaker D
Nature Chemical Biology	Cellular Active N-Hydroxyurea Inhibitors of Human Flap Endonuclease 1 Co-crystallise in the Active Site of Human Protein and Prevent Reaction by Blocking Substrate Double Nucleotide Unpairing	Exell J, Thompson M, Finger L, Abbott M, Debreczeni J, McWhirter C, Jones. C, Nissink W, Ward T, Durant S, Grasby J
Cell Metabolism	Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes	Segerstolpe A, Palasantza A, Eliasson P, Andersson E, Andreasson A, Sabirsh A, Clausen M, Bjursell M, Smith D, Ammala C, Sandberg

Single Molecule Detection

Impacting projects today with technology of tomorrow

In the past, we have always had to study the average of our reagents. Single Molecule Science means that we can look at individual, specific molecules rather than averages and therefore get significantly better quality data. We can also begin to study sub-sets of molecules which can provide very interesting insights in the discovery space.

This year our Discovery Sciences team, along with key external partners, have pioneered three world-class platforms that enable kinetic and structural studies at the single molecule level.

Total Internal Reflection Fluorescence (TIRF) Microscopy: the single molecule microscope

Total Internal Reflection Fluorescence (TIRF) microscopy is a technique to image fluorescently tagged molecules in real time. Using a special lens, a laser illuminates the bottom of a glass coverslip at an angle where it is totally internally reflected. This causes an oscillating electric field - an evanescent wave - to penetrate the interface but only to a depth of about 200nm before it decays. This allows for selective excitation of surface-bound fluorophores, while non-bound molecules are not excited.

At AstraZeneca we have a unique TIRF microscopy platform, primarily developed in-house and our team is leading the field when it comes to applying this technology to drug discovery. The technique has ultra-high sensitivity that has allowed us to track molecules at concentrations a thousand-fold lower than previous assays as well as detect very weak interactions.

Our work in this area has already resulted in three papers in high quality journals as well as several invitations to speak on the topic at various conferences.

Scientist perspective

"Typically we run biochemical cellular assays that require a high concentration of molecules or cells to get the read-out for the assays. With this technology we can watch a single molecule in action, following its binding to a receptor or to monitor its catalytic properties. This means it is possible to observe the action of a single molecule rather than an ensemble of molecules. Combining the resulting data with the read-outs of multiple molecule scans we can find information that would have been lost by measuring a collection of molecules alone."

This year we have gained a lot of experience with the platform in early stage drug discovery where we have demonstrated ligand receptor selectivity, profiled the interaction of nuclear receptors with cofactors and measured kinetic binding data for unstable targets. Looking to the future, we are excited to explore the enormous potential of TIRF microscopy in late stage discovery programmes, in particular with regard to biomarker detection.

Optical Tweezers: determining mode of action at a single-molecule level

Correlative Tweezers combined with Fluorescence Microscopy (CTFM) allow the collection of detailed information on a wide range of molecular mechanisms with sub-pico Newton force resolution and sub-nanometer position resolution. Lasers are used to control magnetic beads that capture and hold molecules of interest such as a DNA. The molecules can then be manipulated and the resultant changes in forces measured. In addition, real-time fluorescence imaging allows visualisation and characterisation of ligand binding interactions, such as small molecule or proteins binding to DNA.

DNA processes such as transcription, replication, repair and modification can be modelled to track the kinetics of each component in real-time with high resolution at the single-molecule level to determine the mode of action of compounds. This visualisation and unique high resolution elucidation of mechanisms of action for protein-protein or DNA-protein interactions is not currently accessible by traditional methods.

Scientist perspective

"The ability to physically see single protein molecules interact with DNA is very exciting. We believe this technology will have a big impact on our pre-clinical work as the identification and characterisation of novel modes of action and interaction mechanisms

Molecular Rift: a hands-on experience for the single molecule

At AstraZeneca, we have developed a next-generation virtual reality molecular viewer, Molecular Rift, which creates a virtual reality environment steered with hand movements. Traditional 3D visualisers 'just' show molecules on a screen in front of you; with Molecular Rift a drug designer can enter a protein-ligand complex. Metaphorically speaking we remove the digital screen and let the user step into molecules, such as a protein-ligand complex, to look around.

The system uses the Oculus Rift headset with a Leap Motion Sensor, which was recently released offering a higher resolution and accuracy for gesture recognition. In addition, by using the Leap Motion infrared camera, we have achieved an augmented reality. This means that the user can still visualise their surroundings through the Oculus Rift, allowing them to see other people, and is one step towards a more collaborative virtual reality.

Although, to date, Molecular Rift may be seen as a specialised tool in development, we are confident that this way of interacting with molecules will impact the way future design will be performed.

will allow focused progress for compounds modulating protein-protein or DNA-protein interactions important in disease states and highlight new directions in drug discovery."

In 2016, in collaboration with Imperial College and Lumicks, this technology has already been used to uncover novel binding characteristics of a strategically important DNA interacting protein. Fully characterising the binding capabilities will allow better modulation and control of the activity of this high value target.

Cryo-Electron Microscopy (CryoEM): Expanding the impact of structural biology

Structural biology plays a significant role in the discovery of new medicines. Techniques that allow us to model and visualise, at atomic resolution, the structures of the protein molecules which drive disease, and which our drugs bind to and modulate, have allowed the design of new medicines such as osimertinib. However, currently these protein structures are only really accessible by crystallography and we are unable to crystallise many of the proteins we are interested in.

Single molecule cryo-electron microscopy is changing the structural world. The last few years have seen technical advances that have enabled a step change in the capability of electron microscopy and there are now an impressive number of high resolution protein structures that have been determined by this technique. For the structural biologist this is transformational, as many target proteins

important to drug discovery, such as integral membrane proteins or large multicomponent macromolecular machines, now become accessible for study for the first time.

The technique requires that highly homogenous protein solutions are frozen (in liquid ethane) in a single molecule thick layer of vitreous ice. A number of individual molecules (~100,000) are then observed in the microscope. Through a series of image analysis algorithms a 3D reconstruction of the molecular structure of the target protein is derived.

Scientist perspective

"Having access to this technology is a major evolution of our team in Discovery Sciences and being based in Cambridge, at the heart of the recent advances, really helps keep AstraZeneca at the leading edge in the industry. CryoEM still has some way to go before atomic resolution models become routine, but to be part of an organisation investing early collaborating with the best external groups in the world, and positioning it for the first time within the drug discovery setting is really exciting."

With our strong classical crystallographic capabilities and ability to produce high quality proteins, Discovery Sciences is perfectly placed to take advantage of this technology. In our first year, we have already exceeded expectations by delivering two novel structures of complex molecular systems for the DNA damage response initiative in IMED Oncology.

Drug Safety and Metabolism

✓ Cells under a microscope

“Our Drug Safety and Metabolism journey is about us leading in all aspects of pre-clinical safety in addition to drug metabolism and pharmacokinetics (DMPK). In 2016 we have made excellent progress towards this vision. Our focus is in three key areas: cross species comparison of toxicity such as using an *in vitro* organoid system to compare species sensitivities, toxicokinetic and toxicodynamic modelling of organ risk incorporating cross-species *in vitro* and *in vivo* data and integrated pharmacokinetic/

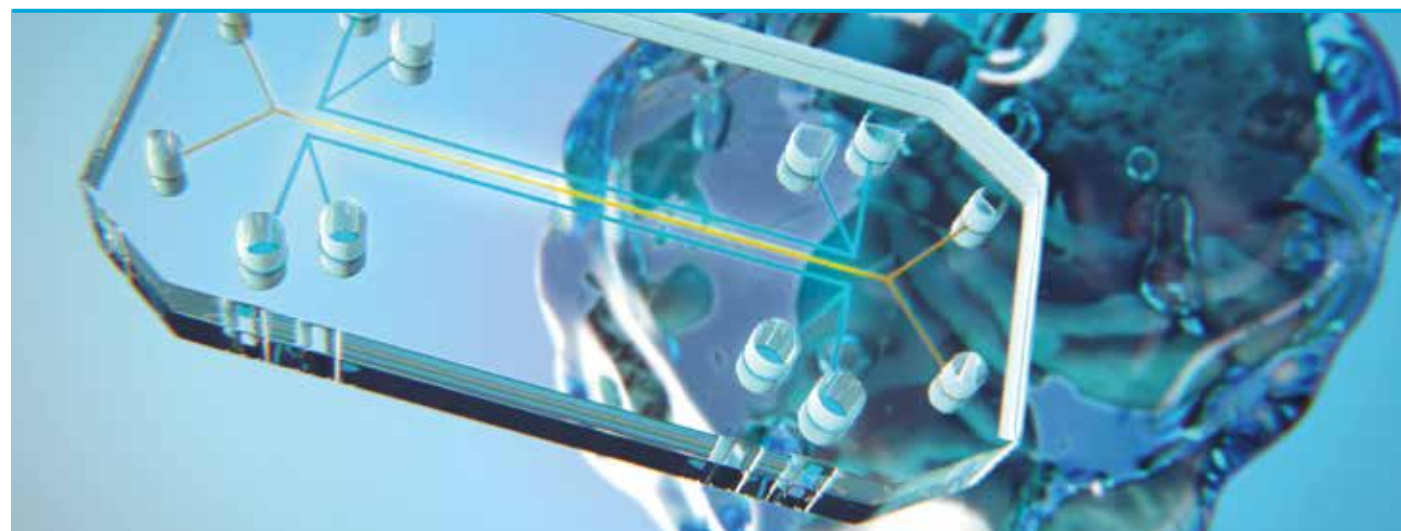
pharmacodynamic (PK/PD) data, to better predict risk in humans. Embedding disease characteristics of the patient population is critical, for example, haemodynamic measures in healthy young animals may not be representative of measures in elderly patients. In addition, there has been significant progress in optimising drug delivery that can improve an unacceptable risk benefit profile by increasing drug uptake at the target tissue.”

Stefan Platz, VP Global Drug Safety and Metabolism



Drug Safety and Metabolism

Drug Safety and Metabolism (DSM) is split into nine functions with the purpose of driving science to bring better, safer medicines to patients sooner. We utilise our vast range of expertise to design and deliver fully comprehensive, tailored safety packages to support project decision-making and enable pipeline progression across our main therapy areas.



This year we expanded our organisation with the formation of dedicated teams for New Modalities, Microphysiological Systems (MPS) and Translational Biomarkers and Bioanalysis.

To align with our strategic investments in antisense oligonucleotides and modified RNA, the New Modalities Group will focus on safety considerations associated with novel therapeutic approaches and their delivery.

MPS are miniaturised models that combine engineering and biology to generate organ function *in vitro* to emulate human biology at the smallest acceptable scale. MPS models enable scientists to link organs together and discover key factors involved in organ cross-talk that drive particular disease phenotypes – generating data with a high likelihood of clinical translation and offering a real alternative to the use of animals in drug discovery. By developing

a MPS Centre of Excellence we can increase our focus on the development and delivery of MPS models that will be adopted across the research organisation as drug discovery platforms, as well as advancing our understanding of disease pathways.

The Translational Biomarkers and Bioanalysis group has been formed to expand our analytical expertise to support two critical areas of DSM research. Firstly, to develop novel safety biomarkers for use in translational prediction of target organ safety risk from pre-clinical to the clinic, and secondly to support safety, PK and PKPD assessment of modRNA, ASOs and CRISPR modalities.

Quantitative risk assessment has been an area of outstanding achievement in 2016, particularly the exceptional work and progress in modelling and simulation, which is becoming increasingly integral to our approach. The group has delivered

significant support across the portfolio and has been critical to decision making in three key projects:

CDK9: Modelling supported identification of dosing schedule with an acceptable safety profile to advance.

KITm: Modelling the set criteria for candidate drug target profile and confidence in safety profile to select and advance lead molecules.

AZD2014 + Palbo: Modelling informed selection of next clinical schedule incorporating seven day holiday.

We have enhanced our quantitative risk assessment capabilities by bringing together sophisticated models and mathematical algorithms to allow us to predict safe doses for humans more precisely and help achieve maximum therapeutic effect with minimal safety risks.

△ Microphysiological systems
- biochip with cellular matter



This year we expanded our organisation with the formation of dedicated teams for New Modalities, Microphysiological Systems (MPS) and Translational Biomarkers and Bioanalysis.”



People spotlight

Lyn Rosenbrier-Ribeiro

Lyn Rosenbrier-Ribeiro leads the Secondary Pharmacology group in Discovery Safety. Lyn gained her PhD at the University of Manchester investigating the molecular mechanisms of drug metabolism regulation during *in vitro* hepatocyte differentiation.

The dual PI3Kγδ inhibitor program in RIA was identified to have potent off-target ENT1 inhibitor activity. In asthmatic patients, adenosine challenge leads to increased dyspnoea and bronchoconstriction. ENT1 inhibition can lead to increased local concentrations of adenosine and known ENT1 inhibitors have been linked to a higher incidence of these safety effects. Understanding the *in vitro-in vivo* translation of ENT1 inhibition and ability of this compound to sensitise the airways was essential to assess the risk of progressing their lead molecule. Lyn performed a semi-quantitative translational safety analysis using a set of marketed drugs with ENT1 activity to demonstrate the level of pharmacological coverage of ENT1 required to drive these detrimental effects. Bronchospasm was found to be a risk for respiratory patients only, and based on the current estimated human exposure values and the expected low incidence rate, a safety margin of 30-300 fold was deemed acceptable for the lead molecule. This is a great example of patient centric risk assessment and the work was recently published in .

Jay Mettetal

Jay Mettetal is the Leader of the Safety and absorption, distribution, metabolism and excretion (ADME) modelling function in DSM and is responsible for application of quantitative approaches to translating drug safety from discovery to the clinic. Jay earned his PhD in Physics at MIT on an NSF Graduate Fellowship. He has over 15 publications in the fields of Systems Biology and Quantitative Pharmacology.

A key impact for the Safety and ADME Modelling function in 2016 was the delivery of translational PK/PD modelling of KDR-induced BP risk for the KITm programme. In order to differentiate from competitor compounds the KITm project team needed to avoid hypertension caused by KDR (VEGFR2) inhibition, which is seen with several cancer drugs in the clinic. The DSM safety team sought to provide the team with guidance on how KDR inhibition translated into blood pressure (BP) elevation and incidence of hypertension. The approach used PK/PD models extracted from literature reports of BP changes and comparing this to PK/PD models of in house *in vivo* rat telemetry data. By correcting for *in vitro* potency such as in porcine aortic endothelial (PAE) assay and considering different PK drivers we were able to give an *in vitro* cut-off for selectivity in lead series of compounds. The modelling work gave the project team information to not only effectively prioritise compounds but also to know which subseries were sufficiently de-risked and could therefore select molecules based on other key criteria than KDR margins.

Highlights

We set out to	We delivered
Utilise the expanded Mass Spectrometry Imaging (MSI) platform to assess drug target distribution within organs	<p>We applied in-house MSI technologies in a clinical setting. AZD2811 is an Aurora B kinase inhibitor that showed promising results in acute myeloid leukaemia (AML) patients but was limited by therapeutic index. The drug was encapsulated into a novel polymeric nanoparticle (NP) formulation, ACCURINS®, and MSI helped to compare the distribution of NP-formulated drug with deuterated drug by dosing them simultaneously in the same animals. Results confirmed NP-delivered drug distribution to be predominantly in tumour periphery.</p> <p>During a subsequent dose escalation study of NP-delivered AZD2811, one patient developed a rash and we analysed a clinical sample for the first time using in-house MSI facilities. We used desorption electrospray ionisation (DESI) MSI to visualise different layers of skin and were able to localise the drug within the papillary dermis with no other drug formulation constituents being detected.</p>
Develop messenger RNA and New Modalities with our partner Moderna	<p>We achieved successful submission of the pre-clinical safety data package for AZD8601 (VEGF-A), a modified RNA therapy, designed to provide a unique regenerative treatment option for patients with heart failure, diabetic wound healing and other ischemic vascular diseases. Significant progress with AZD8601 was made in 2016 to enable the first time in man in January 2017 and marks an exciting milestone in our ongoing collaboration with Moderna Therapeutics.</p> <p>We also achieved the aspirational IMED subcutaneous stretch objective of demonstrating a tolerable formulation with a predicted 10-fold therapeutic window and therefore enabling progression of CVMD modified RNA projects in 2017.</p>
Develop novel lung function models	<p>We developed and validated two new novel lung function models, IPP-HOP, which combines plethysmography measures and telemetry to provide respiratory pattern data as well as resistance and compliance, and a novel electrophysiology model that assesses the sensory nerve irritation liability of these inhaled agents.</p> <p>The validation of these models has used a translational approach based on known clinical agents and their effects in patient populations; both models have been incorporated in to the new inhaled <i>in vivo</i> strategy, being used on projects, pre-clinical development, to provide a thorough risk assessment of the respiratory system.</p>
Implement a new target liver strategy	<p>We introduced a new hepatic cell line based spheroid model in Q2 2016. It is one of the first human organoid based hepatic safety assays. It is cost effective and significantly increases sensitivity by 30 per cent and specificity by 20 per cent compared to previous models.</p>
Advance our microphysiological systems (MPS) models	<p>We demonstrated, together with our partners at TissUse, a physiological glucose homeostasis when human liver spheroids are connected in the same system to human pancreatic islet spheroids. We also characterised a bone marrow on a chip model using human bone marrow stem cells in a bioengineered microenvironment, which mimics the bone marrow niche. Excitingly these cells mature into haematopoietic lineages. Our successful collaboration with Emulate (a Harvard spin-off) has enabled us to test compounds from an active Oncology project to enhance our human risk assessment, following detection of hepatotoxicity <i>in vivo</i>.</p>
Enhance the prediction in the chemical toxicity space	<p>We have further defined our algorithms in the chemical toxicity space in 2016, to enhance the quality of the chemical substrate in the discovery process. Examples of impact on the portfolio include the early integrated assessment, which includes a review of the chemical structure and properties as well as off-target pharmacology of hit series. This enables deselection of chemical series with intrinsic safety concerns and focus on the most promising starting material. Our predictive computational tools are increasingly exploiting the highly innovative Conformal Prediction framework, which provides scientists with statistical confidence in the predictions. In addition, our structural and off-target pharmacology safety analysis influences chemical design during LO programs such as, SYKB, SERD-BC, PI3Kyō and TRPC6. We also work with IMED project medicinal chemists as part of a chemical toxicology network to promote good practice and understand needs.</p>

Innovative approaches to quantitative risk assessement

Building our quantitative risk assessment capabilities is extremely important because it allows us to predict safe doses for humans more precisely and accurately achieve maximum therapeutic effect, with minimal safety risks. This year we have seen many elements come together to significantly improve the precision and accuracy of our assessments. These innovative approaches have impacted across the IMED portfolio, as demonstrated by these examples.

Using 3D MiniGut models to measure intestinal toxicity pre-clinically

Oncology drugs frequently encounter intestinal toxicity as a dose-limiting adverse event. We partnered with inventors of the MiniGut intestinal organoids, Hans Clevers’ lab at the Hubrecht Institute, to enhance our ability to investigate and understand intestinal toxicity pre-clinically. One of our Oncology programmes encountered dose limiting intestinal toxicity in pre-clinical studies. In response to this we developed multiple MiniGut models using stem cells from different species and demonstrated that human intestinal cells are significantly more resilient to the drug-mediated intestinal toxicity than those species used in pre-clinical studies. This data contributed to the progression of the clinical programme where previously it may have been terminated.

Modelling and simulation to optimise dosing schedules

Quantitative risk assessment in CDK9 projects showed hematological toxicity in pre-clinical studies with very narrow therapeutic index, and the team looked to open the window by selecting an optimal dosing schedule. A modelling and simulation approach was performed for both efficacy and safety with endpoints of neutrophil effects and tumour survival to identify the optimal schedule. The model suggested that a reasonable therapeutic margin could be obtained by going to a clinical schedule that split each dose into two separate doses - specifically going from one day on/13 days off, to two days on/12 days off.

Sophisticated modelling to better predict toxicity of the DNA Damage Response portfolio

The clinical utility of combining Oncology treatments is frequently limited by additive or synergistic tolerability issues. Optimisation of dose and schedule in the clinic can be slow and costly, often leading to abandonment of combinations. Development of predictive humanised *in vitro* models will provide key data that can be used to guide prioritisation of clinical dosing schedules and combination partners. Those with most favourable therapeutic index can be prioritised for evaluation in pre-clinical *in vivo* studies and in the clinic.

A key target organ for toxicity with Oncology agents is bone marrow. This year we have seen initiation of the development and the validation of a bone marrow MPS, in which we can build a greater understanding of the time course and mechanism underlying bone marrow toxicity. There is also the potential to use fluid handling tools to control drug exposure in this model to enable *in vivo* like evaluation of PK/PD relationships.

A recent example of how this type of approach can impact projects is illustrated by the development of a model for the dose-limiting neutropenia, seen in the clinic when one of our Oncology compounds was given in combination with another compound. The model was built using clinical PK/PD data and mechanistic data on the effects of the combination derived from the *in vitro* bone marrow models. The model has helped the team to identify dosing schedules that will likely alleviate the neutropenia and will now be tested in the clinic.

A selection of key collaborations in 2016

1.

Harvard University, US

In collaboration with Discovery Sciences and Professor Keith Joung we are investigating novel technologies for the determination of ‘off-target’ effects of the CRISPR/Cas9 technology in *in vitro* and *in vivo* systems.

2.

Cancer Research, UK

We have been awarded £20 million as principal investigators in a winning Cancer Research UK Grand Challenge consortium. The consortium builds on existing strong collaborations including the National Physical Laboratory, the Beatson Institute and Imperial College London, as well as forges new ones. The research will focus on using MSI technologies to generate “A Complete Cartography of Cancer”.

3.

Medical Research Council (MRC), Laboratory of Molecular Biology (LMB), UK

We are currently investigating cell-autonomous mechanisms for circadian regulation of membrane excitability and contractility in cardiomyocytes with Dr John O’Neil.

4.

University of Florida, US

A collaboration to develop quantitative translational understanding of cardiac contractility between in house *in vitro* systems, *in vivo* telemetry and measures of contractility in the clinic using systems pharmacology models.

5.

University of Edinburgh, UK

We are collaborating with Professor Jamie Davies to evaluate mini-kidneys as an *in vitro* model for investigating nephrotoxicity.

6.

University of Cambridge, UK

Along with LHASA and GSK we are identifying adverse outcome pathways related to structural cardiotoxicity.

7.

University of Nijmegen, The Netherlands

Through our collaboration with Dr Martijn Wilmer we are investigating a kidney cell model for improved prediction of human renal clearance, drug-drug interactions.

8.

University of Cambridge, UK

We are collaborating with the University of Cambridge on a GSK funded two-year post-doctorate investigating Drug Induced Mitochondrial Toxicity in the Context of Hypoxia.

9.

Karolinska Institute, Sweden

A collaboration to test the evaluation of advanced 3D airway epithelial/fibroblast model with immune component for toxicity testing with Dr Mattias Svensson.

10.

Translational Quantitative Systems Toxicology, IMI-2 consortium, Belgium

In collaboration with industry and academic collaborators across Europe, we have initiated a €10 million, five year project to develop improved quantitative and translational systems toxicology models. The ultimate aim for this project is to develop novel approaches that improve quantitative and translational toxicology understanding and therapeutic margin predictions in cardiovascular, liver, gastrointestinal and kidney organ systems. Led by Jay Mettetal, AstraZeneca will lead the computational modelling elements of this collaboration bringing our expertise to bear in safety and absorption distribution metabolism and excretion (ADME) modelling.



Key publications in 2016

Publication	Title	Author
Science Translational Medicine	Aurora kinase inhibitor nanoparticles target tumours with favourable therapeutic index in vivo	Foster J, Goodwin RJ, Swales JG, Strittmatter N
Diabetes, Obesity and Metabolism	L-Arginine promotes gut hormone release and reduces food intake in rodents	Alamshah A, McGavigan A, Spreckley E, Kinsey-Jones J, Amin A, Tough I, O’Hara H, Moolla A, Banks K, France R, Hyberg G, Norton M, Cheong W, Lehmann A, Bloom S, Cox H, Murphy K
NeuroImage	Simultaneous imaging of multiple neurotransmitters and neuroactive substances in the brain by desorption electrospray ionization mass spectrometry	Mohammadreza S, Strittmatter N, Nilsson A, Kallback P, Alvarsson A, Zhang X, Vallianatou T, Svenningsson P, Goodwin R, Andren P
Archives of Toxicology	A Multi-Center Assessment of Single Cell Models Aligned to Standard Measures of Cell Health for Prediction of Acute Hepatotoxicity	Sison-Young R, Lauschke V, Johann E, Alexandre E, Antherieu S, Aerts H, Gerets H, Labbe G, Schofield C, Stahl S, Lovatt C, Holder J, Richert L, Kitteringham N, Jones R, Elmasry M, Weaver R, Hewitt P, Ingelman-Sundberg M, Goldring C, Park K
British Journal of Pharmacology	Neutrophil Maturation Rate Determines the Impact of Dipeptidyl Peptidase 1 Inhibition on Neutrophil Serine Protease Activity	Gardiner P, Wikell C, Clifton S, Shearer J, Benjamin A, Peters S
Molecular Pharmaceutics	Flagging drugs that inhibit the bile salt export pump	Montanari F, Pinto M, Khunweeraphong N, Wlcek K, Sohail MI, Noeske T, Boyer S, Chiba P, Stieger B, Kuchler K, Ecker GF
Molecular Pharmaceutics	Use of HuREL® human co-culture system for prediction of intrinsic clearance and metabolite formation for slowly metabolized compounds	Hultman I, Vedin C, Abrahamsson A, Winiwarter S, Darnell M
Toxicological Sciences	Cardiac non-myocyte cells show enhanced pharmacological function suggestive of contractile maturity in stem cell derived cardiomyocyte microtissues	Ravenscroft S, Pointon A, Williams A, Cross M, Sidaway J
Toxicological Sciences	The lack of mutagenic potential of a guanine-rich triplex forming oligonucleotide in physiological conditions	Saleh A, Fellows M, Ying L, Gooderham N, Priestley C
International Journal of Pharmaceutics	Excised segments of rat small intestine in Ussing chamber studies: A comparison of native and stripped tissue viability and permeability to drugs	Sjogren E, Eriksson J, Vedin C, Breitholtz K, Hilgendorf C
PLoS One	Claudin-2 expression levels in ulcerative colitis development and validation of an in-situ hybridisation assay for therapeutic studies	Randall K, Henderson, N, Reens, J, Eckersley, S, Nyström, A, South, M, Balendran, C, Böttcher, G, Hughes, G, Price, S
Journal of Pharmaceutical Sciences	Modelling Organic Anion Transporting Polypeptide 1B1 (OATP1B1) inhibition to elucidate interaction risks in early drug design	Zamora I, Winiwarter S
Toxicologic Pathology	Femoral head growth plate dysplasia and fracture in juvenile rabbits induced by off-target anti-angiogenic treatment	Hall AP, Mitchard T, Rolf MG, Stewart J, Duffy P
Regulatory Toxicology and Pharmacology	Extending Quantitative structure–activity relationship, (Q)SAR, to incorporate proprietary knowledge for regulatory purposes: A case study using aromatic amine mutagenicity	Ahlberg E, Amberg A, Belke L, Bower D, Cross K, Custer L, Dobo K, Ford K, Van Gompel J, Harvey J, Masamitsu Honma M, Jolly R, Joossen E, Kemper R, Kenyon M, Kruhlak N, Kuhnke L, Leavitte P, Neilan C, Naven R, Quigley D, Shuey D, Sprikl HP, et al.

Early Clinical Development

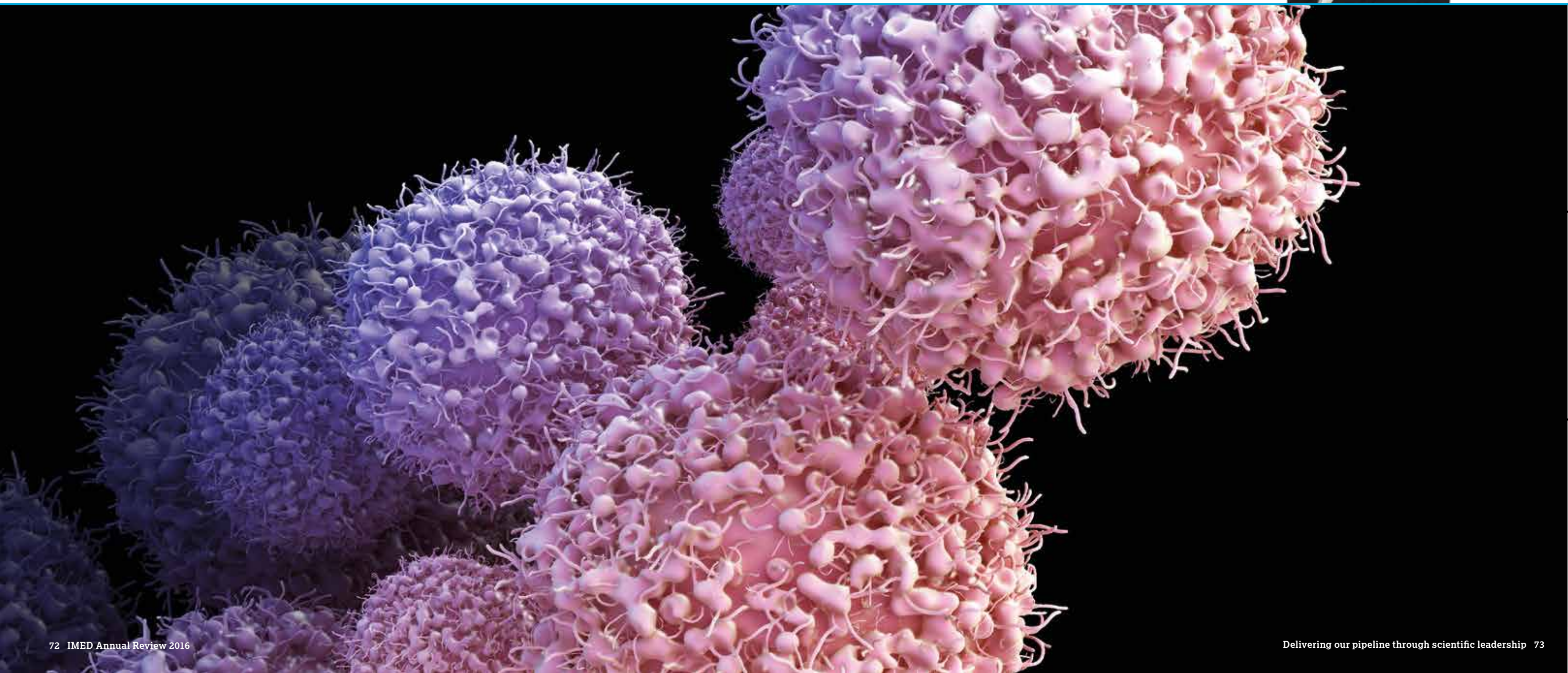
“In 2016, three years since the launch of the Early Clinical Development (ECD) organisation, we have established our three strategic pillars of innovation in clinical trials, integrating data to knowledge and achieving earlier human target validation. ECD continues to attract world class talent across our capability areas and our scientists are increasingly published in high impact journals, both of which reflect our position at the industry forefront of translational

clinical science. We continue to improve all aspects of operational delivery, reflected in industry-leading study cycle times and saving more than 50 hours per person through simplification. In addition we have developed a significant strategic partnership with Covance to make our Clinical Operations even more efficient.”

Anthony Johnson, VP Early Clinical Development



Immune cells



Early Clinical Development

2016 has been a year of great progress and delivery for Early Clinical Development (ECD). In the last 12 months we have demonstrated our strength as skilled translational clinical scientists, reflected in several of our high impact publications and in clinical trial efficiencies, for example simplification of our clinical pharmacology packages based on innovative modelling techniques.

Our role in ECD is all about testing if the research taking place across the IMED Biotech Unit can transform patients' lives – it is the place where science meets the patient. Our talented people lead this important work by designing and delivering innovative clinical studies, integrating data, informing research and development and accelerating human target validation.

In the last 12 months we have really seen the results of embedding our key leadership behaviours - being collaborative, being entrepreneurial and agile and being pioneering to follow the science.

Being agile has enabled the team to leverage adaptive trial design in the BEECH study (AZD5363 with paclitaxel for advanced breast cancer), targeting AKT1 and the ATM inhibitor programme where delivering real-time pharmacokinetic data enabled faster decision making. We have also demonstrated agility through our flexible resourcing of several programmes including acalabrutinib, the TLR9 agonist and oral Selective Glucocorticoid Receptor Modulator (SGRM) to improve quality and efficiency. In a Chronic Obstructive Pulmonary Disease (COPD) study, AZD7624, an isoform specific

inhaled p38 MAP kinase inhibitor failed to show any benefit in patients with COPD, so the study was terminated as soon as possible. By moving quickly, identifying and initiating opportunities where appropriate while also stopping work when it's no longer the right thing to do, we have been able to realise significant quality, time and cost efficiencies.

By pioneering new innovations such as our clinical trial software tools: REACT, PROACT and Watcher, we are helping our team ensure that IMED and AstraZeneca are at the forefront of a revolution in the way that early phase clinical trials are carried out. We are making them smarter, faster and more cost-effective, so that more patients can benefit from advances in medical science as quickly and safely as possible.

An exciting example of our commitment to collaboration is a pan-European Paediatric Basket Study using a number of our Oncology assets, which began in 2016. By working with other organisations across Europe we hope to bring the right medicine to the right paediatric patients even faster.



By moving quickly, identifying and initiating opportunities where appropriate while also stopping work when it's no longer the right thing to do, we have been able to realise significant quality, time and cost efficiencies."

We design and deliver innovative clinical studies

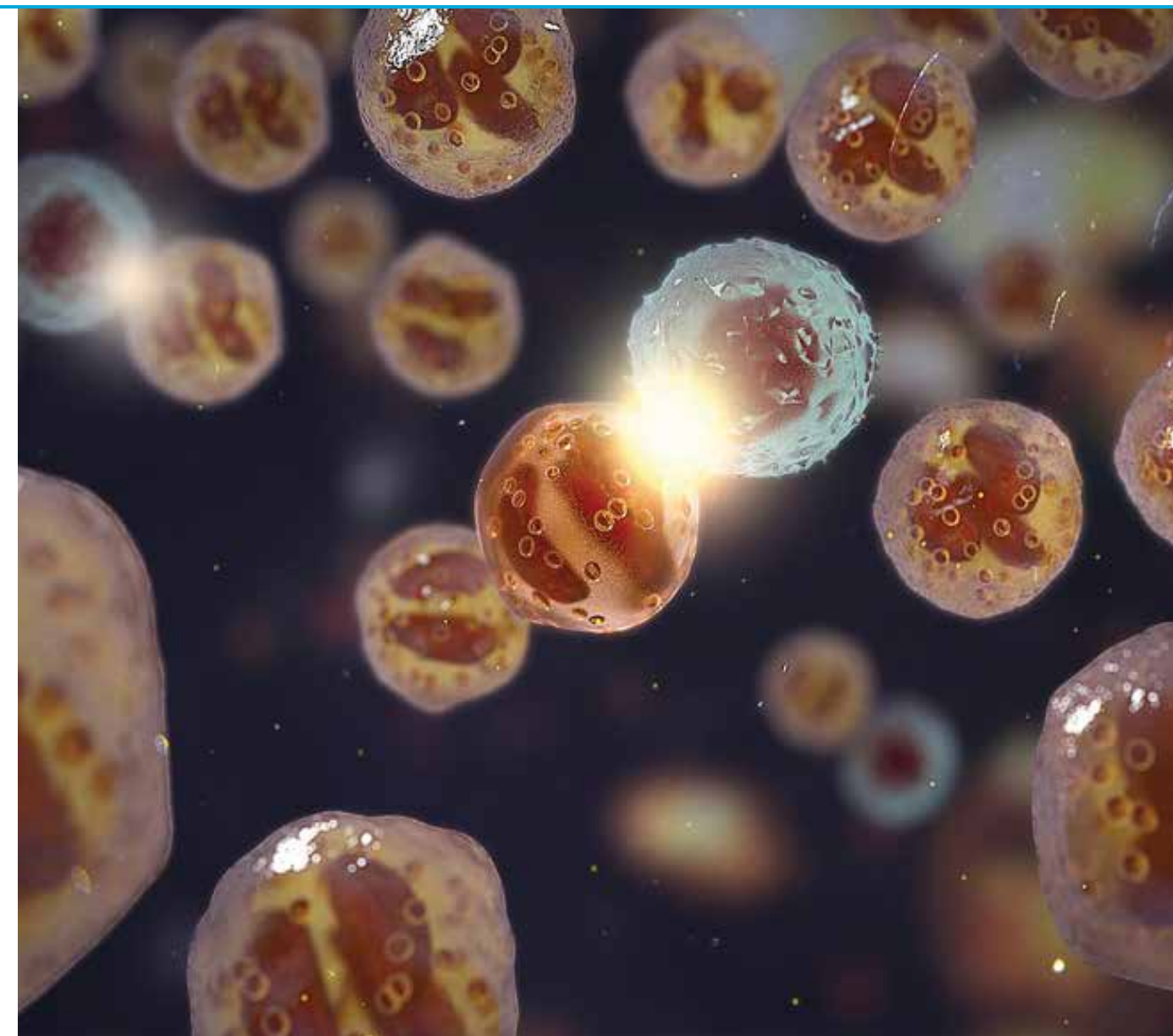
A key highlight this year in the delivery of innovative clinical studies has been our continued pioneering approach to innovative molecularly stratified multi-drug studies, known as 'umbrella' or 'basket' trials. In an 'umbrella' trial, patients with a single disease are treated with different treatments specific to their disease mechanism as indicated through biomarkers. For example, this year we have initiated a Phase Ib study, BISCAY, to evaluate four different immunotherapy and small molecule targeted therapies in patients with metastatic muscle-invasive bladder cancer. Patients are assigned to the appropriate study module based upon the specific gene mutations in their tumour.

In addition to this we are very proud to have pioneered and successfully implemented several novel study endpoints, reducing sample sizes and shortening trials to promote agile progression through clinical development. We developed CompEx for a Phase II study in asthma, which incorporates clinically relevant deteriorations as well as traditional exacerbations. CompEx allowed us to halve the sample size and is now being used as an exploratory endpoint in ongoing clinical studies. We also completed Phase IIa study in COPD within three months using ExDo, a novel design that was enriched for outcome. If we had used COPD exacerbations, the traditional primary endpoint, the study would have taken four times as long and required a significantly larger patient population.

50

Key to the collection of data is our Real-time Analytics for Clinical Trials (REACT) tool, which is now being applied to over 50 clinical trials across the portfolio

✓ Eosinophil prior to apoptosis



Highlights

We set out to	We delivered
Drive progression across the pipeline portfolio	<p>We achieved 96 publications – seven of which were High Impact and 41 High Quality. These demonstrated world-class early clinical development science in Oncology, RIA, CVMD, Quantitative Clinical Pharmacology (QCP), Biometrics and Study Operations.</p> <p>We led clinical progression across all of our main therapy areas, including first-dose milestones across our portfolio. This included seven Phase I first time in man including AZD4831 (MPO) and AZD5634 (ENaC), 12 Phase IIa starts including five NMEs such as AZD1419 (TLR9) for treatment of asthma and AZD6738 (ATR) in combination with olaparib for patients with gastric cancer, and three Phase IIb starts for non-NMEs including savolitinib + osimertinib in lung cancer patients.</p>
Implement innovative study designs across the core therapeutic areas	<p>We pioneered basket and umbrella studies including the E-SMART paediatric cancer trial, BISCAY, in Oncology and our PI3 kinase study in Oncology.</p> <p>We delivered innovative endpoints such as CompEx and ExDo in RIA that successfully reduced sample size, trial length and saved significant cost.</p> <p>We boosted trial recruitment by incorporating circulating tumour DNA (ctDNA) tests to identify patients with a rare genotype in an early phase Oncology trial.</p> <p>We reduced the cost of the clinical pharmacology package for AZD1775, our Wee1 inhibitor, by a third with an estimated reinvestment of \$11 million using innovative trial design.</p>
Integrate data to inform research and development	<p>We integrated renal data from 4,894 Type 2 diabetes patients and used this for modelling over time. The analysis increased confidence in the investment decision to progress the renal outcome study by providing evidence dapagliflozin is expected to protect the kidney like empagliflozin.</p> <p>We continued to deliver innovation through our Real-time Analytics for Clinical Trials (REACT) tool, which this year allowed us to adjust our savolitinib trial in real-time. We also used data generated through REACT to conduct sophisticated modelling, which significantly accelerated our ATM inhibitor (AZD0156) programme.</p> <p>We completed advanced ADME and PK modelling using data collected throughout our savolitinib Phase II program. At the End-of-Phase II meeting with the FDA, this data was deemed sufficiently informative to stand as surrogate to a variety of studies normally proposed. This is an unprecedented approach by the FDA and reflects our industry leading position in this area.</p>
Accelerate human target validation	<p>We delivered data to accelerate the human target validation of our VEGF-A programme in heart failure. We found that the different genotypes are significantly associated with decreased plasma VEGF-A protein concentrations, reduced ejection fraction and coronary flow reserve. These findings have accelerated human target validation for VEGF-A in patients.</p> <p>In the FLAP SMAD study, the team established the quantitative relationship between plasma AZD5718 exposure and the plasma biomarker LTB4. This assessment will be used to guide dose for the planned Phase IIa in patients. We are also using an in-house database, based on plasma samples, to identify potential new targets for Heart Failure with preserved Ejection Fraction (HFpEF).</p>
Nurture values and leadership behaviours consistent with our culture	<p>We optimised the way we work by focusing on key behaviours aligned to our AstraZeneca Values:</p> <p>Being entrepreneurial and agile – as demonstrated this year through our adaptive trial design for AZD7594, our inhaled SGRM. Also in the early termination of our AZD7624 trial in COPD following conclusive efficacy data generated using our novel ExDo endpoint in half the time, using half the patients.</p> <p>Being pioneering to follow the science – we constantly drive innovative approaches and technologies such as our pioneering modelling techniques that have significantly reduced the cost of our clinical pharmacology packages. We have also developed new endpoints such as CompEx saving time, money and influencing regulators, as well as gaining approval for leaner Clinical Pharmacology packages which use modelling to reduce the requirement for additional trials.</p> <p>Being collaborative – this forms part of everything we do, both across AstraZeneca and with external partners. A particular highlight this year has been our collaboration with the Karolinska Institute heralding generation of transcriptomes from glomerular and tubular tissues from diabetic nephropathy and healthy kidneys and a publication in Science relating to cardiometabolic risk.</p>

People spotlight

Melinda Merchant

Melinda Merchant is a Senior Medical Science Director who serves as lead for the Boston Oncology Therapeutic Medical Unit and represents ECD on the Site Leadership Team. A pediatric oncologist with a PhD in Immunology, her prior expertise in immunotherapy has been valuable in the early clinical development of AZD4635 (A2aR) and implementation of the Phase I First-Time-in-Human trial this year. Her collaborative efforts with IMED and Acerta are reflected in the successful Candidate Drugs AZD5991 (MCL1), AZD0466 (Bcl2/xL), and AZD1390 (ATM-BBB).



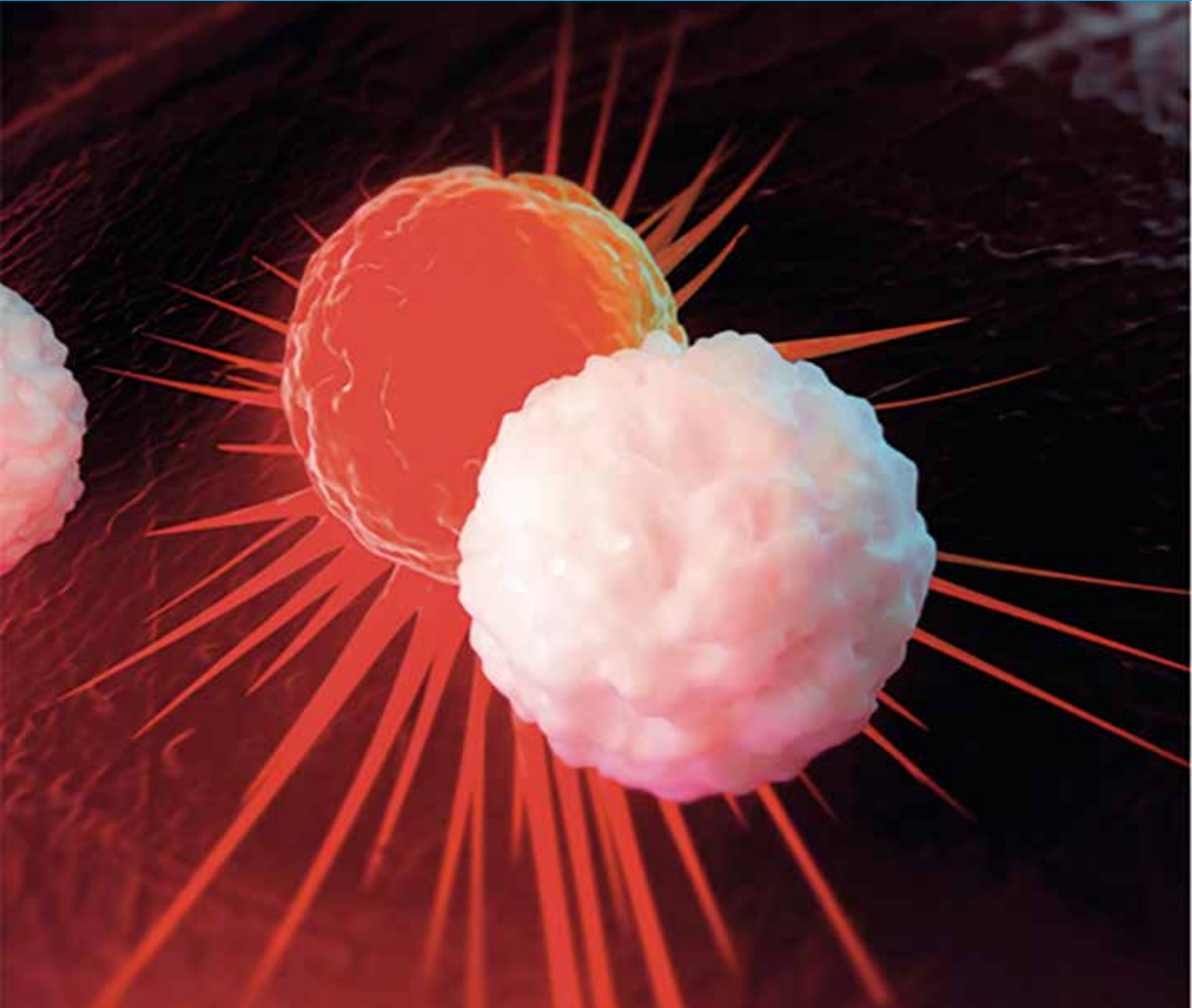
Allan Vaag

Allan Vaag is an endocrinologist specialising in diabetes research with an emphasis on the pathophysiology of Type 2 diabetes. Allan has published 340 peer-reviewed articles with one in *Nature* and another in *Nature Communications* in 2016. His H-index is 68 and has more than 20,000 citations. Allan is head of the ECD CVMD Therapeutic Medical Unit and is a member of the ECD leadership team. He serves on the CVMD Research Board, is a member of the internal advisory board for the Dapa mechanistic studies and has co-organised collaborative cross functional teams across IMED, as well as ECD clinical project challenge and journal club meetings. Allan is involved in developing several explorative studies accelerating human target validation in CVMD.



Steve Rennard

In 2016 Stephen Rennard became Head of the Clinical Discovery Unit for RIA and CVMD and a member of the ECD leadership team. Steve has helped lead a team effort to advance human target validation and patient segmentation. He has also contributed to the leadership of the NOVELTY study in collaboration with Global Medical Affairs and to the Targeted Genome Editing project in collaboration with DS. Working with RIA, he has been a leading contributor to the development of a discovery research programme focussing on COPD and regenerative medicine. Steve has authored over 700 publications, 24 of which were in 2016, his H-index is 88 and he has over 34,800 citations. This year Steve was also elected as a Professorial Fellow at Homerton College, University of Cambridge and was published in the *New England Journal of Medicine*.



Immune response to cancer - white blood cells attacking a cancerous cell



We accelerate human target validation

This year we have accelerated human target validation (HTV) for VEGF-A in post-Myocardial Infarction patients as part of our ongoing collaboration with Moderna Therapeutics. We did this by identifying genotypes that are significantly associated with decreased plasma VEGF-A protein concentrations, reduced ejection fraction and coronary flow reserve. This will help inform patient segmentation moving forward.

Our scientific leadership in this area was further demonstrated by our pioneering approach to HTV. In the FLAP SAD/MAD study, the team established the quantitative relationship between plasma AZD5718 exposure and the plasma biomarker LTB4. This assessment will be used to guide dose for the planned

Phase IIa in patients. We are also using in-house integrated clinical databases (RECIPE, PROFLOW), which have now been made open access internally, to provide HTV data for ongoing clinical projects FLAP, MPO and VEGF, as well as to identify potential new targets for cardiometabolic research area with focus on heart failure and high risk coronary artery disease.

We integrate data to inform research and development

Dapagliflozin is our SGLT2 inhibitor that improves glycaemic control in adults with Type 2 diabetes. The team wanted to determine whether dapagliflozin confers renal protection similar to the recent positive empagliflozin outcome trial. Renal data (eGFR) from 4,894 Type 2 diabetes patients in eight Phase II and III trials was integrated and used for modelling over time. The model demonstrated an overall renal protection potential for all levels of eGFR baseline versus placebo. The beneficial effect was dose dependent. This finding underpinned AstraZeneca's investment decision to progress the renal outcome study by providing evidence that dapagliflozin will protect the kidney like empagliflozin.

Key to the collection of data is our REACT tool, which is now being applied to around 110 studies across 25 programmes across the portfolio. This allows us to work in an agile way by making adjustments while the trial is ongoing. For example this year, during a savolitinib trial, real-time visualisation of tumour response and biomarker data highlighted that therapy was most effective in MET+ patients allowing us to focus the clinical trial on the right patients.

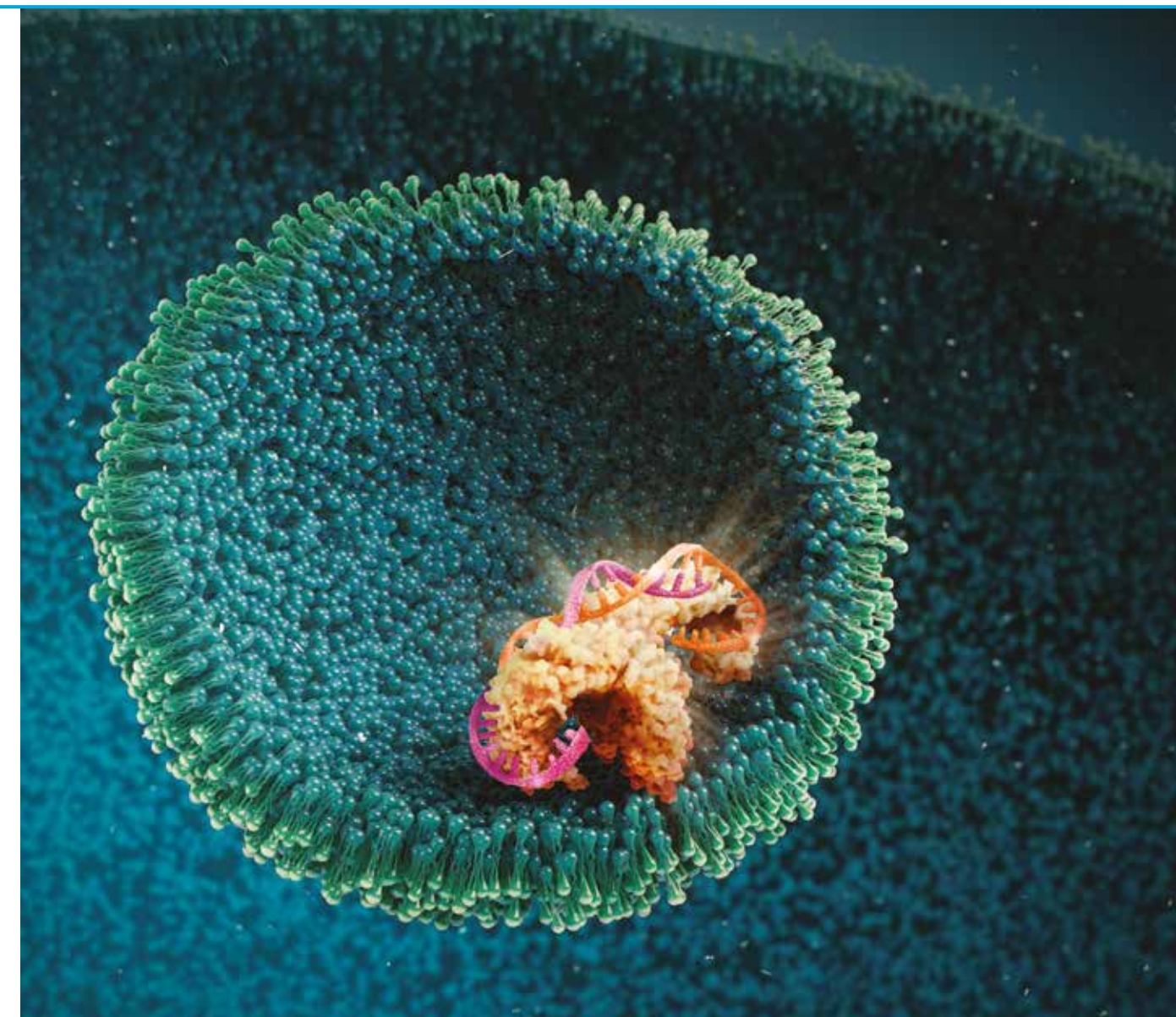
Watcher is an early form of Artificial Intelligence focused initially on liver function. This software confirms whether a patient has abnormal liver function and provides an initial assessment as to the possible cause. A Watcher collaboration with the savolitinib team has delivered a pilot based on a full retrospective analysis of current Phase II study data in REACT and the system will now be deployed in the forthcoming Phase III study in papillary renal cell carcinoma (PRCC). This current implementation of Watcher applies clinical heuristics to support the interpretation of Liver Function Tests in order to ensure that any Drug Induced Liver Injury (DILI) or potential Hy's Law event is quickly identified and notified to the clinical study team. The system is designed to reason over the REACT data continuously and in real-time. Watcher is planned to be deployed in the BISCAY study soon.



Key to the collection of data is our Realtime Analytics for Clinical Trials (REACT) tool, which is now being applied to around 110 studies across 25 programmes across the portfolio.”

110

studies across 25 programmes across the portfolio.



TLR9 endosome and receptor

A selection of key collaborations in 2016

1.

University of Cambridge, UK

ECD supports the Experimental Medicine Initiative (EMI) with the University of Cambridge School of Clinical Medicine. Through this collaboration we are currently funding a PhD student modelling cardiovascular toxicology, a second PhD student investigating Apelin endocrinology and an Academic Clinical Lecturer working in nephrology. EMI aims to recruit three clinical PhD students and six Academic Clinical Lecturers over the next three years.

AstraZeneca hosted the inaugural meeting of the EMI in Cambridge which attracted over 60 researchers to hear Professors Ian Wilkinson and Tim Eisen (ECD) introduce the goals of the initiative. This strategic collaboration is supported by the University of Cambridge in partnership with the Cambridge University Hospitals, NIHR Cambridge Biomedical Research Centre, AstraZeneca and GSK.

Tony Johnson VP ECD, has a direct collaboration with Professor Kevin O’Shaughnessy, Reader in Clinical Pharmacology at the University of Cambridge and Honorary Consultant Physician at the Cambridge University Hospitals NHS Foundation Trust. The collaboration currently entails a post-doc working on cardiovascular/renal science and targets.

ECD Biometrics has an affiliation with the Medical Research Council Biostatistics Methodology Hub with a post-doc engaged in this area and funded by ECD.
2.

Sahlgrenska University Hospital, Sweden

A collaboration to characterise human kidney tissue was successfully initiated and the first transfers of kidney material between the parties has now been completed. The tissue will be used to gain knowledge about kidney biology and function to inform new ways of treating and preventing kidney disease.

3.

Karolinska Institute and Gothenburg University, Sweden

A particular highlight this year has been collaboration with the Karolinska Institute (KI) heralding generation of transcriptomes from glomerular and tubular tissues from diabetic nephropathy and healthy kidneys and a publication in *Science* relating to Cardiometabolic risk loci. Through the ECD-initiated collaboration with Dr Lars Lund at KI, based on the KaRen cohort with a comprehensive integrated clinical dataset, IMED scientists are identifying new targets for Heart Failure with preserved Ejection Fraction (HFpEF), with one first target presented recently.
4.

Sarah Canon Research Institute (SCRI), US

Collaboration between Global Medicines Development (GMD) /ECD and SCRI. Successful face to face transition meeting in July in Nashville to transfer AZD1775 to GMD, with the support and input from SCRI.
5.

University of British Columbia (UBC), Canada

AstraZeneca and UBC are partnering with the Prevention of Organ Failure (PROOF) Centre on the Canadian Study of Prediction of Death, Dialysis and Interim Cardiovascular Events (CanPREDDICT) – a study designed to improve the understanding of determinants of renal and cardiovascular (CV) disease progression in patients with chronic kidney disease.
6.

University of Toronto, Canada

AstraZeneca and Professor David Cherney (University of Toronto) submitted an ESCR to investigate effects of dapagliflozin on albuminuria and renal function in non-diabetic CKD patients. Professor Richard Gilbert (University of Toronto), was consulted regarding potential impact of having reduced selectivity towards SGLT1 (as seen with canagliflozin).

7.

European Medicines Agency (EMA), UK

The EMA has asked AstraZeneca to provide input to guidance on genomics in clinical trials. Cath Mela from Clinical Sample and Bioanalytical Sciences (CSBS) was the ECD representative in the AstraZeneca cross-functional contributor group which provided feedback on two guidance documents in May/ June 2016. The final document is scheduled for 2017.
8.

Covance Laboratory Strategic Partnership, Global

We have built a strategic partnership to simplify Clinical Sampling Operations, Bioanalysis and Speciality Laboratory contracting and are working with 50 full-time employees from Covance who are dedicated to this alliance. This has provided improved governance procedures and saved both money and time for science through standardised procedures.
9.

Manchester Cancer Research Institute, The Christie and the University of Manchester, UK

ECD has established a collaboration to develop and implement iDecide, our cutting edge clinical informatics R&D framework. This facilitates rapid interpretation of results, accelerates early identification of safety and efficacy signals, and improves understanding of the patient experience. We are collaborating with leaders in information technology and artificial intelligence (AI) to fundamentally change the way clinical trials are performed.
10.

The French National Cancer Institute and Gustave Roussy, France

We are collaborating as part of AcSé-eSMART, a pan-European Paediatric Basket Study using a number of our Oncology assets. This collaborative paediatric cancer study aims to double in two years the number of new drugs that will be offered to children based on the molecular profile of their tumour.



Key publications in 2016

Publication	Title	Author
New England Journal of Medicine	Clinical significance of symptoms in smokers with preserved spirometry	Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R, Rennard S, Tashkin DP, Han MK
Nature	Genome-wide associations for birth weight and correlations with adult disease	Horikoshi M, Vaag A et al
Science	Cardiometabolic risk loci share downstream Cis and Trans genes across tissues and diseases	Franzen O, Ermel R, Cohain A, Di Narzo A, Akers N, Talukdar H, Foroughi-Asl H, Giambartolomei C, Fullard J, Sukhvasi K, Köks S, Gan LM, Gianarelli C, Kovacic J, Betsholtz C, Losic B, Michael T, Hao K, Roussos P, Skogsber J, Ruusalepp A, Schadt E, Björkegren J
Nature Medicine	Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer	Carter L, Rothwell DG, Mesquita B, Snowton C, Leong HS, Fernandez-Gutierrez F, Li Y, Burt DJ, Antonello J, Morrow CJ, Hodgkinson CL, Morris K, Priest L, Carter M, Miller C, Hughes A, Blackhall F, Dive C, Brady G
Nature Reviews Clinical Oncology	Clinical development of new drug–radiotherapy combinations	Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, Clay R, Adams RA, Baird RD, Billingham L, Brown SR, Buckland S, Bulbeck H, Chalmers AJ, Clack G, Cranston AN, Damstrup L, Ferraldeschi R, Forster MD, Golec J, Hagan RM, Hall E, Hanauske A-R, Harrington KJ, Haswell T, Hawkins MA, Illidge T, Jones H, Kennedy AS, McDonald F, Melcher T, O’Connor JPB, Pollard JR, Saunders MP, Sebag-Montefiore D, Smitt M, Staffurth J, Stratford IJ, Wedge SJ
The Lancet Respiratory Medicine	Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial	Richter K, Puu M, O’Byrne P, Metev H, Keen C, Nair P, Uddin M, Larsson B, Cullberg M
American Journal of Respiratory and Critical Care Medicine	Exome array analysis identifies a common variant in IL27 associated with chronic obstructive pulmonary disease	Hobbs BD, Parker MM, Chen H, Lao T, Hardin M, Qiao D, Hawrylkiewicz I, Sliwinski P, Yim JJ, Kim WJ, Kim DK, Castaldi PJ, Hersh CP, Morrow J, Celli BR, Pinto-Plata VM, Criner GJ, Marchetti N, Bueno R, Agusti A, Make BJ, Crapo JD, Calverley PM, Donner CF, Lomas DA, Wouters EF, Vestbo J, Paré PD, Levy RD, Rennard SI, Zhou X, Laird NM, Lin X, Beaty TH, Silverman EK, Cho MH
American Journal of Respiratory and Critical Care Medicine	A new approach for identifying patients with undiagnosed chronic obstructive pulmonary disease	Martinez F, Mannino D, Leidy NK, Malley KG, Bacci ED, Barr RG, Bowler RP, Han ML, Houfek JF, Make B, Meldrum CA, Rennard SI, Thomashow B, Walsh J, Yawn BP
American Journal of Respiratory and Critical Care Medicine	Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β 2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE2SPOND). A Randomized Clinical Trial	Martinez FJ, Rabe K, Anzueto A, Sethi S, Pizzichini E, McIvor A, Siddiqui S, Rekeda L, Zetterstrand S, Alagappan V, Miller C, Reisner C, Rennard SI
European Respiratory Journal	Circulating desmosine levels do not predict emphysema progression but are associated with cardiovascular risk and mortality in chronic obstructive pulmonary disease (COPD)	Rabinovich1 RA, Miller BE, Wrobel K, Ranjit K, Williams MC, Drost E, Edwards LD, Lomas DA, Rennard SI Agusti A, Tal-Singer R, Vestbo J, Wouters EFM, John M, van Beek EJR, Murchison JT, Bolton CE, MacNee W and Huang JTH

Pharmaceutical Sciences

“By establishing Pharmaceutical Sciences as a function within the IMED Biotech Unit, we are giving teams across IMED access to our cutting edge science and unique skillset earlier in the drug discovery journey. Already we are reaping the rewards of having pharmaceutical science clearly represented on IMED project teams where we contribute to problem solving with a view to potential future large scale production. This has

contributed to changes in direction of early projects that could facilitate the smooth progression through clinical development in the future. Despite being less than a year old, we have already seen some really exciting science, both internally and through our collaborations with specialised biotech companies, driving progression and enabling future molecules.”

Anders Holmén, VP Pharmaceutical Sciences



✓ Microfluidiser making nanoparticles



Pharmaceutical Sciences

The Pharmaceutical Sciences function was established as part of the IMED Biotech Unit in 2016 to meet the needs of an increasingly diverse and complex portfolio across our main therapy areas. We are a dedicated team bringing specialist skills and cutting-edge science to influence the design of new molecules. Our unique approach gives IMED teams access to excellence in organic synthesis, route design, solid state chemistry, biopharmaceutics and analytical chemistry, as well as our expertise in cutting-edge drug delivery systems to support our ever-expanding drug platforms and modalities.

Our work is focused in three key areas:

Early chemical development where we have a highly innovative team providing a powerful resource across the IMED Biotech Unit. Our unique approach of bringing those designing synthetic molecules into the same team as those producing them has already reaped rewards, including many high impact publications in 2016.

Early product development where we utilise our specific expertise in the formulation of products based on established technologies for candidates going into clinical testing, including device strategies for inhalation and parenteral drugs in early development. Access to this specialised science within the IMED Biotech Unit has resulted in developing innovative new ways of working, increasing efficiency and reducing costs.

Advanced drug delivery where our remit is to deliver cutting-edge technology to enable effective molecules of the future. By focusing on cellular targeting, improving cellular uptake and enhancing drug delivery, we aim to improve target efficacy and delivery of both small molecules and new modalities such as microRNA, messenger RNA and antisense oligonucleotide therapies.

In 2016 we have already seen significant benefits of bringing our unique set of skills to project teams across the IMED Biotech Unit. A key highlight has been our work with the Cardiovascular and Metabolic Diseases (CVMD) team manufacturing the world's first modified RNA therapeutic product as part of our collaboration with Moderna Therapeutics. We have also been working on some really exciting science using nanoparticle technology in drug targeting with the Oncology team, which was published in *Science Translational Medicine* in 2016.

Through our co-exclusive license with Pfizer for access to the BIND Therapeutics ACCURINS® we successfully encapsulated our targeted Aurora B kinase inhibitor, AZD2811, into a novel polymeric nanoparticle formulation. The manuscript highlights how the team developed the first nanoparticle pre-clinical candidate, through careful characterisation of efficacy, safety, pharmacokinetics and distribution in pre-clinical models.

With the Respiratory, Inflammation and Autoimmunity (RIA) team, we are focused on developing new ways to evaluate inhaled compounds in the pre-clinical phase, using our inhalation technology platforms including nebulisation, dry powder and pressurised metered dose inhalation devices. This year we met an important milestone where we took AstraZeneca's first inhaled oligonucleotide into Phase II and going forward we are broadening the scope towards inhaled proteins and new modalities.



Large scale lab - rotating flask boiling off solvent to produce the drug product

Highlights

We set out to	We delivered
Successfully establish new function within IMED	We established a dedicated team of 180 people across our Boston, Cambridge, Gothenburg and Macclesfield sites which, along with several external partners, truly makes us a global function. We developed a function with the breadth of talent and skills to meet the needs of an increasingly diverse and complex portfolio.
Innovate in early chemical development by bringing together a unique mix of specialities	<p>We developed reliable and efficient ways to prepare compounds using the team's expertise in chemical process development and analytical chemistry. The synthetic production of MEDI4276, an anti-HER2 antibody drug conjugate, took 36 steps with high potency intermediates making scaling up production unusually challenging. By utilising a high containment facility and modifying the route of synthesis, the team's innovative approach exceeded expectations with a significant increase in product yield, contributing to the compound achieving first time in man in 2016.</p> <p>The team has also established efficient manufacturing techniques such as continuous processing or "flow chemistry" within early development. For example, we ran three different continuous processes in the production of one of our compounds; two chemical stages as well as the conversion of a racemic mixture to the desired single isomer starting material using simulated moving bed chromatography.</p>
Develop clinical trial materials for the first ever large scale modified RNA clinical trial in humans	<p>We successfully delivered the regulatory clinical trial application (CTA), the validated methods and the product for the world's first clinical trial utilising modRNA as a therapeutic agent in collaboration with Moderna Therapeutics.</p> <p>All drug product related Chemistry, Manufacturing and Control (CMC) activities were performed in-house by implementing novel technologies and new ways of working. The complexity of the drug substances demanded that new analytical methods for modRNA, based on electrophoresis and High Performance Liquid Chromatography (HPLC) had to be set up and validated to Good Manufacturing Practice (GMP) level.</p> <p>The generated internal knowledge, capabilities and innovations will pave the way for future modRNA and other new modality projects.</p>
Build partnerships and collaborations	We built new strategic alliances with academic institutions to strengthen the scientific ecosystems around our major sites and further drive innovative delivery of new medicines to patients. We are also building new strategic alliances with biotechnology companies and key academics to access frontline science and technology.
Demonstrate scientific leadership	We delivered 19 high quality and three high impact publications since joining IMED in 2016. In addition, we have received 19 invitations to speak at various congresses, including the Swedish Society of Toxicology Annual Meeting 2016.



✓ Large scale lab - chromatography

People spotlight

Annette Bak

The recruitment of Annette Bak, Senior Director, Advanced Drug Delivery, strengthens our Chemistry, Manufacturing and Control (CMC) knowledge within pre-formulation, formulation development and drug delivery. Her research interests include characterisation and drug delivery of macromolecules such as peptides via injectable and alternative routes such as oral and transdermal.

Annette is also active in the area of pharmaceutical cocrystal design to optimise physicochemical properties, formulation design to ensure sufficient and targeted pre-clinical and clinical exposure, and strategies to ensure effective project translation from discovery to early development. Annette has authored more than 35 publications and has been an invited speaker/presenter at over 30 scientific venues.



Ulrika Tehler

Since 2011 Ulrika Tehler, Associate Principal Scientist, RIA Early Product Development, has focused on drug delivery to the lungs. She has been a major contributor to the development of an internal *in silico* mechanistic modelling tool for inhaled drug delivery and pioneered the inhaled dissolution area within AstraZeneca. Ulrika is an interdisciplinary scientist renowned for building relationships across departments and delivering results and innovative solutions to projects.



Jeremy Parker

Jeremy Parker is AstraZeneca's Principal Scientist for New Modalities and Tissue Targeting, leading the chemistry activities on the development and commercialisation of a range of new therapeutic modalities including antibody drug conjugates, dendrimer drug conjugates and polymer drug conjugates. His interests include contemporary synthetic methodology, route selection, linker chemistry and the synthesis of a wide range of New Therapeutic Modalities.



Using nanomedicines to enable innovative cancer medicines with improved therapeutic index

Lack of therapeutic index remains a major challenge in developing innovative cancer medicines. Nanomedicines can be used to change a candidate drug's biodistribution to target tumours and also regulate the rate of drug release from a nanoparticle to improve safety and efficacy. Pharmaceutical Sciences has championed using nanomedicine approaches to improve therapeutics index and enable project progression.

AZD2811 is an Aurora B kinase inhibitor that showed promising results in acute myeloid leukaemia patients but was limited by therapeutic index. Through collaboration with BIND Therapeutics, whose assets were subsequently acquired by Pfizer, we successfully encapsulated AZD2811 into a novel polymeric nanoparticle formulation (ACCURINS®) using an ion pairing approach. AZD2811 nanoparticles increase biodistribution to tumour sites and provide extended release of drug in the tumour. This is currently being clinically evaluated as a treatment for haematological and solid tumours and is currently in Phase I MAD study. This is the first AstraZeneca nanomedicine project in clinical development and the first non-cytotoxic drug in clinical development in a polymeric nanoparticle. This work resulted in a high impact *Science Translational Medicine* paper published in February 2016.

In collaboration with Starpharma and using their dendrimer technology, a second nanomedicine approach has been adopted. In this approach the drug is conjugated to a dendrimer resulting in both improved tolerability and solubility of a lipophilic drug. A number of targets in our Oncology portfolio are currently being evaluated with this technology.

Pharmaceutical Sciences has also implemented the innovative modelling efforts to help in the design phase and built an internal capability to produce prototype nanoparticles, enabling rapid exploration in internal projects. In addition, the team has been driving science through collaboration across IMED, to further understand the technology and translational elements of nanomedicines including potential impact in combination therapy.

Our approach of using nanoparticle technology as part of the discovery phase to enable new candidate drugs from challenging targets is industry-leading and our work in the area has

gained a strong scientific reputation in the nanomedicine space. In 2016, the team achieved a high impact review in *Advanced Drug Delivery* as well as the *Science Translational Medicine* paper, and two further high quality papers in the area, presenting at a number of key conferences and connecting with several key academic groups and labs within the drug delivery field.

2016

In 2016, the team achieved a high impact review in *Advanced Drug Delivery* as well as the *Science Translational Medicine* paper, and two further high quality papers in the area, presenting at a number of key conferences and connecting with several key academic groups and labs within the drug delivery field.



◀ Large scale lab - vessel in a continuous flow reactor

A selection of key collaborations in 2016

1.

Starpharma, Australia

This collaboration is to explore the benefits of Starpharma's dendrimer technology to improve the therapeutic index of drugs in AstraZeneca's Oncology portfolio and pipeline.
2.

University of Cardiff, UK

In collaboration with Professor Arwyn T. Jones at the University of Cardiff, we are working together to characterise and understand the intracellular delivery and trafficking pathways of mRNA delivery systems in different tumour cell lines. By gaining a greater understanding of how the delivery systems enter and are trafficked by different cell types, we aim to explore how this knowledge can be applied to design and develop improved strategies for the efficient intracellular delivery of nucleic acids and other macromolecules.
3.

University of Gothenburg, Sweden

Working together with Professor Hadi Valadi this collaboration studies exosomes as an mRNA delivery system. This collaboration aims to evaluate the possibility of using Lipid Nanoparticle (LNPs) to load a modified mRNA into exosomes originating from different cell types. Using LNPs, we aim to further optimise the mRNA loading process of exosomes and to evaluate transfection of mRNA loaded exosomes *in vitro* and *in vivo*.
4.

University of Durham, UK

In collaboration with Professor Jonathan Steed at the University of Durham, we are focused on small molecule gels as targeted crystallization media for solid form discovery. Gels, formed by liquid trapped within a porous web of nanometre-scale fibres, hold many technological possibilities, for example as selective sorbents or uptake agents.

5.

University of Cambridge, UK

In collaboration with Professors Ian Paterson and David Spring at the University of Cambridge, we are working to further understand and advance Antibody Drug Conjugate (ADC) Chemistry. Innovative science is key to progression of such 'next-generation' therapeutics, where the potential of targeted therapy avoids dose-limiting toxicity of chemotherapy that occurs because of its effects on normal cells. The development of new linkers and warheads by synthetic chemists will be crucial to the further advancement of the field and the emergence of next generation ADCs.
6.

The Cambridge Crystallographic Data Centre (CCDC), UK

Joining the Crystal Form Consortium, we are working with leading chemists with the aim to derive knowledge from small molecule crystal structures to inform solid form selection. The Crystal Form Consortium is a collaborative venture bringing together development chemists from leading companies in the industrial sector with software, database and research experts at the CCDC. The Consortium currently has 14 member organisations spanning major pharmaceutical and agrochemical businesses around the world.
7.

University of Notre Dame, US

In Collaboration with Professor Olaf Wiest, we aim to develop a method that can predict enantioselectivity for given substrates and catalysts, with a high accuracy. The method has been implemented as a virtual screening capability that is synergistic with the robotic screening facility used by Pharmaceutical Science in Macclesfield UK. By selecting only ligands that are expected to give high selectivity, the robotic screening can be concentrated on efficiency and stability, potentially improving the screening capacity by 1-2 orders of magnitude.

8.

Ludwig-Maximilians-University Munich, Germany

Together with Professor Joachim Rädler, we are using a small angle x-ray scattering to study how the core (bulk phase) of lipid nanoparticles (LNP) respond to pH changes. We are also studying single cell mRNA translation using – ie mRNA uptake and protein synthesis – of mRNA LNPs and in a third part of this collaboration the adsorption of proteins on LNP surface (using fluorescence correlation spectroscopy).
9.

Curtin University, Perth, Australia

In collaboration with Professors Andrew Rohl and Julian Gale, we are using computer simulation to model the physical performance of molecular crystals, aimed at building a computational methodology for the identification and quantification of crystalline slip planes and allowing for distinguishing between elastic and plastic deformations in materials.
10.

University of Innsbruck, Austria

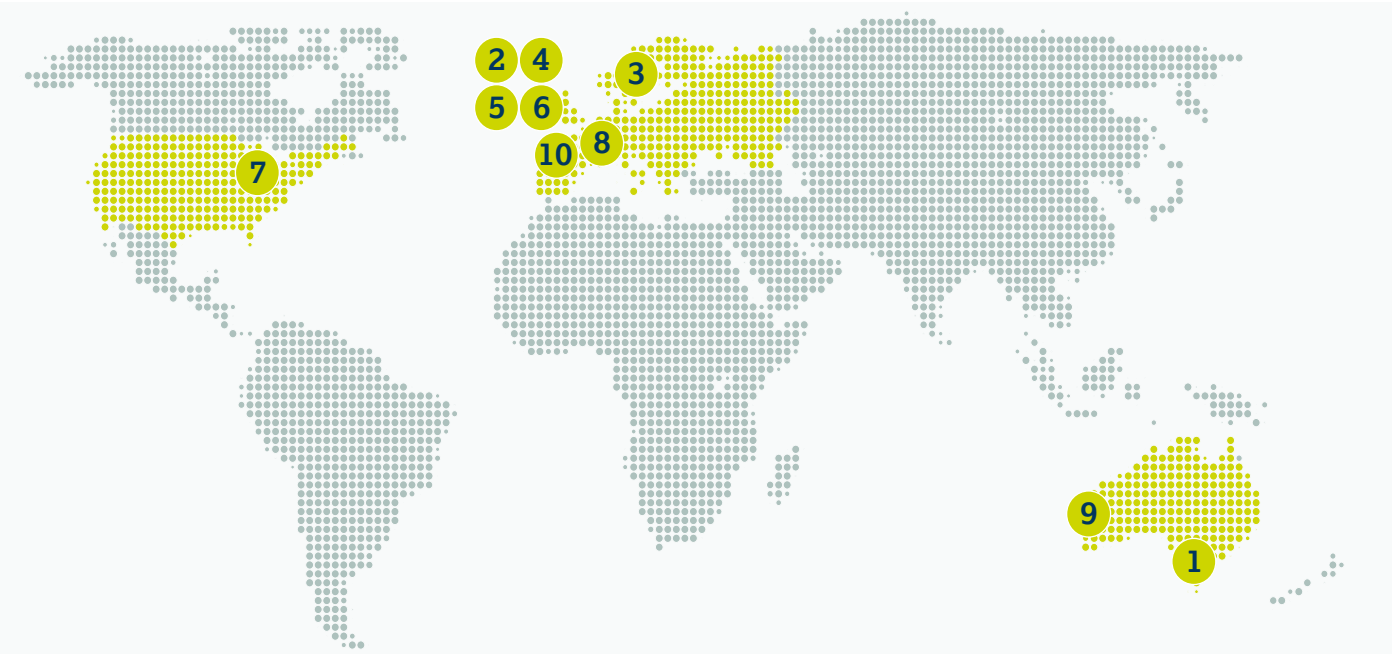
With Andreas Bernkop-Schnürch of the University of Innsbruck, we are researching self-emulsifying drug delivery systems (SEDDs). SEDDs are isotropic mixtures of oils, surfactants and solvents/co-solvents that form stable emulsions in the gastrointestinal (GI) tract and have shown promise for oral delivery of peptide drugs. The aim is to exploit the application of SEDDs optimised for oral delivery of antisense oligonucleotides.



^ TNO gastrointestinal model 1 (TIM1)
upper gastrointestinal tract

Key publications in 2016

Publication	Title	Author
Advanced Drug Delivery Reviews	Challenges and strategies in anti-cancer nanomedicine development: an industry perspective	Hare J, Lammers T, Ashford M, Puri S, Storm G, Barry S
Chemical Communications	Clearing the undergrowth: detection and quantification of low level impurities using 19F nuclear magnetic resonance (NMR)	Moutzouri P, Kiraly P, Phillips A, Coobmes S, Nilsson M, Morris G
Organic Process Research and Development	An enantioselective hydrogenation of an alkenoic acid as a key step in the synthesis of AZD2716	Karlsson S, Sorensen H, Andersen SM, Cruz A, Ryberg P
Nature Reviews Materials	Cancer nanomedicine: is targeting our target?	Lammers T, Kiessling F, Ashford M, Hennink W, Crommelin D, Storm G
Chemical Communications	Stabilisation of amorphous form of ROY by presence of a predicted co-former interaction	Corner P, Harburn J, Steed J, McCabe J, Berry D



Nucleotide platforms: AstraZeneca’s pioneering new modality science

Advances in our understanding of molecular biology and genomics, technological developments to synthesise and manipulate nucleic acid, as well as advanced drug delivery systems have opened up an extremely exciting opportunity to use nucleic acids as therapeutic agents.

At AstraZeneca, through our collaborative approach, many candidates in our pipeline utilise new modalities and in 2016 we saw significant progression thanks to the great science being delivered across the IMED Biotech Unit. New modalities provide the opportunity to design therapeutics to disease mechanisms previously considered difficult, if not impossible, to target.

Synthetic messenger RNA

Messenger RNA Therapeutics™ is a novel drug technology that leverages the fundamental role that mRNA plays in protein synthesis, to produce human proteins inside patient cells. Synthetic messenger RNA is delivered directly to tissue, stimulating the production of intracellular and secreted therapeutic protein, without triggering an innate immune response. This unique approach opens up new treatment options for a wide range of diseases that cannot be addressed today using existing technologies.

We have been working in close collaboration with Moderna Therapeutics™ to discover, develop and commercialise this pioneering technology for the treatment of serious cardiovascular, metabolic and renal diseases, as well as cancer. This year, we have progressed the first candidate, AZD8601, towards clinical development, resulting in the first patient being successfully dosed in January 2017.

AZD8601 encodes for vascular endothelial growth factor-A (VEGF-A), a protein known for stimulating tissue repair and cardiac regeneration. AZD8601 is directed via local tissue injection and initiates a strong, local and transient surge of VEGF-A expression, which may lead to the creation of more blood vessels and improved blood supply. The compound has been shown to improve cardiac function and increase neovascularisation in animal models with heart failure and has also shown efficacy in animal models with diabetic wounds.

The programme represents a new scientific and medical approach that could one day provide a unique regenerative treatment option for patients with heart failure or after a heart attack, as well as for diabetic wound healing and other ischaemic vascular diseases.

Anti-microRNA

MicroRNAs are small RNA molecules, typically 20 to 25 nucleotides in length, that do not encode proteins but rather regulate gene expression. More than 800 microRNAs have been identified in the human genome, and over two-thirds of all human genes are believed to be regulated by microRNAs. A single microRNA can regulate entire networks of genes and microRNA expression, or function, has been shown to be significantly altered or dysregulated in many disease states. Developing chemically modified single stranded oligonucleotides that target microRNAs, anti-miRNAs, offers a unique approach to treating disease by modulating entire biological pathways.

During 2016, we have worked with Regulus to discover and develop microRNA therapeutics for potential application in cardiovascular, metabolic and renal diseases, as well as cancer. As a result of this research, 2016 saw progression into the clinic for AZD4076 - a GalNAc-conjugated anti-microRNA, targeting miR103/107 as a treatment for diabetic patients with non-alcoholic steatohepatitis (NASH). Increased expression of miR-103/107 in the liver has been associated with insulin resistance in people with NASH. Pre-clinical studies have shown AZD4076 to affect biological pathways implicated in NASH progression, as well as improved insulin sensitivity and glucose tolerance in animal models.

800

microRNAs have been identified in the human genome

Antisense oligonucleotides

Antisense oligonucleotides are synthetic single stranded strings of nucleic acids that bind to RNA and thereby alter or reduce expression of the target RNA. They can reduce the expression of proteins by breakdown of the targeted transcript, alternatively they can restore protein expression or modify proteins through interference with pre-mRNA splicing. Antisense drugs can potentially be created for any target including many previously considered un-druggable by traditional small molecule technology.

We have been working in collaboration with Ionis Pharmaceuticals to discover and develop antisense drugs to treat cancer by combining our expertise in developing anti-cancer agents with Ionis’ antisense technology platform.

One of the candidates in clinical development that has shown significant progression this year is AZD9150, a generation 2.5 antisense oligonucleotide that prevents expression of signal transducer and activator of transcription 3 (STAT3). STAT3 is a transcription factor that plays a critical role in normal cell proliferation, differentiation, and apoptosis. It has been shown that STAT3 signalling creates an immune suppressive environment in tumours which can contribute to escape from checkpoint inhibitor treatment. Suppression of STAT3 using AZD9150 has been shown in animal models to enhance response to checkpoint inhibitors and, this year, we were excited to progress the combination of AZD9150 with durvalumab into Phase II.

Personalised Healthcare and Biomarkers

✓ Minute pieces of circulating tumour DNA (ctDNA) in the bloodstream

“We aim to use Personalised Healthcare (PHC) to transform patients’ lives through personalising treatment. Many of our drug launches now rely on diagnostic tests and biomarkers to match AstraZeneca medicines to patients most likely to benefit.

In 2016 we launched six diagnostic tests linked to our medicines, through partnerships with diagnostic companies. In particular, AstraZeneca’s first Food and Drug Administration (FDA) approved companion diagnostic based on circulating tumour DNA enabled lung cancer patients unable to provide a tissue sample to be offered

osimertinib as a treatment option. We also delivered our first diagnostic beyond Oncology; the Nova Biomedical Pro Uric Acid Test, a point-of-care test that measures response to gout treatment.

We announced our industry-leading genomics initiative, led by Professor David Goldstein, in April. This unprecedented strategy focuses on the analysis of genome sequence from two million patients to identify new targets and biomarkers linked to mechanisms of disease, integrated across our entire research and development pipeline.”

Ruth March, VP Personalised Healthcare and Biomarkers



Personalised Healthcare and Biomarkers

Personalised Healthcare (PHC) is at the heart of our science based approach to drug development. We have invested heavily in the skills, partnerships and technology to achieve this, with 95% of our small-molecule pipeline and more than 80% of our clinical pipeline now following a PHC approach. We are well on track to deliver around 50 drug launches with a companion diagnostic test by 2023.

In 2016 we worked with our expert partners to launch six diagnostic tests linked to our medicines, increasing our total number of diagnostics launched since 2014 to 15. Our focus on scientific innovation has led to AstraZeneca's first FDA approved circulating tumour DNA (ctDNA) companion diagnostic, the Roche 'cobas® EGFR Mutation Test v2', expanding the option for treatment with osimertinib to non-small cell lung cancer (NSCLC) patients who are unable to provide a tissue sample.

Our commitment to bring PHC to patients across AstraZeneca's main therapy areas has resulted in our first diagnostic outside of Oncology: the Nova Biomedical Pro Uric Acid Test, a hand held point-of-care test aligned to lesinurad, which can be used to measure a patient's response to gout treatment.

Looking forward to our next wave of PHC innovation, we announced the launch of an industry-leading integrated genomics initiative focused on the analysis of genome sequence from two million patients, aimed at validating new targets and biomarkers linked to mechanisms of disease. We welcomed Professor David Goldstein to the team, who will lead the scientific direction of the initiative, while continuing in his full-time role at Columbia University Medical Center.

During 2016, we began to build our in-house centre for Genomics Research, analysing genomic data from academic partners as well as our own clinical trials, to help apply these potentially ground-breaking insights across our entire research and development pipeline.



David Goldstein

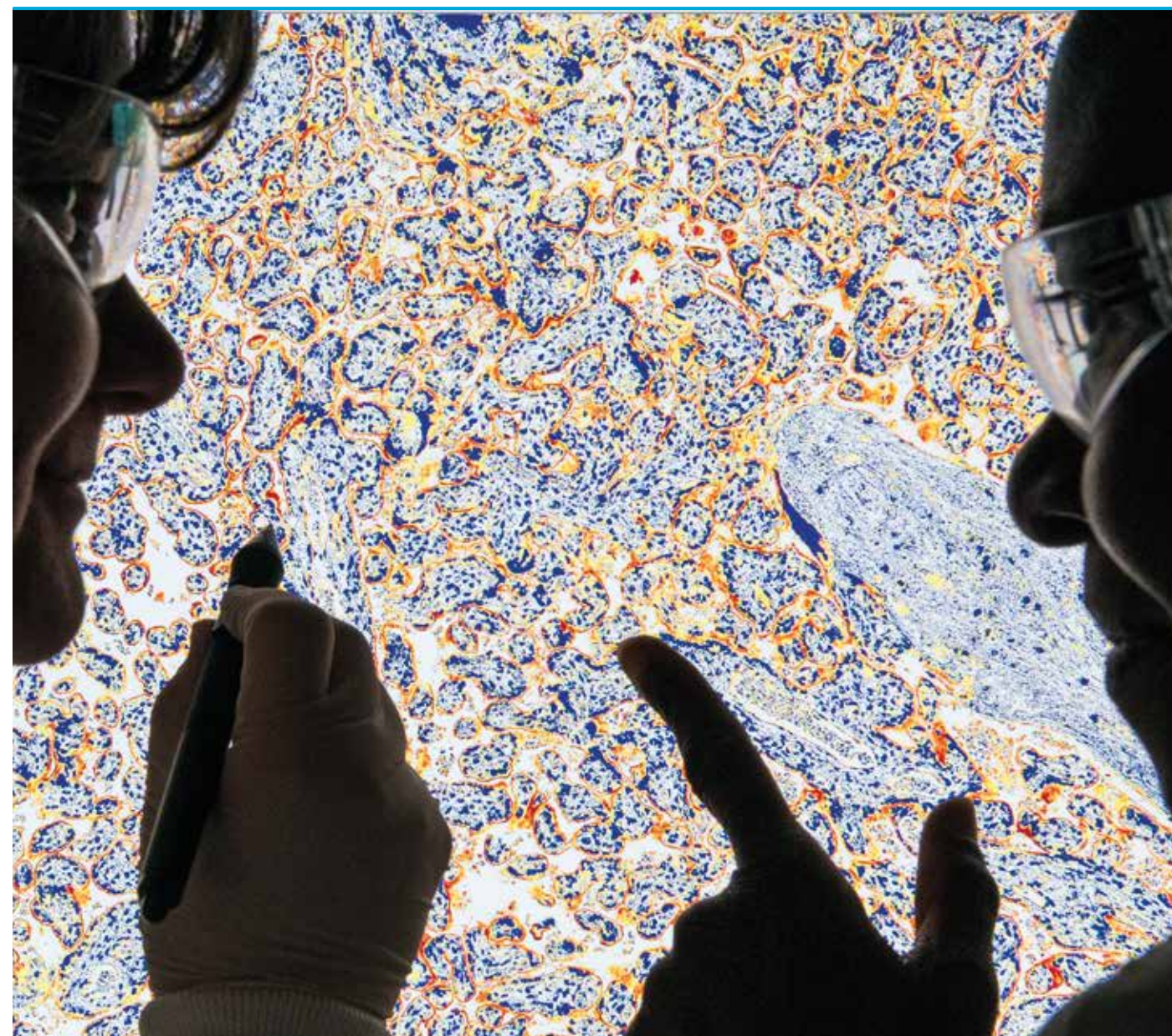
Professor David Goldstein joined AstraZeneca in September to lead our integrated genomics initiative. David is the Director of the Institute for Genomic Medicine and Professor of Genetics and Development at Columbia University. He is renowned for his research on human genetic diversity, the genetics of disease and pharmacogenetics. Professor Goldstein received his PhD in biological sciences from Stanford University and has previously held positions at University College London and Duke University, North Carolina. He has published over 250 papers in the field and is a recipient of the Royal Society Wolfson Research Merit Award.

Bringing personalised healthcare to patients with respiratory disease

As part of our drive to accelerate delivery of personalised healthcare across our main therapy areas, we have developed an innovative prototype point-of-care diagnostic test for eosinophilic respiratory disease. The prototype combines novel electrochemistry and metallic nanoparticle signaling with traditional immunoassays, to provide sensitive and quantitative detection of soluble biomarkers. We have successfully demonstrated proof of concept in a pilot clinical study and with our partners, AgPlus Diagnostics Ltd (UK), we aim to deploy the hand-held prototype test into early clinical trials. This diagnostic can be advanced to help physicians in specialty and primary care to rapidly identify the right respiratory treatment for the right patient.

50

We are well on track to deliver around 50 drug launches by 2023 requiring a diagnostic test.



< Investigation of protein expression in a positive control tissue core on a Tissue Microarray (TMA) slide containing non-small cell lung cancer

Highlights

We set out to	We delivered
Deliver personalised healthcare (PHC) to patients	<p>We launched six diagnostic tests with our diagnostic partners, linked to three AstraZeneca medicines:</p> <p>Roche ‘cobas® EGFR Mutation Test v2’ tissue (Japan) and plasma test (US, Japan) for selecting patients with the T790M mutation for treatment with osimertinib.</p> <p>Nova Biomedical Pro Uric Acid point-of-care (POC) Test (EU), to measure serum uric acid as a biomarker for patient response to gout treatment, including lesinurad.</p> <p>Qiagen’s therascreen BRCA 1-2 next-generation sequencing (NGS) FFPE Kit and Multiplicom’s BRCA Tumour MASTR™ Plus; two CE-IVD-labelled molecular diagnostic tests, on complementary platforms, for selecting patients with BRCA1 and BRCA2 mutations for treatment with olaparib.</p> <p>We are committed to matching the right patients to medicines in our clinical trials with over 80% of our clinical pipeline having a PHC approach.</p>
Bring the benefits of personalised healthcare (PHC) beyond Oncology to all therapy areas	<p>We initiated, in addition to the launch of the Nova Biomedical Pro Uric Acid Test (EU), the development of an innovative point-of-care diagnostic for respiratory patients with our partner AgPlus Diagnostics Ltd.</p> <p>We are carrying out genomics research on approximately 20,000 samples from CVMD clinical studies with associated clinical endpoints.</p>
Drive new technologies and novel ways of approaching diagnostic testing	<p>We delivered the world’s largest and most comprehensive studies in NSCLC and squamous cell carcinoma of the head and neck (SCCHN) comparing commercially available PD-L1 assays. Our industry leading approach supports patients treated with PD-1 and PD-L1 antagonists in clinical practice.</p> <p>We used innovative BEAMing digital PCR technology to implement a highly sensitive, AKT1 mutation ctDNA plasma test (Sysmex Inostics, Inc). The test was used to prospectively select patients for a new medicine in a clinical trial, accelerating study recruitment by screening patients who would not otherwise have had the opportunity to participate.</p> <p>We delivered proof of concept data for a novel method (‘CAm-seq’) to identify EGFR T790 mutations using cutting-edge Nanopore sequencing technology (Oxford Nanopore MinION instrument). The assay takes us beyond the prospects of current sequencing technologies and has the potential to deliver rapid, non-invasive, portable diagnostic ctDNA testing in the future.</p>
Transform discovery and development with an integrated genomics approach	<p>We launched an integrated genomics initiative to transform drug discovery and development across our entire research and development pipeline. Together with several high-profile collaborators, we will leverage information from an unprecedented two million genome sequences.</p> <p>Renowned genomics expert Professor David Goldstein joined AstraZeneca in September and will be responsible for driving the scientific progress of the initiative.</p>
Establish leading scientific reputation in personalised healthcare	<p>Our PHC approach is industry leading; we have achieved more FDA approvals for PHC drugs in the last two years than any other pharmaceutical company.</p> <p>We have signed 10 new collaboration agreements with diagnostic companies, increasing our investment to over \$160 million. We are also partnering with a number of leading academic centres, including Stratified Medicines Scotland Innovation Centre, Columbia University, University of Helsinki, Montreal Heart Institute and Wellcome Trust Sanger Institute.</p> <p>We have demonstrated our scientific leadership through three high impact and 36 high quality publications in peer-reviewed journals this year.</p>

People spotlight

Alexander Kohlmann

Alexander Kohlmann is a leader in innovative diagnostic science, whether using novel ctDNA testing or multi-gene panel next-generation sequencing; recently, his collaboration with the CRUK-Cambridge Institute, using a portable third generation Nanopore sequencing device, has generated exciting proof-of-principle data. Alexander has published over 120 peer-reviewed papers to date and is using experience gained in his previous role from the Munich Leukemia Laboratory to spearhead a new wave of companion diagnostic tests in AstraZeneca. As franchise lead for haematology programmes in PHB’s Oncology companion diagnostic unit, he has delivered central prospective diagnostic testing for early and late stage Oncology programmes (e.g. PARP inhibitor olaparib and MET inhibitor savolitinib).



Jill Walker

Jill Walker is a recognised leader in the diagnostic science of PD-L1 testing, representing AstraZeneca on the cross-industry Blueprint Consortia and directing an unprecedented series of large-scale assay comparison studies that have established AstraZeneca as an industry leader. As Executive Diagnostic Director for our immuno-oncology programs, Jill uses her background in clinical and diagnostic development to drive testing and diagnostic submissions for durvalumab and the combination of durvalumab and tremelimumab in over 10 pivotal clinical studies. Jill has co-authored some of the most significant publications in the field and has extensive experience in international diagnostic regulatory interactions.



Largest and most comprehensive PD-L1 assay comparison

Patients whose tumours express PD-L1 are more likely to benefit from immuno-oncology therapies. We set out to compare the four commercially available diagnostic tests that measure PD-L1 expression; Dako 22C3, Dako 28-8, Ventana SP263 (developed in partnership with MedImmune) and Ventana SP142. These assays have been developed independently and use different antibody clones, immunohistochemistry protocols, scoring algorithms and cut-offs.

We conducted the largest and most comprehensive PD-L1 assay comparison studies in 500 tissue samples from patients with NSCLC (using Dako 22C3, Dako 28-8, Ventana SP263) and in 500 samples from patients with head and neck squamous cell carcinoma of the head and neck (SCCHN) cancer (using Dako 22C3, Dako 28-8, Ventana SP263, Ventana SP142).

Our results in NSCLC were presented at the American Association for Cancer Research (AACR) congress in 2016, showing an overall percentage agreement of >90% across the three commercially available tests.

At the European Society for Medical Oncology (ESMO) 2016 congress, we presented the comparison data for SCCHN showing high-level agreement between three assays (Dako 22C3, Dako 28-8, Ventana SP263), but clear differences with Ventana SP142 (both for tumour and immune cell staining).

Results from this study are already being applied in clinical development, using diagnostic science to help interpret results from the many PD-L1 tests available. We expect that this data will lead to better use of scarce clinical resources and clearer decisions for patients.

500

We conducted the largest and most comprehensive study to compare the assays analysing squamous cell carcinoma of the head and neck (SCCHN) tissue samples from 500 patients

PHC adoption across AstraZeneca pipeline

Phase I - 27 New Molecular Entities		Phase II - 27 New Molecular Entities	
Small molecule	Large molecule	Small molecule	Large molecule
AZD0156 ATM solid tumours	MEDI0562# hOX40 solid tumours	AZD1775# Wee1 solid tumours	MEDI-573# IGF metastatic breast cancer
AZD2811# Aurora solid tumours	MEDI0680 PD-1 solid tumours	AZD4547 FGFR solid tumours	MEDI0382 GLP-1/glucagon diabetes/ obesity
AZD4635 A2aR inhibitor solid tumours	MEDI1873 G1TR solid tumours	AZD5363# AKT breast cancer	MEDI4166 PCSK9/GLP-1 diabetes/CV
AZD8186 PI3Kβ solid tumours	MEDI4276 HER2 solid tumours	savolitinib# MET pRCC	MEDI6012 LCAT ACS
AZD9496 SERD ER+ breast	MEDI-565# CEA BITE GI tumours	vistusertib (AZD2014) mTOR 1/2 solid tumours	AZD9412# Inhaled β1FN asthma/COPD
AZD4831 MPO HFpEF	MEDI9197# TLR 7/8 solid tumours	AZD9150# STAT3 haems & solids	tezepelumab# TSLP asthma/atopic dermatitis
AZD5718 FLAP CAD	MEDI9447 CD73 solid tumours	AZD5069 CXCR2 haems & solids	inebilizumab# CD19 neuromyelitis optica
AZD8601# VEGF-A cardiovascular	MEDI8111 Rh-FactorII trauma/bleeding	AZD3759 EGFR-BBB NSCLC CNS mets	mavrilimumab# GM-CSFR rheumatoid arthritis
AZD0284 Inhaled RORγ psoriasis	MEDI9314 IL4R atopic dermatitis	AZD6738 ATR solid tumours	MEDI5872# primary Sjögren's syndrome
AZD5634 Inhaled ENaC cystic fibrosis	MEDI1814# amyloidβ Alzheimer's disease	AZD4076 miR103/107 NASH	MEDI3902¶ Psl/PcrV pseudomonas
AZD7986# DPP1 COPD	MEDI7352 NGF/TNF osteoarthritis pain	abediterol# LABA asthma/COPD	MEDI4893 staph alpha toxin SSI
AZD9567 oral SGRM RA	MEDI0700# BAFF/B7RP1 SLE	AZD1419# TLR9 asthma	MEDI8852 influenza A treatment
AZD8871# MABA COPD	MEDI4920 CD40L-Tn3 pSS	AZD7594 Inhaled SGRM asthma	MEDI8897# RSV passive prophylaxis
	MEDI7734 ILT7 myositis	AZD3241 MPO Multiple System Atrophy	
<div><div>Includes significant fixed dose combination projects, and parallel indications that are in a separate therapeutic area</div><div># Partnered; ¶ Registrational Phase II/III study</div><div>Pipeline correct as of Q4 2016.</div></div> <div><div>RIA</div><div>CMVD</div><div>Oncology</div><div>Other</div><div>Project with PHC Approach</div><div>PHC Not Applicable</div></div>			

PHC adoption across AstraZeneca pipeline

Phase III and Life Cycle Management - 19 Entities	
Small molecule	Large molecule
acalabrutinib# BTK inhibitor B cell malignancy	moxetumomab pasudotox# PLAIT CD22 HCL
selumetinib MEK 2Ldiff.thyroid	durvalumab# PD-L1 2L bladder
olaparib / BRCAm ovarian & breast	tralokinumab IL-13 severe asthma
osimertinib EGFR NSCLC	benralizumab# IL-5R severe asthma
fulvestrant ER antagonist breast	anifrolumab# IFNαR SLE
ticagrelor P2Y12 acute coronary syndromes	
dapagliflozin SGLT2 Type 2 diabetes	
saxagliptin DPP4 Type 2 diabetes	
exenatide GLP1 Type 2 diabetes	
epanova omega-3-carboxylic acids hypertryglyceridaemia	
roxadustat# HIFPH anaemia CKD/ESRD	
ZS-9 potassium exchanger hyperkalaemia	
PT010 LABA/LAMA/ICS COPD	
AZD3293# BACE Early Alzheimer's disease	

✓ DNA strand and red blood cells



Key publications in 2016

Publication	Title	Author
OncoTarget	Performance of Multiplicom's BRCA MASTR Dx kit on the detection of BRCA1 and BRCA2 mutations in fresh frozen ovarian and breast tumor samples	Badoer C, Garrec C, Goossens D, Ellison G, Mills J, Dzial M, El Housni H, Berwouts S, Concolino P, Guevellou VG, Delnatte C, Favero JD, Capoluongo E, Béziau S
Journal of Thoracic Oncology	PD-L1 Immunohistochemistry (IHC) Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project	Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, Richardson W, Towne P, Hanks D, Vennapusa B, Mistry A, Kalamegham R, Averbuch S, Novotny J, Rubin E, Emancipator K, McCaffery I, Williams JA, Walker J, Longshore J, Tsao MS, Kerr KM
Journal of Thoracic Oncology	Circulating Free Tumor-derived DNA (ctDNA) Determination of EGFR Mutation Status in Real-world European and Japanese Patients with Advanced non-small cell lung cancer (NSCLC): the ASSESS Study	Reck M, Hagiwara K, Han B, Tjulandin S, Grohé C, Yokoi T, Morabito A, Novello S, Arriola E, Molinier O, McCormack R, Ratcliffe M, Normanno N
British Journal of Cancer	A pipeline to quantify serum and cerebrospinal fluid microRNAs for diagnosis and detection of relapse in paediatric malignant germ cell tumours	Murray MJ, Bell E, Raby KL, Rijlaarsdam MA, Gillis AJ, Looijenga LH, Brown H, Destenaves B, Nicholson JC, Coleman N
Annals of Oncology	A comparative study of PD-L1 diagnostic assays in squamous cell carcinoma of the head and neck (SCCHN)	Ratcliffe MJ, Sharpe A, Rebelatto M, Scott M, Barker C, Scorer P, Walker J
Journal of Alzheimer's Disease	AZD3293: Pharmacokinetic and pharmacodynamic results in healthy subjects and patients with Alzheimer's disease	Cebers G, Alexander RC, Haeberlein SB, Han D, Goldwater R, Ereshefsky L, Olsson T, Ye N, Rosen L, Russell M, Maltby J, Eketjäll S, Kugler AR
PLoS ONE	Optimised pre-analytical methods improve KRAS mutation detection in circulating tumour DNA (ctDNA) from patients with non-small cell lung cancer (NSCLC)	Sherwood JL, Corcoran C, Brown H, Sharpe AD, Musilova M, Kohlmann, A
Clinical Cancer Research	Comparison of Pre-clinical Activity of Osimertinib with Other EGFR-TKIs in EGFR-Mutant non-small cell lung cancer (NSCLC) Brain Metastases Models, and Early Evidence of Clinical Activity in Patients with Brain Metastases	Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, Pickup K, Jordan A, Hickey M, Grist M, Box M, Johnström P, Varnäs K, Malmquist J, Thress KS, Jänne PA, Cross D
Journal of Medical Genetics	Meta-analysis of genome-wide association studies of high-density lipoprotein (HDL) cholesterol response to statins	Postmus I, Warren HR, Trompet S, Arsenault BJ, Avery CL, Bis JC, Chasman DI, de Keyser CE, Deshmukh HA, Evans DS, Feng Q, Li X, Smit RAJ, Smith AV, Sun F, Taylor KD, Arnold AM, Barnes MR, Barratt BJ, Betteridge J, Boekholdt SM, Boerwinkle E, Buckley BM, Ida Chen Y, de Craen AJM, Cummings SR, Denny JC, Dubé MP, Durrington PN, Eiriksdottir G, Ford I, Guo X, Harris TB, Heckbert SR, Hofman A, Hovingh GK, Kastelein JJP, Launer LJ, Liu C, Liu Y, Lumley T, McKeigue PM, Munroe PB, Neil A, Nickerson DA, Nyberg F, O'Brien E, O'Donnell CJ, Post W, Poulter N, Vasan RS, Rice K, Rich SS, Rivadeneira F, Sattar N, Sever P, Shaw-Hawkins S, Shields DC, Slagboom PE, Smith NL, Smith JD, Sotoodehnia N, Stanton A, Stott DJ, Stricker BH, Stürmer T, Uitterlinden AG, Wei W, Westendorp RGJ, Whitsel EA, Wiggins KL, Wilke RA, Ballantyne CM, Colhoun HM, Cupples LA, Franco OH, Gudnason V, Hitman G, Palmer CNA, Psaty BM, Ridker PM, Stafford JM, Stein CM, Tardif J, Caulfield MJ, Jukema JW, Rotter JI, Krauss RM

Journal of Molecular Diagnostics	Ultrasensitive Detection of Multiplexed Somatic Mutations Using Matrix Assisted Laser Desorption/Ionization - Time of Flight (MALDI-ToF) Mass Spectrometry	Mosko MJ, Nakorchevsky AA, Flores E, Metzler H, Ehrich M, van den Boom DJ, Sherwood JL, Nygren AO
PLoS ONE	Characterisation of FGFR1 locus in squamous non-small cell lung cancer (sqNSCLC) reveals a broad and heterogeneous amplicon	Rooney C, Geh C, Williams V, Heuckmann JM, Menon R, Schneider P, Al-Kadhimi K, Dymond M, Smith NR, Baker D, French T, Smith PD, Harrington EA, Barrett JC, Kilgour E

A selection of key collaborations in 2016

1.

Roche, US
Our collaboration delivered a regulatory approved blood based diagnostic for T790M testing, which allows patients access to osimertinib in cases where there is no biopsy sample available.
2.

Roche Tissue Diagnostics, US
A collaboration that supports projects across numerous indications. In the area of immuno-oncology, specifically the durvalumab programme, the partnership focuses on delivering a PD-L1 diagnostic assay based on SP263 aimed at optimising treatment decisions for patients.
3.

Foundation Medicine, US
Working with Foundation Medicine enables AstraZeneca to use comprehensive genomic profiling for patient stratification in clinical trials – an approach being followed in several programmes currently in clinical development.
4.

Human Longevity Inc, US
This collaboration allows AstraZeneca to share up to 500,000 DNA samples with Human
5.

Stratified Medicine Scotland Innovation Centre, UK
A collaboration to enable access to genomic results from thousands of DNA samples. Through this collaboration, partners will be able to recall patients for further genetic and clinical evaluation to gain additional insights.
6.

Columbia University Medical Center, US
A collaborative genomic initiative between AstraZeneca and Columbia University Medical Center to analyse and extract meaning from genomic datasets, including those from patients with medical records held in the New York Presbyterian/Columbia University Medical Center's clinical data warehouse.
7.

AgPlus Diagnostics, UK
Through our collaboration with AgPlus, we aim to make a rapid and innovative handheld point-of-
8.

Myriad Genetics, US
We expanded our companion diagnostic collaboration to seek Japanese regulatory approval for the BRACAnalysis CDx, to select patients with BRCA1/BRCA2 mutations for treatment with olaparib.
9.

Cancer Research UK Cambridge Institute, UK
This collaboration delivered proof-of principle cutting-edge nanopore third-generation sequencing data using the Oxford Nanopore Technologies MinION device.
10.

The Institute for Molecular Medicine, Finland
This collaboration studies AZ genes of interest in the Finnish population, which is known to carry a higher than normal frequency of rare genetic variants. Finland's integrated health record system and national biobanking law facilitate the invitation to recall volunteers carrying these variants for thorough clinical evaluation.
- Longevity, Inc (HLI), from which HLI will sequence exomes or genomes. These genomic samples will include those donated by patients under optional informed consent in AstraZeneca's clinical trials.
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Therapy area progress

IMED functions

Collaborating for science innovation

An environment where science thrives

Harnessing the code of life to develop new treatments

A genome is the full set of instructions needed to make every cell, tissue and organ in our bodies. In humans, the genome consists of more than three billion DNA base pairs, which together define us as unique individuals. Although most of the information in the genome is the same between individuals, there are small differences that scientists believe can combine with environmental influences to cause diseases such as diabetes, asthma or cancer.

Studying genome sequences across large populations allows the development of innovative new treatments and helps to target the right patient to the right medicine.

For decades, scientists have predicted that one day, genomic studies would transform drug development and patient care. Now is a pivotal time in genomics research where we can start to harness the power of the genome. This is why we have launched an integrated genomics initiative, advised by Professor David Goldstein, to transform drug discovery and development.

The genomics initiative is centred on samples donated by patients through clinical trials. The full genome sequence from these patients will be combined with extensive clinical and drug response data from clinical studies. This insight will be combined with genomic information from collaborative partners in a bespoke database, so the knowledge gained from an unprecedented two million genomes can be applied comprehensively across our entire research and development pipeline.

By embedding genomics across all research and development platforms, our genomics initiative will help us to deliver novel insights into the biology of diseases, enable the identification of new targets for medicines, support selection of patients for clinical trials and allow patients to be matched with treatments more likely to benefit them.

Harnessing the power of the genome through technological advances in next generation sequencing and bioinformatics

Until recently, DNA sequencing remained prohibitively expensive and too slow to be used routinely in drug discovery and development. The first human genome was sequenced in 2003, a remarkable breakthrough in genomics, which took 10 years to complete and cost nearly \$3 billion. Using next-generation sequencing (NGS) we can now sequence whole human genomes in only a few days, for less than \$1,000.

Genomic data from this initiative will be combined with extensive clinical data, including up to 500 measurements per patient from our clinical trials. The latest big data analytical techniques will be used to integrate and mine this data, giving a unique opportunity to analyse the influence of genomics, not only on the causes of disease, but also on response to treatment. The scale of this data is needed to identify those very rare genomic differences that interact with the environment to cause disease.

Key facts

We are working with public and private partners including Human Longevity Inc (HLI), The Sanger Institute, Helsinki University, Montreal Heart Institute, Genomics England, Stratified Medicine Scotland and Columbia University Medical Center.

We will analyse sequences from up to two million genomes including ~500,000 samples from AstraZeneca's clinical trials, donated by patients from the past 15 and next 10 years.

Genomic data will be integrated with clinical data in a bespoke, integrated database of at least five petabytes (PB).

Latest big data analytical techniques will be used to understand the influence of genomics on the causes of disease as well as response to treatment.

This initiative will transform our entire pipeline driving drug discovery and development across all our therapeutic areas.

An innovative model of collaboration with global partners

To achieve this ambitious initiative we are working with the best private and public partners, each carefully selected to bring complementary expertise and access to unique genomics databases. Our private partner, Human Longevity Inc (HLI), brings world-leading sequencing expertise and machine learning analytics. Our public partners, including The Sanger Institute, Helsinki University, Montreal Heart Institute, Genomics England, Stratified Medicine Scotland and Columbia University Medical Center bring both disease area and genomics expertise.

Driving progress across our pipeline

This unprecedented genomics initiative will generate knowledge to be applied across our entire pipeline and will drive drug discovery and development across all our therapeutic areas. It will allow us to identify new biomarkers and targets for medicines and understand which medicines will work best for which patients.

In discovery, our understanding and research will be transformed by unlocking hidden causes of disease, uncovering innovative drug targets linked to molecular mechanisms.

In development, newly identified biomarkers will allow us to better select the right patients for the right clinical trials targeting the underlying genomic mechanisms of disease.

At launch, we will be well placed to deliver better medicines, faster, to the right patients to achieve the best medical outcome.



Now is a pivotal time in genomics research, where we can start to harness the power of the genome.”

Understanding the biology of disease today to develop the treatments of tomorrow

The successful treatment of many of today's health disorders relies on uncovering the causes of disease so that we can develop new medicines. By combining our skills in drug discovery and development and our unique collection of research samples and data with leaders in industry and academia, we will maximise the potential for discovering and developing new treatments in areas of high unmet medical need.

Harnessing the latest genomics knowledge and techniques today will help us to gain new understanding of disease to develop the treatments of tomorrow, in our mission to push the boundaries of science to deliver life-changing medicines to patients.

500,000

genomic samples with clinical data from AstraZeneca clinical trials

10,000

It would take 10,000 years to listen to 5 petabytes (PB) of music

Stratified Medicine Scotland

The partnership between AstraZeneca and the Stratified Medicine Scotland Innovation Centre, which represents NHS Scotland, Scottish Universities and industry partners, will offer unique opportunities. The initiative will not only have access to genomic results from thousands of DNA samples generously donated for research by patients in Scotland but, due to the healthcare system in Scotland, our partners will also be able to recall patients for further genetic and clinical evaluation to gain additional insights.

Access to this resource of genomics results aligned to patient records has great potential in helping us to find new drug targets and improve the way we identify patients most likely to benefit from novel therapies.

Max Planck Institute and AstraZeneca: Joining forces across industry and academia to discover novel chemistry approaches in Cardiovascular and Metabolic Disease (CVMD)

At AstraZeneca, we believe that successful drug discovery comes about through industry working in partnership with academia. That's why we're incredibly proud of our collaboration with the Max Planck Institute. Initially established four years ago, this successful partnership was extended in 2014 to a satellite unit, which is linked to IMED CVMD and now embedded in the Max Planck Institute Dortmund.

With our scientists directly embedded within the group of Herbert Waldmann and working side by side with researchers at the institute in an open, innovative and creative environment, we are gaining access to a different kind of knowledge and relaxing the boundaries between academia and the pharmaceutical industry.

“

In really successful collaborations, both partners must have a scientific stake in the project; they must accept and value the weaknesses and the strengths, the limitations and the needs of both partners. In the collaboration with AstraZeneca these prerequisites are fully met.”

Professor Herbert Waldmann, Director, Department of Chemical Biology, Max Planck Institute Dortmund, Germany

Our collaboration with the Max Planck Institute has provided us with an interface between the disciplines of chemistry and biology. The basis of the collaboration is to discover and develop new chemical modalities that will address the most demanding biological targets, both in basic science and drug discovery.

New modalities are important, as classical modalities such as small molecules have limitations when addressing challenging targets. Within CVMD, new modalities such as stabilised peptides, macrocycles and molecular conjugates present a novel and innovative way to address these challenging targets and through our collaboration with the Max Planck Institute we are now in a position to find new compound classes to allow us to do this.

At the satellite unit, we are specifically focused on the modulation and activation of transcription factors – important biological targets, but which today are considered undruggable. Our work has already resulted in the discovery of compounds that bind to transcription factors and we are now determining if they modulate their activity and the biology influenced by them. This would be a great achievement as, if successful, this approach could enable a whole new range of therapeutic options in many diseases. Therefore, the work being done has the potential to drive science forward and be truly ground-breaking.

We have also seen significant progress with our work on complex phenotypic screens using human derived material within AstraZeneca. Through this collaboration we have learnt state-of-the-art approaches for phenotypic screen evaluation and target deconvolution, which have resulted in the generation of several targets for our CVMD portfolio. The collaboration has also given us access to new collaborations through the Institute's network.

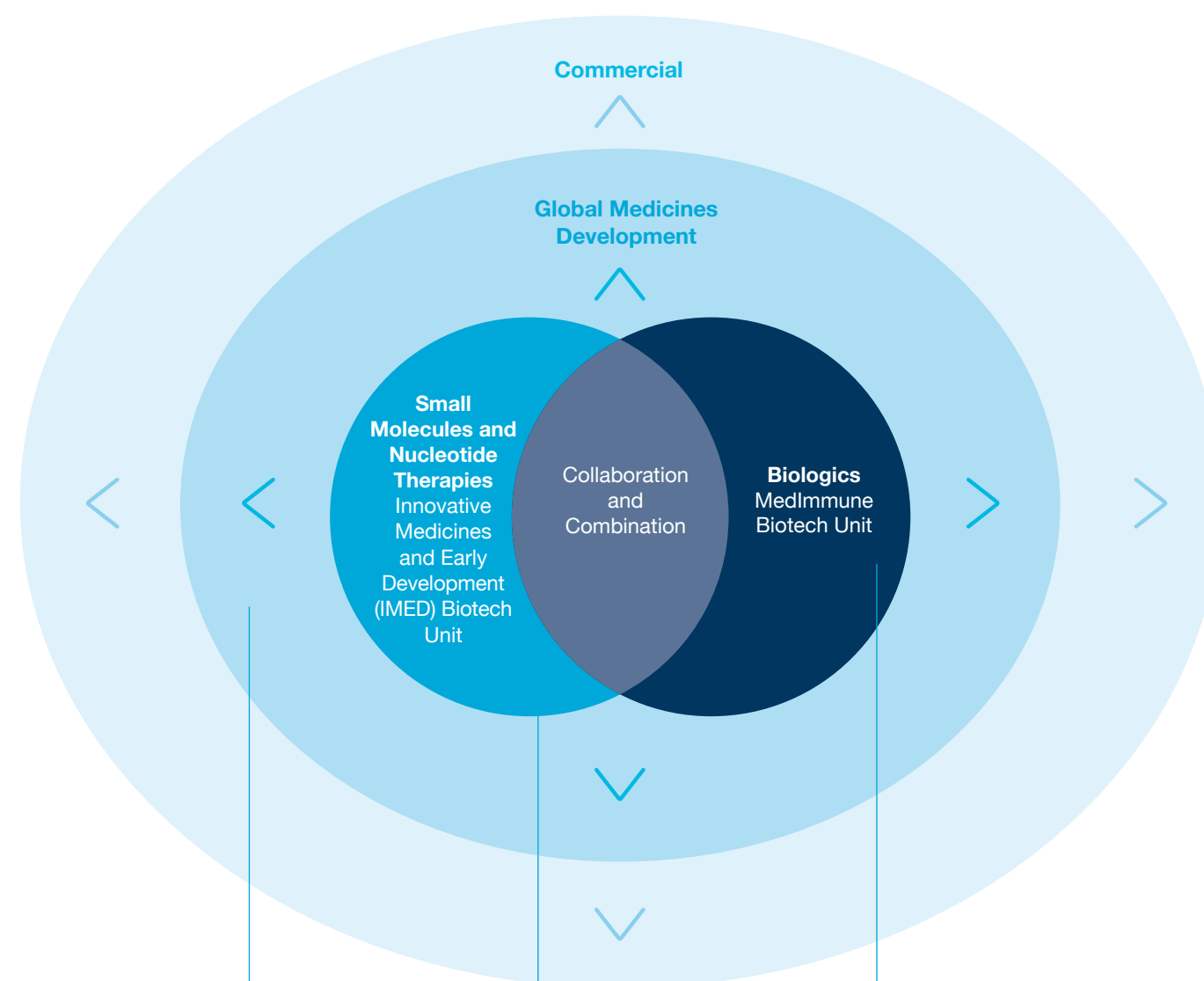
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The skills and expertise of the Max Planck Institute, especially in chemical biology, peptides and natural products, complements very well the competence that we have been building up in new modalities chemistry at AstraZeneca in Gothenburg.”

Eric Valeur, Associate Director, New Modalities, AstraZeneca

Enterprise leadership through collaboration

The IMED Biotech Unit plays a critical role in driving AstraZeneca's success. Working together with MedImmune, our global biologics arm, and Global Medicines Development (GMD), our late-stage development organisation, we are ensuring we deliver a sustainable and innovative pipeline.



Our IMED Biotech Unit applies its skills, capabilities and technologies across the company to enable the AstraZeneca R&D engine and accelerate the progress of the pipeline. Through great collaboration across our three science units we are confident we can deliver the next wave of innovative medicines to transform the lives of patients around the world.

Combining expertise to advance new cancer treatments

Despite major advances in healthcare and science, the world still faces unmet medical needs. More than eight million lives are lost each year to cancer, with one in six people developing the disease in their lifetime.

IMED and MedImmune are exploring novel combinations of immunotherapies based on innovative antitumour strategies to fight a wide range of cancers.

AZD6738 (ATR) (small molecule) + olaparib (small molecule)	Durvalumab (PDL-1) (large molecule) + AZD6738 (ATR) (small molecule)	osimertinib (small molecule) + savolitinib (small molecule)
Synergy among two molecules with the same mechanisms	Synergy between mechanisms	Synergy in certain cancers only when combined
Phase II gastric cancer	Phase I squamous cell cancer (head and neck)	Phase II early responses in non-small cell lung cancer

IMED Biotech Unit

Focuses on using state-of-the art discovery platforms and translational science in small molecules, oligonucleotides and other emerging technologies.

Global Medicines Development (GMD)

Focuses on late-stage development of our innovative pipeline, transforming exciting science into valued new medicines and ensuring patients around the world can access them.

MedImmune

Focuses on biologics research and development in therapeutic proteins, monoclonal antibodies and other next-generation molecules to attack a range of diseases.

Antibody Drug Conjugates

Developing the next generation of Antibody Drug Conjugates (ADCs) is one of the four strategic pillars of the AstraZeneca and MedImmune Oncology strategy in advancing cancer therapies. It provides a great example of how we combine the expertise of IMED and MedImmune to develop a targeted ADC approach with the potential to optimise delivery of the cancer drug to the tumour.

An ADC is a three-component system consisting of a potent cytotoxic agent and a biodegradable linker, known collectively as the ‘payload’, and a monoclonal antibody. The antibody binds to specific markers at the surface of the cancer cell and the whole ADC is then internalised within the cancer cell where the cytotoxic agent is released.

ADC payloads are highly complex organic molecules with a typical synthesis of 30-40 steps which, combined with their high cytotoxicity, makes them very complicated to handle.

MEDI4276, an anti-HER2 antibody drug conjugate currently in Phase I, has a 36-step synthetic route to the cytotoxic agent and conjugation to the antibody and includes several high potency intermediates, which make scale-up for production particularly challenging.

This year, the Pharmaceutical Sciences team in IMED worked closely with the Antibody Discovery and Protein Engineering group at MedImmune to bring expertise in chemical process development and analytical chemistry to address these challenges. By utilising a high containment facility and modifying the route of synthesis, the team’s innovative approach delivered the complex ADC payload with an increased product yield and reduced cost, contributing to MEDI4276 achieving first time in man in 2016.

“

Collaborating as a cross-functional team, together with our IMED Biotech Unit colleagues we are advancing our Oncology portfolio in both small molecules and biologics. By following the science, our teams are united in their efforts to fight cancer, leveraging our combined expertise to progress our overarching immuno-oncology strategy to get treatment options to patients as quickly as possible.”

David Berman, Head of Oncology Innovative Medicines unit and Senior Vice President, MedImmune

Osimertinib

Through 2016 we have continued to see impressive progression with osimertinib following the 2015 US Food and Drug Administration (FDA) approval in non-small cell lung cancer (NSCLC). Key to delivering this success is the collaborative approach of the IMED Biotech Unit with Global Medicines Development (GMD) to drive science forward, and with our Commercial organisation to ensure this science translates into new understanding of treatment with healthcare professionals and therefore new options for patients.

As an evolution to the approved companion diagnostic test which identified the EGFR-T790M mutation using tumour-biopsy samples, the Personalised Healthcare and Biomarkers (PHB) team in partnership with Roche drove the development of an innovative blood-based circulating tumour DNA (ctDNA) diagnostic test. By working closely with teams across

AstraZeneca as well as regulatory agencies, we achieved FDA approval of the diagnostic in September 2016 – a world first. Furthermore, colleagues in PHB and IMED Oncology worked with our commercial teams to successfully define the clinical utility and enhance market uptake, enabling NSCLC patients unsuitable for tumour biopsy to be tested with a non-invasive option and providing results with a rapid turnaround time to help make osimertinib available to the ~40 per cent of patients with NSCLC eligible for treatment but unable to provide a tissue biopsy.

IMED Oncology continues to collaborate with teams across AstraZeneca to evaluate the emerging mechanisms of osimertinib resistance. Working closely with GMD, we have been able to fill data gaps through the collection of paired tumour biopsies as part of the Phase III FLAURA study, investigating osimertinib as first-line treatment

in NSCLC. In addition, the IMED Biotech Unit has pioneered the use of various plasma assays to monitor for primary osimertinib resistance using both baseline and early time-point blood samples from the completed AURA trials, which demonstrated the benefits of osimertinib as second line therapy. This ground-breaking collaborative effort has established AstraZeneca as a scientific leader in the NSCLC community, which has been demonstrated through invited speakerships at FDA workshops and international conferences, as well as through publication of numerous high impact papers.

Collaborating across AstraZeneca

Discovery Sciences

Where it all begins – seeking potential hits for new drug targets to fuel the AstraZeneca pipeline.

Drug Safety Metabolism

Delivering a safe and effective pipeline – testing the safety of how drugs metabolise in the body.

Pharmaceutical Sciences

Turning science into medicine – developing the first formulations of potential medicines to determine how they are delivered in the human body.

Early Clinical Development

Where science meets the patient – conducting clinical trials to test potential medicines in humans for the first time, plus quantitative modelling to inform clinical drug development for IMED and GMD.

Personalised Healthcare and Biomarkers

Making medicine personal – partnering across science units and commercial teams to deliver a personalised healthcare approach and companion diagnostics.

IMED Operations

Making great science possible – working with groups across the enterprise to deliver excellence in cross-functional portfolio, facility and systems management.

“

The osimertinib team worked seamlessly across organisational boundaries. You couldn’t tell who was from which group – the energy was electric! It was ‘all hands on deck’ and an exceptional example of how a shared passion for making a difference to patients’ lives brings out the best in our AstraZeneca people.”

Ruth March, VP Personalised Healthcare and Biomarkers

“

The availability of an Food and Drug Administration (FDA) -approved, blood-based companion diagnostic is a tremendous step forward for patients with lung cancer in need of a high-quality test that provides results with a rapid turnaround time. This development offers an important option for the identification of the T790M mutation in patients with metastatic EGFR mutation-

positive non-small cell lung cancer (NSCLC) who have progressed on an EGFR TKI medicine, for whom a tissue biopsy may not be feasible. Delivering targeted therapies, such as osimertinib, to the right patients at the right time demonstrates our commitment to testing and quality companion diagnostics.”

Andrew Coop, Vice President, US Medical Affairs, Oncology, AstraZeneca

Collaborating and sharing data to redefine the future of drug discovery

Our teams are leading the way in creating open research environments that go beyond the usual collaboration models. We are always on the lookout for novel ways of working with others to advance medical science and speed up delivery of new medicines to patients.

In 2016, we continued to build our network of innovative collaborations with academic institutions, biotech and pharmaceutical companies in our main therapy areas. Our pioneering work in genomics is truly best in class, with collaborations including Human Longevity, Wellcome Trust Sanger Institute, Stratified Medicines Scotland and the Institute for Molecular Medicine. We also forged collaborations to work on rapidly-evolving technologies such as modified mRNA, epigenetic drivers, bicyclic peptides and innovations in personalised healthcare—driving scientific progress across our entire portfolio.

Out-licensing is another area of focus to ensure we are developing indications that will benefit patients outside our main therapy areas. This includes our work with BioHaven Pharmaceuticals on Rett syndrome (RTT), a neurological disorder caused by mutation of the X-linked MECP2 gene that results in

the progressive disruption of excitatory and inhibitory neuronal circuits. We are also working with Miotherix on P2RX7 purinoceptor up-regulation, which has been shown to be responsible for the death of muscles in the mdx mouse model of DMD and human DMD lymphoblasts via autophagy.

“My experience of working with the scientists at AstraZeneca has been excellent – both in terms of their genuine desire to contribute to driving the projects forwards and in terms of the clear and open communication and intent.”

Simon Ward, Drug Discovery Centre, University of Sussex, UK

“Partnering with academic and industry scientists outside AstraZeneca is critical. Combining our strengths and resources with the expertise and knowledge of our partners will ultimately benefit patients.”

Kumar Srinivasan, VP Scientific Partnering and Alliances, IMED Biotech Unit

Highlights

Partnering: strengthening our focus on scientific leadership

We partner with top scientists from across the globe. In 2016, our IMED teams established around 35 major collaborations covering our main therapy areas and exciting new technologies that are set to drive progress in medical science innovation for years to come.

We are also committed to ensuring that we contribute to scientific advances that will benefit patients outside our main therapy areas; we do this through Open Innovation and externalisation.

In 2016 alone:

We marked the first programme from our collaboration with Moderna Therapeutics to progress towards clinical trials when we filed a Clinical Trial Application (CTA) for AZD8601 with the Paul Ehrlich Institute and the German Federal Ministry of Health. This significant step highlights our progress towards treatment for serious cardiovascular, metabolic and renal diseases as well as cancer.

In Respiratory, we announced a key licensing agreement with our partner Insmed for the global exclusive rights to AZD7986, a novel oral inhibitor of dipeptidyl peptidase I (DPP1). AZD7986 may decrease the damaging effects of inflammatory diseases, such as non-cystic

fibrosis bronchiectasis, by inhibiting DPP1 and its activation of NSPs.

Our multi-target collaboration across Respiratory and Cardiovascular and Metabolic Diseases (CVMD) with Bicycle Therapeutics, for the identification and development of a novel class of small molecule medicine called bicyclic peptides (Bicycles®), has allowed us to explore the possibilities of overcoming many of the limitations for existing drug modalities.

We also bolstered our partnerships in CVMD with our worldwide collaboration with APT Therapeutics. Our investigation of an innovative human apyrase therapy, for the treatment of thrombotic disease, is uniquely different from current FDA-approved antithrombotic drugs that can increase bleeding risk.

Our success in existing partnerships has also led to further scientific innovation. We entered into a partnership with Eli Lilly & Company (Lilly) to co-develop MEDI1814, an antibody selective for amyloid-beta 42, which is currently in Phase I trials as a potential disease-modifying treatment for Alzheimer's disease. This agreement builds on our existing collaboration related to AZD3293, a BACE inhibitor in two pivotal Phase III trials.



A global science network

With research facilities in a number of the world's established and emerging scientific centres, we recognise the importance of leveraging our footprint to connect with the best external science, accelerating our scientific partnerships and alliances with leading academic and biotech partners around our sites as well as in other key locations across the globe. Our open innovation partnerships with academic translational drug discovery centres and government-linked agencies include leading global scientific institutions, which help facilitate our interactions with prominent scientists. Our partners include:

United Kingdom: Cancer Research UK (CRUK) and the Medical Research Council (MRC).
United States: National Institutes of Health (NIH) and the National Center for Advancing Translational Research (NIH-NCATS).
Taiwan: National Research Program for Biopharmaceuticals (NRPB).
Singapore: National Health Innovation Centre (NHIC).
Australia: Universities of Queensland and Adelaide commercialisation units, UniQuest and Adelaide Research & Innovation.

✓ Scientist examining a human placenta double stained using two different fluorescent antibodies and a nuclear counterstain by confocal microscopy



“AstraZeneca has been very bold in making things available to academia, from talking to academia on their own terms, to learning from academia and gently teaching us about themselves. We feel we’re dealing with colleagues.”

Sir Hugh Pelham, Medical Research Council Laboratory of Molecular Biology, UK

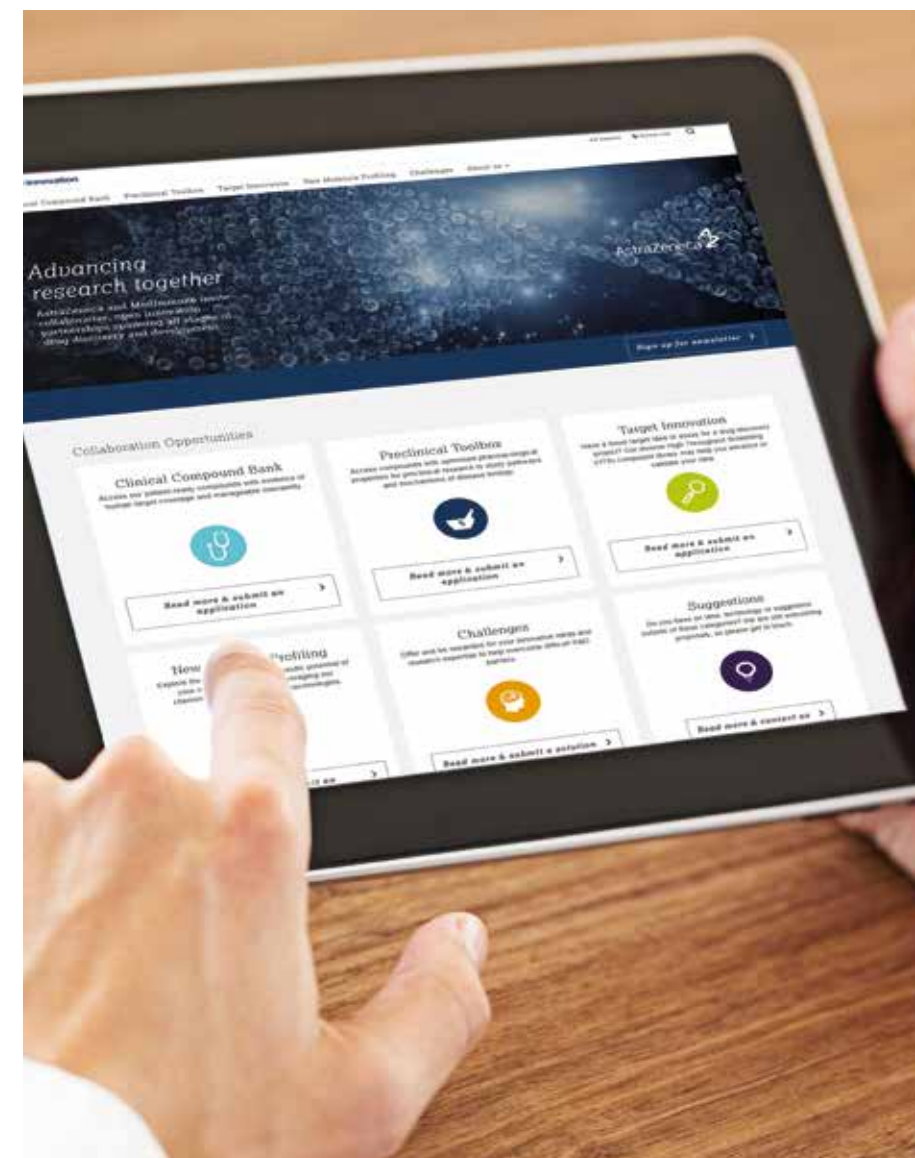


“Collaborating with AstraZeneca has led to a completely new and exciting model for academic-industry partnership. We work side-by-side with AstraZeneca scientists to connect our advanced computational and genomic approaches with deep disease area and drug development expertise at AstraZeneca Emerging Innovations (AZEI) in a way that allows for rapid and nimble exploration of new therapeutic opportunities.”

Joel Dudley, Director of the Institute for Next Generation Healthcare and Associate Professor of Genetics and Genomic Science, The Icahn School of Medicine at Mount Sinai

Open innovation

Our Open Innovation programme, designed to create a permeable research environment where scientists both inside and outside AstraZeneca can more freely share their ideas and collaborate on projects, achieved great success in 2016. We reached 150 partnerships and have now received over 400 proposals since launch in 2014.



“

I appreciated the openness in our discussions and the data and advice I received from AstraZeneca. The process of obtaining the drug has been straightforward and I am already making plans for another project that I would like to discuss with AstraZeneca. AstraZeneca should be congratulated for their Open Innovation initiative and sharing with the academic community their compounds for repurposing. It would be nice if the rest of big pharma could follow AstraZeneca's example in this matter.”

Efi Kokkotou, Beth Israel Deaconess Medical Center, Harvard University, USA

◀ AstraZeneca Open Innovation website

An invitation to innovate

Momentum for our Open Innovation programme in 2016 was impressive. Our Open Innovation portfolio now has 22 ongoing or planned clinical trials and over 100 ongoing or planned pre-clinical trials. We also launched two target innovation projects in 2016 with the Centre for Drug Research and Development (CDRD), Canada's national drug development and commercialisation centre, and with medical research charity MRC Technology (MRCT) in the UK.

At the heart of our Open Innovation programme is our collaborative environment. We recently redesigned our Open Innovation portal to make it easier than ever for potential partners to investigate the compounds and tools available to them and submit proposals across a range of drug discovery and development activities. Our Open Innovation partners can now access over 250,000 compounds from our collection for screening a novel drug target.

Our Open Innovation portal makes it easy for external scientists to access our full range of Open Innovation programmes and find ways to advance medical science together:

A compound bank of 'patient-ready' active and discontinued compounds.

A pharmacology toolbox of compounds with strong pharmacological properties.

A collaborative effort to validate new targets, which may include high-throughput screening.

Advanced cheminformatic capabilities to explore therapeutic potential of new molecules.

R&D challenges open to anyone willing to offer innovative solutions.

We believe that by sharing knowledge and resources with other scientists, we collectively stand a much better chance of delivering novel effective treatments for serious diseases. One example of how we are putting Open Innovation into action is NiCoLa-B, the world's most advanced drug discovery robot, which is capable of making drug discovery smarter, faster and cheaper. We are making NiCoLa-B available to external research partners including Cancer Research UK and the Medical Research Council to help accelerate their medicines research.

Since its launch in 2014, our Open Innovation programme has established a proven track record of success:

Received over 400 proposals from scientists in 28 countries across four continents.

Formed 150 new partnerships – 90 per cent with academic scientists and 10 per cent with science companies.

Initiated or planned, with our partners, over 150 pre-clinical and 30 clinical studies.

“

At AstraZeneca, we have great scientists doing truly groundbreaking research. But in order to speed up the delivery of the next generation of medicines, we also need to access the best science outside our labs. We are always looking for new ways of working with academic or industry researchers who share our passion for advancing the science and helping patients with unmet medical needs. We pride ourselves on being one of the most porous and open collaborators in our industry.”

Mene Pangalos, Executive Vice President IMED Biotech Unit and Global Business Development

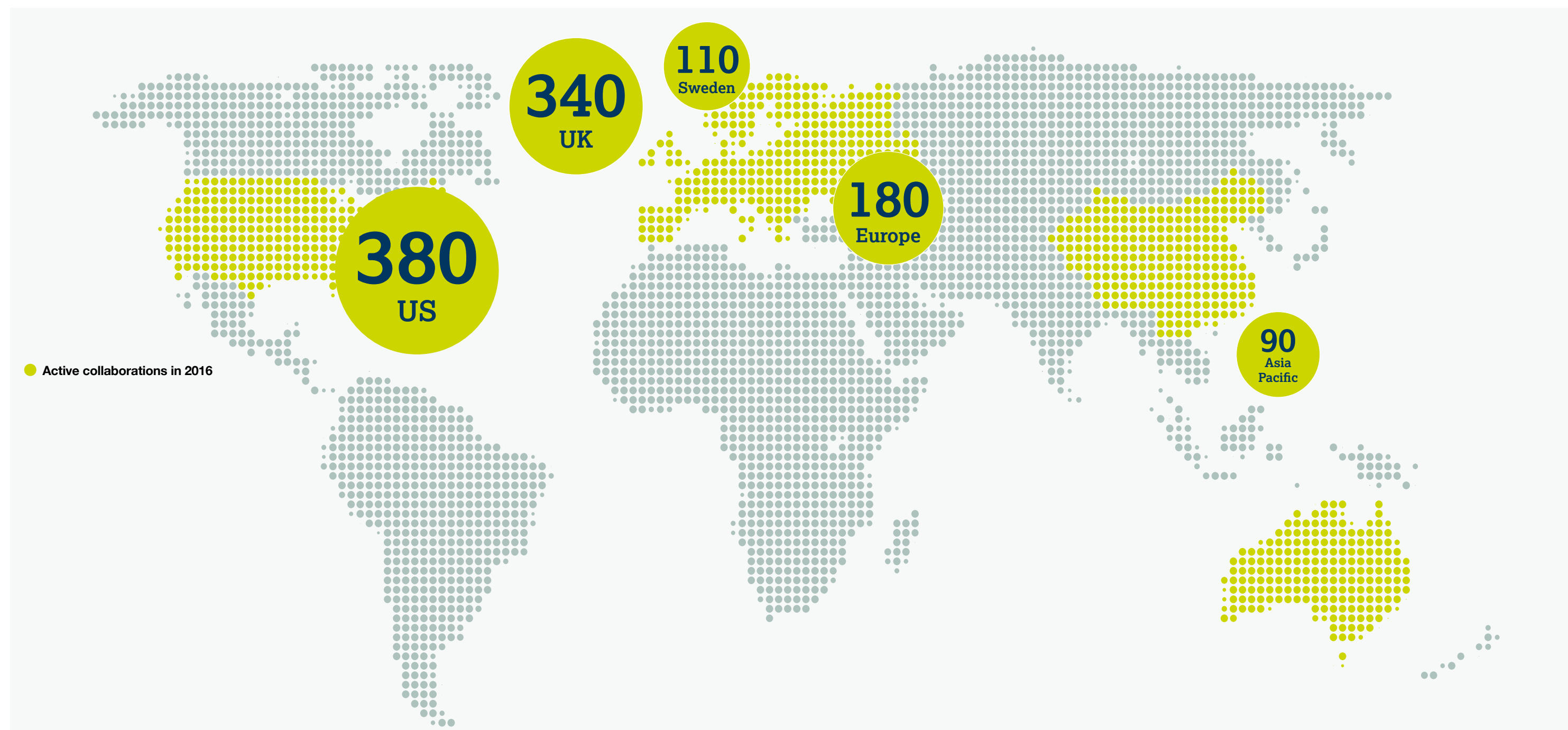
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I hope that our pioneering approach to Open Innovation will spread across the industry and academia and become the new normal. It is enabling us to advance projects that neither we nor our partners would be able to do alone and create new therapies for patients.”

Craig Wegner, Executive Director, Emerging Innovations, Scientific Partnering & Alliances, IMED Biotech Unit

Innovation without boundaries

With research facilities in a number of the world's established and emerging scientific centres, we recognise the importance of leveraging our footprint to connect with the best external science, accelerating our scientific partnerships and alliances with leading academic and biotech partners around our sites as well as in other key locations across the globe.



Foundation Medicine and AstraZeneca: Driving precision in Oncology

Established in 2012, our work with Foundation Medicine has come a long way in the last five years – the collaboration has become deeper and more complex and we now have a partnership that spans our entire Oncology pipeline, starting off in early Phase I trials right through to our marketed products.

Our partnership centres on personalised healthcare – getting the right treatments to the right patients at the right time. Foundation Medicine is one of the pioneers in developing methodologies for DNA sequencing and by using their technology, we can comprehensively assess tumour samples from our early clinical trials to understand the biomarkers associated with a response to our drug programmes. We are then able to take those markers and develop them into assays to accelerate patient recruitment for clinical trials and ultimately companion diagnostics for approved drugs.

Foundation Medicine can look at over 300 genes and comprehensively assess the profile of a tumour and because of this, we have been able to make discoveries, including identifying that somatic BRCA1 and BRCA2 mutations would confer susceptibility to PARP inhibitors.

We have also identified a whole series of genes involved in homologous DNA repair beyond BRCA1 and BRCA2 that are important in predicting which patients will respond to this class of therapeutic. In addition, we have developed new biomarker strategies involving analysis of chromosomal copy number changes that we believe are going to be able to expand the range of patients who can be treated with several other classes of drugs in AstraZeneca's pipeline.

The future of our collaboration looks bright and over the past five years we have been able to begin to routinely characterise the DNA based underpinnings of a given patient's tumour. This means that testing is becoming more widely used and doctors are beginning to understand it better – which ultimately benefits patients.



“AstraZeneca has a tremendous and diverse portfolio of Oncology assets, but for me, one of the most exciting pieces or most rewarding pieces is the thought and science that drives their application and integration of those assets into clinical trials and clinical practice.”

Vincent Miller, Chief Medical Officer, Foundation Medicine

“This collaboration is special because of our shared philosophy on the importance of identifying the right patients for the right targeted therapies and our desire to leverage all the tools available to us to make that a reality. The clinical and scientific thought leaders at AstraZeneca are very much respected within Foundation Medicine. They are really the right partners for us to collaborate on truly advancing the field of molecularly focused medicine.”

Melanie Nallicheri, Chief Business Officer and Head of Biopharma, Foundation Medicine

Inspiring great scientists

Our commitment to scientific leadership rests on our ability to attract and retain the best scientists. Nowhere is this commitment more evident than in the way we recruit, develop and inspire our people. In 2016 alone, the IMED Biotech Unit welcomed 125 new starters.

We want to attract the brightest minds, the best talent, the boldest innovators – people who share our passion for science and belief in the possible. In return, we offer a working environment that truly reflects our ambition to push the boundaries of science – a place where curiosity, innovation and collaboration flourish, where drive and determination is rewarded and where great science comes alive.

Diversity

We believe that great science comes from diverse teams with different backgrounds. And the vision for our workforce is that it reflects the diversity of our patient population. That's why we are committed to creating an inclusive environment for our people and to foster this in 2016, all of our line managers received unconscious bias training.

As part of creating a diverse workforce we are committed to increasing the number of women in senior scientific roles. Since 2015 we have increased the number of women in senior scientific roles to 38 per cent and our aim is to further increase this going forward.

Our 'Women as Leaders' programme gives our female scientists a chance to come together to discuss issues such as career progression and personal development, with a view to increasing their awareness of opportunities and the confidence to pursue them. People that have attended the programme have seen a 30 per cent promotion rate, and gained sponsors, coaches and mentors. 120 women have now attended and the programme has been rolled out globally.

Our 2016 Annual Women's Summit, held in Gothenburg, Cambridge and Gaithersburg brought together over 1,100 employees to actively participate in conversations on diversity and inclusion in the workplace.



“

We've made sure we have a balanced recruitment process, we've trialled blind screening of CVs to remove unconscious bias to gender. We also employ diverse panels for all our interviews. This helps us ensure we recruit the best person for the right role.”

Amy Taylor, Associate Director, Strategic Planning and Operations, ECD, Chairperson, Network of Women UK

Development

Continuous development of our people is high on our agenda and the majority of our development comes from on-the-job experience. From our Development Marketplace to cross-team secondments and shadowing opportunities, our programmes ensure we continue developing the skills and capabilities to equip our scientists to be the best they can be. Throughout 2016, we saw more than 60 IMED colleagues take up assignments outside their core role to broaden their learning and experience.

In 2016 we welcomed more talented colleagues to our team, including accomplished scientists, respected academics and new graduates. They came for many reasons – the commitment to great science, the opportunity for personal development, the open culture, the inspiring values, the chance to be part of something life-changing. Whatever the reason, they have joined a truly great place to work.



“

My secondment in IMED Communications has given me a great opportunity to learn new strategies, strengthen my network and push my boundaries. And because it is a part-time assignment, I still get to do a job I love driving delivery for Oncology clinical projects.”

Melinda Foulk, Drug Project Information Manager, IMED Operations

Our people make us stand out and our values define us:

We follow the science

We put patients first

We play to win

We do the right thing

We are entrepreneurial



“

Thanks to the IMED graduate programme, I have gained experience from both IMED RIA and CVMD. Foremost, this has given me a comprehensive knowledge of drug development, but also a broad network of scientists. This has proven to be very valuable and continuously provides me with new ideas.”

Linn Strindhagen, IMED Graduate Scientist

Inspiring great scientists

Time for Science

As scientists, our focus must remain on breakthrough science in order to ensure we deliver life changing medicines.

In 2016, IMED saved over 100,000 hours to free up more Time for Science. By creating process efficiencies and time savings through better meetings, simplified procedures, improved IT and increased lab support, we have made significant progress.



In PHB, Time for Science is all about making the impossible, possible. What this means is that not only do we release time for science, but we also deliver more to our ultimate customers, the patients.”

Ruth March, VP Personalised Healthcare and Biomarkers



Time for Science means efficiency, innovation and energising. It reduces bureaucracy and allows our scientists to focus on science – so critical for our success.”

Tony Johnson, VP Early Clinical Development



Highlights from our Time for Science initiative include:

>6,000 hours saved through analysis and management of next generation sequencing data through better IT, robotics and automation.

1,400 hours saved through automated technology for high-throughput screening of human adipocytes.

1,600 hours saved through improved project planning, tracking and reporting through a cloud-based solution.

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1,400

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Our strategic science centres

UK – Cambridge

In 2013, AstraZeneca announced plans to move its UK research activities to a new \$500 million facility in the centre of Cambridge. Our new facility at the Cambridge Biomedical Campus will become AstraZeneca's largest centre for Oncology research, as well as hosting scientists focused on cardiovascular and metabolic diseases (CVMD); respiratory, inflammation and autoimmune diseases (RIA); and conditions of the central nervous system.

2016 has seen almost 2,000 employees move to Cambridge, to start the process of bringing together under one roof our small molecule and biologics research capability from both AstraZeneca and MedImmune for the first time in the UK.

AstraZeneca's registered address has now moved to the Cambridge Biomedical Campus, 1 Francis Crick Avenue, at which marks a key point in delivering our science-led strategy. The construction of the new R&D centre and corporate headquarters continues and the growing Campus will successfully create an optimum environment for emerging businesses to thrive.

UK – Macclesfield

Our Macclesfield site is an important hub for AstraZeneca and the second largest pharmaceutical manufacturing site in the world.

A centre of innovation, science and high-tech manufacturing, it's a place where molecules are turned into medicines and is home to the Pharmaceutical Sciences team, who joined the IMED Biotech Unit in 2016. With large-scale lab facilities, the site hosts cutting-edge technology to enable the Pharmaceutical Sciences team to implement intelligent design of medicines and delivery systems.

Seven miles away at Alderley Park, now owned by Manchester Science Partnerships, we retain a small number of IMED scientists until the R&D exit of the site is complete and colleagues join together in our new Cambridge facility.

Sweden – Gothenburg

Our strategic R&D centre in Gothenburg is the centre of our research for two of our main therapy areas; CVMD and RIA. It is also home to a large number of our scientists from our early phase Discovery Sciences function and our Drug Safety and Metabolism (DSM) team. In addition to this we have teams from IMED Operations, Scientific Partnering & Alliances, Early Clinical Development (ECD) and Personalised Healthcare and Biomarkers (PHB). During 2016 we also welcomed a new function, Pharmaceutical Sciences.

All our sites create an environment to share ideas and aim to tap into great science. Our Gothenburg 'Coffee Lab' helps employees based there do just that. The Coffee Lab is the place to meet and share ideas, and in 2016 we saw true evidence of our culture of collaboration pushing the boundaries of science, with breakthrough modalities now in development.

US – Boston

Boston is home to AstraZeneca's small molecule research in North America, with state-of-the-art laboratories, just west of the city centre. Our scientists focus on the discovery and development of new medicines for Oncology and conditions of the central nervous system, in collaboration with other functions from across IMED.

Our Boston site is developing a clear identity and advancing the goal of a culture in which 'everyone knows everyone'. A key highlight for the site has been the cross-functional teams from Oncology, Discovery Sciences, Pharmaceutical Sciences, DSM and ECD delivering innovative ways to target a trio of new drug targets (MCL1, CDK9 and Bcl2/xL) for the Oncology cell death portfolio.

In Boston we are involved in a number of local academic and industry collaborations. Our partnership with Tufts University is a true academia-industry hybrid, where a group of our scientists are working within Tufts' Neuroscience department. In addition, our collaborations with Foundation Medicine, Dana-Farber Cancer Institute and Massachusetts General Hospital drive innovative pre-clinical and clinical science for discovering and developing new cancer medicines.

China – Shanghai

Our small-molecule research facility in China is located at the Zhangjiang High Tech Park in the Pudong area of Shanghai. Our research teams here focus on discovering potential new medicines that meet the unique needs of patients in Asia and drive forward translational science across our main therapy areas.

Below: AstraZeneca's Strategic R&D Centre in Gothenburg



Vibrant BioHubs

Our BioHubs offer an energising environment enabling cross-fertilisation of ideas.

Gothenburg

Our Gothenburg BioHub continues to grow and foster life science discovery with a total of 20 companies now part of the hub, including our first international company, MentorMate, who announced their decision to join in 2016. AstraZeneca is now in active collaboration with five of the Gothenburg BioHub companies, such as Antares, a company specialising in advanced imaging techniques for use in cardio-metabolic and respiratory clinical trials. By combining different values, ideas and perspectives in the same place, our vision is to generate a climate of open innovation that will help grow and nurture the Scandinavian life science ecosystem.

Boston

Our Boston site houses Gatehouse Park, which launched in September 2015. The site has undergone a huge transformation in the past year, creating one of the Boston-area's fastest growing BioHubs. In addition to the Neuroscience function, which has now moved to the hub, six research companies are in place sharing and exchanging ideas - two of which, Persomics and Morphic TX, expanded their presence in 2016.

Alderley Park

The BioHub at Alderley Park supports the creation and growth of successful life science companies, with an optimum environment for emerging businesses to thrive in the the UK. 2016 saw the second anniversary of the Alderley Park BioHub and established the site as the leading science facility in the North of England.

Left: IMED research facility in Boston, US

Right: IMED research facility in Shanghai, China



"AstraZeneca has been on a transformative journey over the past few years, placing great science at the heart of our strategy. In addition to drugs targeting critical cell death pathways, the Boston site has become our centre of excellence for haematological malignancy biology, model systems and drug discovery and is driving our interactions with colleagues at Acerta as we develop the BTK inhibitor, acalabrutinib.

Here on the Boston site, we also have a fantastic opportunity to create a unique research environment – a close, connected group of talented AstraZeneca scientists working alongside innovators and entrepreneurs from the BioHub, as well as Boston academia and industry – allowing us to explore collaboration and interconnectivity between teams even further."

Steve Fawell, VP Head of iScience, IMED Oncology

"Here at AstraZeneca in Gothenburg we have a vision of becoming one of the best R&D sites in the world. We are 2,500 colleagues from over 50 different nationalities all working towards this goal with genuine commitment and enthusiasm.

Having representation from not only all areas of the development process, from first idea to when the medicine reaches the patient, but also from several external biotech companies with whom we share expertise and infrastructure, really forms a unique basis for great science.

To support innovation and collaboration, we have created a working environment in a class of its own and, earlier this year, AstraZeneca Gothenburg was awarded recognition as one of the best workplaces in Sweden."

Jenny Sundqvist, Gothenburg Site Director

Building our future

Our new Cambridge home

Effective since May 2016, Cambridge is now the location of our global corporate headquarters. While construction of our new home and strategic centre continues at 1 Francis Crick Avenue on the Cambridge Biomedical Campus, we have made significant progress in realising our ambition to follow the science here.

Since announcing our move in 2013 we have accelerated our transition to Cambridge ahead of the completion of our new facility, with over 2,000 of our staff now based across interim sites, all of whom are actively engaged in Cambridge's scientific, academic, clinical and business ecosystem. By joining forces with MedImmune, our global biologics research and development

arm, which has a long-standing presence in Cambridge, we have been able to accelerate our scientific productivity and look forward to having both of our science units in the same building.

We are realising the value of co-locating our strategic science centres with leading academic and life science hubs, while also enabling our talent and collaboration partners to deepen their contribution to Cambridge's scientific community.

Our presence here has many facets. We are able to bring and develop our capabilities as a scientific partner, a business, a sustainability-focused corporate citizen and a member of the community, inspiring the next generation of scientists.



CGI image of our new Global R&D Centre, 1 Francis Crick Avenue, Cambridge Biomedical Campus



Being part of the very best science hubs in the world is an integral part of delivering our science-led strategy. Cambridge provides a geographic concentration of scientific talent, technology and diversity in thinking that will enable conversations, partnerships and collaborations. I have no doubt these relationships will lead to new and unanticipated scientific and medical breakthroughs.”

Mene Pangalos, Executive Vice President IMED Biotech Unit and Global Business Development

Establishing Scientific Leadership

2016 was an exciting time for IMED as we continue to establish ourselves in the Cambridge science community. Our new R&D Centre will become the company's largest centre for Oncology research and a centre of excellence for pre-clinical research, medicinal chemistry and high throughput screening. Beyond cancer research, our R&D will focus on cardiovascular and metabolic diseases, respiratory, inflammation and autoimmune diseases and conditions of the central nervous system.

We chose to be in Cambridge because we wanted to be at the heart of one of the best scientific centres in the world and we believe that the next generation of medicines will come from working collaboratively with healthcare, academia, research and business communities.

2016 Highlights on Cambridge Build Progress

1 million total hours worked on our construction site as of August 2016

Completion of the Energy Centre steelwork - this is connected to the R&D Centre by a service tunnel which is 14 metres below Francis Crick Avenue and seven tube carriages long

99.54% waste from the new site has been diverted from landfill (on and off site recycling/incineration)

Virtual reality tour of the R&D Centre developed, where staff can walk around the building to get a feel for what it will be like to work at the new facility

1,000

Lab blocks in the new build are more than 1,000 square metres each

Inspiring the next generation of scientists

Building on more than 25 years presence in the Cambridge science community established by MedImmune, we have seen our initiatives in the local community grow in both depth and range as the size of our employee community grows.

At an academic level, we have three joint schemes developed across AstraZeneca and MedImmune to support more than 80 PhD scholarships and eight clinical lectureships. This represents an annual investment in excess of \$1.5 million once fully up and running.

Our programmes are designed to identify, train and mentor start-up life science businesses. AstraZeneca's volunteer mentors come from a range of roles, with expertise in areas like business development, intellectual property and innovation alliances.

We also have an active community support scheme in Cambridge focused around science-based educational events for young people. Over 160 staff members are actively involved in science outreach in the community and their volunteering supports:

Science in Pictures, an artwork installation displayed on the construction hoardings around our future home on the CBC; it is a collaboration with nine local schools and the imagination and creativity of over 400 local school students aged 7-17.

The Cambridge Science Centre, helping 50,000 children, young adults and their families discover life science.

The Cambridge Science Festival, through outreach activities, talks and sponsorship. In 2016, over 70 staff volunteers took part and overall the Festival attracted 60,000 visitors.

The University Technical College Cambridge, through an annual challenge for 14-18 year olds.

Shaping and delivering science activities and programmes with local schools.

Mentoring young people interested in pursuing science, technology, engineering and mathematics (STEM) careers through our partnership with Career Ready.



◀ Cross section of cells from tumour biopsy. The cells are stained to confirm presence of target receptors for AstraZeneca and MedImmune therapeutic molecules

Opening up our site to staff and visitors alike

In 2016 we hosted visits for employees who will be located in the new building, providing an opportunity to see the progress we are making. Under the close guidance of the new build project team, visits covered key areas of the extensive site located across two plots of land on the Cambridge Biomedical Campus (CBC), with the aim to see progress directly and visualise future workspaces.

Highlights from the site visit tours include:

Mock up space: a testing area designed to try out equipment and materials before these are commissioned. Here employees were able to see early laboratory designs and office layouts and were given a first-hand insight into the thinking and consultation that has been going on to create their collaborative future workplace.

Scale the Energy Centre: a large, three-story building with the purpose of providing uninterrupted, clean energy to our R&D Centre across the road, via an underground tunnel.

Descent into the R&D Centre:

a basement area where the Research Support Facility will be located, enabling employees to walk right through the site and around the perimeter, carefully moving around the construction teams so as not to disrupt the complex building process.

The site has been attracting a great deal of interest both inside and outside our company. With various VIPs visiting over the course of the last few months, we also welcomed the AstraZeneca Board to the site in November. This was a great opportunity to showcase our progress and bring to life how our presence in Cambridge is making a difference to our scientific productivity.

Earning our place in the 'Cambridge Phenomenon'

The success of Cambridge is built on a triple helix of research, industry and government. Together this creates a powerful force for change.

Our 130 strategic collaborations in Cambridge are about advancing the development of life-changing medicines for patients, by working across organisations and bringing together different areas of expertise.

These example collaborations within the Cambridge cluster have unprecedented potential:

Launched an integrated genomics initiative and based our Centre for Genomics Research in Cambridge.

Collaborated with Microsoft to develop a new cancer treatment modelling system.

Initiated multiple drug discovery projects with Cancer Research UK (CRUK), with 60 scientists based in CRUK laboratories at the Cambridge Institute.

Established a collaboration with Bicycle Therapeutics to identify and develop bicyclic peptides for the treatment of respiratory, cardiovascular and metabolic diseases.

Evolved our blue skies collaboration project with the Laboratory of Molecular Biology (LMB), using CryoElectron Microscopy to solve the structures of key targets in the DNA damage response pathway.

Established a world leading mass spectrometry capability jointly across AstraZeneca, MedImmune, the LMB and the University of Cambridge.

Developed the AstraZeneca Medical Research Council (MRC) UK Centre for Lead Discovery.

Initiated a new collaboration with the Crick Institute to explore new avenues of medical research and drug discovery across a broad range of diseases.

Ongoing partnership with Cambridge Judge Business School through the Accelerate programme – designed to identify, train and mentor start-up life science businesses.



CGI images of our new Global R&D Centre, 1 Francis Crick Avenue, Cambridge Biomedical Campus

130

Collaborations across AstraZeneca and MedImmune in Cambridge, UK

Our reputation for scientific leadership

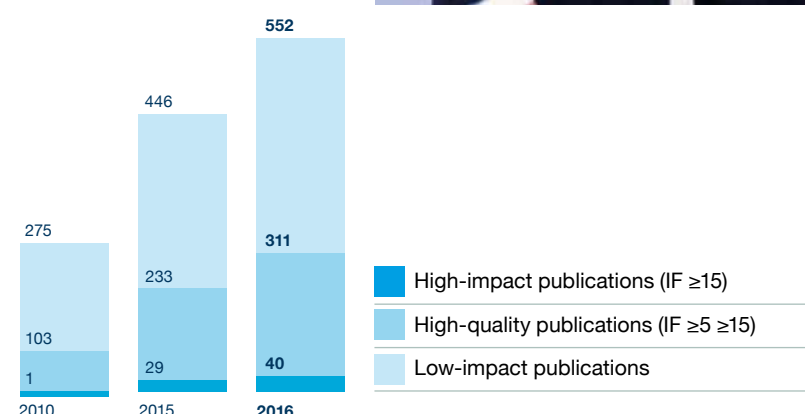
We are entrepreneurs in science, pushing the boundaries of what's possible each and every day. That's why we have cultivated an environment of excellence and open collaboration, together with a strong track-record of publications. Our entrepreneurial spirit gives our scientists the courage to take smart risks and not be discouraged by failure - we empower our scientists to not only keep abreast of the latest developments and breakthroughs, but to drive them.

Our ongoing commitment to develop a thriving science environment has generated significant progress in 2016, both inside the IMED Biotech Unit and within the broader scientific ecosystem.

Our publications

Our IMED scientists consistently publish in peer-reviewed journals with high impact and respected influence across the scientific community, validating our innovative work and reinforcing our ability to contribute to the foundation of scientific advancement.

We continue to outperform our publication achievements year-on-year and in 2016 we strengthened our scientific reputation through an increased focus on high impact and high quality scientific publications. High impact publications with impact factor ratings ≥ 15 are a hallmark of success for scientists and an important way to help us recruit and retain the best scientists from around the world. 2016 has seen IMED achieve great success in this area with 552 manuscripts published, 40 high impact and 311 high quality.



Exemplar key publications in 2016

Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer	Aurora kinase inhibitor nanoparticles target tumours with favourable therapeutic index <i>in vivo</i>	Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes
Journal of Clinical Oncology	Science Translational Medicine	Cell Metabolism
About the paper: Our scientists have analysed the genotype of patients entering the Phase I clinical study of osimertinib. Using highly sensitive digital PCR assays, the team were able to detect the relevant EGFR mutation (T790M) in tiny pieces of circulating tumour DNA (ctDNA) that are shed into the patient's bloodstream (plasma). The data from over 300 patients showed that those with a plasma detectable T790M EGFR mutation have the same clinical outcomes as those patients with a T790M mutation detected from a tumour biopsy.	About the paper: Through careful characterisation of efficacy, safety, pharmacokinetics and distribution in pre-clinical models, our scientists have developed the first nanoparticle pre-clinical proof-of-concept. The novel formulation was shown to extend reduction of tumour phosphorylated histone H3 levels <i>in vivo</i> for up to 96 hours following a single administration. In addition, increased efficacy was observed in multiple tumour models at half the equivalent dose of AZD1152 and showed minimal impact on bone marrow pathology.	About the paper: Patients with diabetes suffer from defects in the pancreatic islets of Langerhans, a functional centre within the pancreas that maintains blood glucose levels. Our team of scientists painstakingly separated over 2200 individual pancreatic islet cells across various islet cell sub-types and then utilised cutting-edge deep RNA sequencing technology at the Karolinska Institute Integrated Cardiometabolic Centre to characterise gene expression.
Impact: The outcomes suggest that patients can first be screened with a blood based test for the T790M mutation and, if positive, offered osimertinib without the need for a tumour biopsy.	Impact: The results demonstrate the ability of ACCURINS® to control release kinetics and maintain a high concentration of an Aurora B kinase inhibitor (AZD2811) at tumour sites. This facilitated prolonged pharmacodynamic effects, resulting in superior tumour growth inhibition and a reduction in off-tissue toxicities.	Impact: These studies have revealed novel functionality across islet cell sub-types demonstrating, for instance, that insulin-producing beta cells are not the only cell type important for glucose control and that there is a complex cell-cell signaling network underlying metabolic control.
Lead AstraZeneca authors: Kenneth Thress, Mireille Cantarini, Carl Barrett	Lead AstraZeneca authors: Susan Ashton	Lead AstraZeneca authors: Carina Åmmälä, Pernilla Eliasson, Eva-Marie Andersson, David Smith



It is so important that we change the perception of industrial science from one that is process driven, to one where we are recognised as translational scientists working at the cutting-edge of innovation. Our Publication Walls are just one example of how we emphasise the quality of our research to collaborators and visitors on our sites as well as to the wider AstraZeneca community."

Mene Pangalos, Executive Vice President IMED Biotech Unit and Global Business Development

IMED Science Awards

The 2016 IMED Science Awards celebrated some of the best breakthrough, high-impact science taking place at AstraZeneca. 160 global nominees were invited to join the IMED Leadership Team and members of the review panel at a black-tie celebratory dinner held in Cambridge.

The awards recognised outstanding scientific achievement; high impact work acknowledged as game changing. Winning teams and individuals received trophies and are also rewarded with tailored opportunities to support future research and enhance their careers.

At this year's event we were delighted that Pascal Soriot, CEO AstraZeneca could join us and present some of the awards. These included the Scientist of the Year to Simon Barry, IMED Oncology, as voted by IMED colleagues for his depth and breadth of scientific achievement across the Oncology portfolio.

✓ Publication wall of fame



IMED Science Retreat

The 2016 IMED Science Retreats were held across four IMED sites – Shanghai, Boston, Cambridge and Gothenburg, showcasing the breadth and depth of our research with over 360 posters presented.

The Science Retreat is an important event in the AstraZeneca calendar, enabling colleagues to immerse themselves in the latest developments outside their own areas of expertise, share ideas and look at how we can innovate new and different ways to drive scientific leadership.

“It’s great to see the different IMED teams interacting around such a vast breadth of science, I’m sure there will be some valuable insights and important actions coming out of this scientific meeting.”

Tony Johnson, VP Early Clinical Development

Our Publication Walls of Fame

To showcase the tremendous progress across IMED in the number and quality of publications, 2016 saw the launch of our Publication Walls of Fame on our sites in Gothenburg, Cambridge, Boston and Macclesfield.

Focusing primarily on our early science success to date, our publication walls are designed to recognise our outstanding scientists, share breakthrough research and showcase AstraZeneca’s scientific excellence with employees and visitors to our sites.



“It was a great pleasure to be invited to the IMED Science Awards celebration and see so many exciting scientists shaping the future of our science. Fantastic innovation, showing how we are really making the impossible, possible. Your research is having a tremendous impact on our pipeline, our company and to patients around the world.”

Pascal Soriot, Executive Director and Chief Executive Officer

High impact publications in 2016

Publication	Title	AstraZeneca and MedImmune authors
Cancer Discovery	Activating ESR1 mutations differentially impact the efficacy of estrogen receptor (ER) antagonists	Morrow C, Weir H, Lawson M, Goeppert A, Mazzola AM, Smith A, Wilson J
Nature Chemistry	An iron-catalysed C–C bond-forming spirocyclization cascade providing sustainable access to new 3D heterocyclic frameworks	Raubo P
Nature Reviews Drug Discovery	DNA-encoded chemistry: enabling the deeper sampling of chemical space	Goodnow R
Science Translational Medicine	AZD3759, a blood-brain-barrier (BBB)-penetrating EGFR inhibitor for the treatment of EGFR mutant non-small cell lung cancer with central nervous system (CNS) metastases	Yang P, Guo Q, Zhang X, Bai Y, Chen K, Cheng Z, Cohen-Rabbie S, Wang Y, Xu J, Yin L, Zhang D
Nature Biomedical Engineering	Long-term self-renewing human epicardial cells generated from pluripotent stem cells under defined xeno-free conditions	Drowley L, Wang Q, Plowright AT
Nature Reviews Cancer	Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer	Hughes A
Chemical Reviews	Ruthenium-CatalyzedAZide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications	Johansson J
Circulation	An IGF1R-Dependent Pathway Drives Epicardial Adipose Tissue Formation After Myocardial Injury	Wang Q, Spaeter D
Circulation	Protective Effects of Ticagrelor on Myocardial Injury After Infarction	Carlsson LG
Science Translational Medicine	Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action	O'Connor MJ
Nature Chemical Biology	Potent and selective bivalent inhibitors of BET bromodomains	Chen R, Dale IL, Robb GR, Bobby R, Boiko S, Callis RJ, Clark E, Flavell L, Holdgate GA, McAlister M, Petteruti P, Saif S, Stratton N, Whittaker DTE, Wilson DM, Yao Y

Publication	Title	AstraZeneca and MedImmune authors
Nature Medicine	PIM1 kinase regulates cell death, tumor growth and chemapy response in triple-negative breast cancer	McEachern K
Nature Chemical Biology	Structural and conformational determinants of macrocycle cell permeability	Over B, Hilgendorf C, Lewis R, Perry M, Tyrchan C
Nature Reviews Clinical Oncology	Imaging biomarker roadmap for cancer studies	Waterton J
Nature Communications	Metal-free photochemical silylations and transfer hydrogenations of benzenoid hydrocarbons and graphene	Bergman J
Nature	Genome-wide associations for birth weight and correlations with adult disease	Vaag A
Cell Discovery	Decreased glutathione biosynthesis contributes to EGFR T790M-driven erlotinib resistance in non-small cell lung cancer	De Bruin EC
Cell Metabolism	Single-Cell Transcriptome Profiling of Human Pancreatic Islets in Health and Type 2 Diabetes	Ämmälä C, Eliasson P, Andersson E, Smith DM, Andréasson A, Bjursell M, Clausen M, Sabirsh A
Cell	A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds	O'Connor MJ
The Lancet Oncology	Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial	Hodgson D, Fielding A, Spencer S, Lowe E, Sovak M
Nature Reviews Materials	Cancer nanomedicine: is targeting our target?	Ashford MB
Nature Chemical Biology	Inhibition of Mcl-1 through covalent modification of a noncatalytic lysine side chain	Su Q, Belmonte M, Aquila B, Hird A, Lamb M, Rawlins PB, Su N, Tentarelli S, Grimster N

Publication	Title	AstraZeneca and MedImmune authors
The Lancet Respiratory Medicine	Efficacy and safety of a CXCR2 antagonist,AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial	Cullberg M, Puu M, Richter K, Keen C, Uddin MK, Larsson B, Malmgren A
Science	Cardiometabolic risk loci share downstream cis- and trans-gene regulation across tissues and diseases	Gan L
Nature Chemical Biology	Cellularly active N-hydroxyurea FEN 1 inhibitors block substrate entry to the active site	Durant S, McWhirter C, Nissink W, Debreczeni J
Journal of Clinical Oncology	Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced Non–Small–Cell Lung Cancer	Thress K, Barrett C, Cantarini MV
The New England Journal of Medicine	Clinical significance of symptoms in smokers with preserved pulmonary function	Rennard SI
Cancer Cell	CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma	Barry ST, Wilson Z
Nature Reviews Clinical Oncology	Clinical development of new drug–radiotherapy combinations	Clack G
Nature	Overcoming mTOR resistance mutations with a new generation mTOR inhibitor	Cosulich SC, McWhirter C, Barratt DG, Klinowska T
Advanced Drug Delivery Reviews	Challenges and strategies in anti-cancer nanomedicine development: an industry perspective	Hare JI, Ashford MB, Barry ST, Puri S

Publication	Title	AstraZeneca and MedImmune authors
Nature Medicine	High-level clonal FGFR amplification and response to FGFR inhibition in a translational clinical trial	Kilgour E, Smith NR, Rooney C
Nature Reviews Drug Discovery	Key factors for successful data integration in biomarker research	Reischl J
Nature Medicine	A human-specific AS3MT isoform and BORCS7 are molecular risk factors in the 10q24.32 schizophrenia-associated locus	Brandon N, Cross AJ
Nature Medicine	Facilitating a culture of responsible and effective sharing of cancer genome data	Barrett C
Nature Reviews Cancer	Defining actionable mutations for Oncology therapeutic development	Carr H, McEwen R
Advanced Drug Delivery Reviews	Cell permeability beyond the rule of 5	Over B
Immunity - cell	Integrative analyses of colorectal cancer show immunoscore is a stronger predictor of patient survival than microsatellite instability	Angell HK, Valge-Archer V
Science Translational Medicine	The tumor microenvironment and Immunoscore are critical determinants of dissemination to distant metastasis	Angell HK, Valge-Archer V
Science Translational Medicine	Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index in vivo	Barry ST, Ashton S, Jewsbury PJ, Ashford MB, Cadogan E, Howes C, Murray J, Goodwin R, Polanska UM, Reimer C, Smith A, Swales JG, Taylor PJ, Wilson J

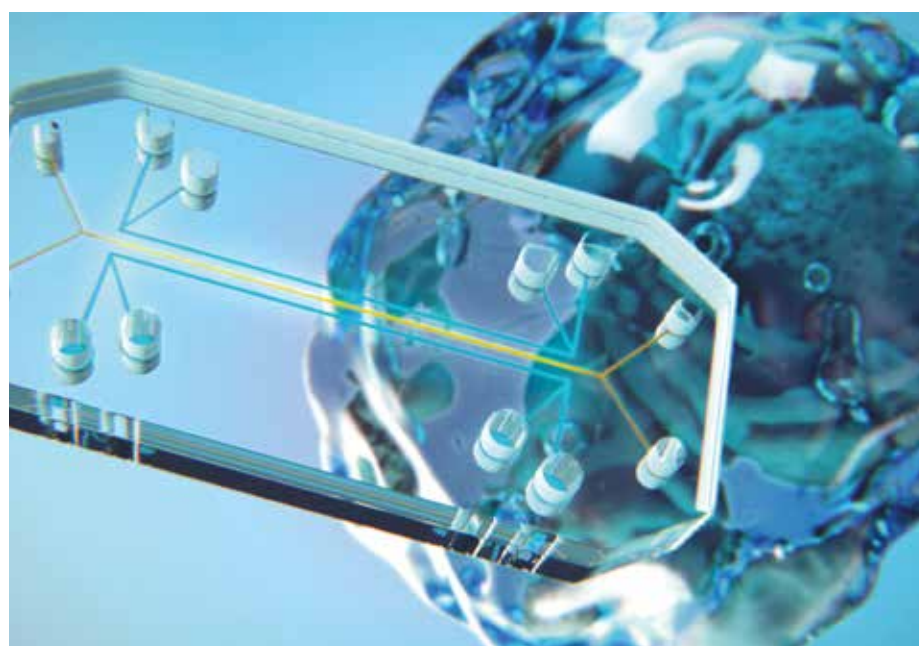
Preparing for the future with our IMED Futures teams

Delivering the next wave of life changing medicines requires a new way of thinking. To ensure the IMED Biotech Unit remains at the cutting-edge of scientific innovation, we established our IMED Futures programme.

We focus on blue sky research to make the impossible, possible.

While we focus on advancing our pipeline today, we are also thinking about the future and what is going to transform the healthcare landscape in the next decade. Emerging technologies such as organs on a chip and innovation in targeted drug delivery are accelerating and changing how we progress scientific research. In the IMED Biotech Unit we are delivering the next wave of innovation by exploring potentially disruptive technologies that make our blue sky ideas a reality.

✓ Microphysiological systems
- biochip with cellular matter



In focus: Humanised mini-organ models

The extracellular matrix (ECM) provides the scaffold that supports the architecture of tissues and organs. It also provides functional cues that support and guide cell differentiation, along with organ structure and functionality.

Through the controlled removal of endogenous cells from rat hearts and kidneys, we have obtained fully decellularized organs with a largely preserved ECM composition and overall organ structure. We are then able to repopulate these scaffolds with human cardiac or kidney cells.

Excitingly, we have observed that the exogenous cells use the ECM derived cues to differentiate, mature and form primitive functional organs. This mean we are able to use these humanised mini-organs to improve our understanding of basic biology in health and disease. And, eventually we will be able to test biological hypotheses and estimate efficacy and organ safety for our targets and molecules.

“We see that current *in vitro* models often have limitations in human translatability. The humanised mini-organ models are aimed at overcoming these limitations and providing a relevant system for a range of applications, such as assessment of drug efficacy, safety and uptake. Availability of patient-derived and CRISPR-engineered human cells combined with the decellularized organ scaffolds will enable generation of highly relevant *in vitro* disease models. This will be pivotal for mechanistic investigations of targets that are not present in standard pre-clinical *in vivo* models. All together it holds tremendous potential for how we can further improve deliver of new innovative drugs to patients.”

**Magnus Althage, Team Leader,
Translational Sciences, IMED CVMD**

Advanced Drug Delivery

Improved understanding of the physiological barriers to efficient drug delivery has resulted in significant advances in delivery systems.

This, coupled with novel analytical and imaging techniques allow for even more sophisticated delivery systems opening up new target space. Our team is looking to improve efficacy by enhancing our targeting capabilities to allow delivery of both small molecules and oligonucleotide therapeutics – miRNA, mRNA and antisense. To do this our team is focused on cellular targeting, improving cellular uptake and enhancing drug delivery and other new modalities. In the latter case, we have a co-exclusive license with Pfizer for access to the BIND Therapeutics ACCURINS® polymeric nanoparticle technology and with Starpharma for exploring their dendrimer technology platform. Both these technologies improve therapeutic index and ability to formulate challenging molecules.

iLead in Lead Generation

Focused on creating a capability that enables our scientists to follow the science and work on any therapeutic target mechanism irrespective of its tractability. We aim to make ‘undruggable’ targets ‘druggable’ by developing strategies that explore next generation approaches to small molecule hit identification and the application of peptides and cyclic peptides as novel therapeutic modalities. Some of the exciting new approaches include Acoustic Mass Spectrometry, where we have invented the ability to use acoustic technology (sound waves) to inject femtolitre volumes of sample into a mass spectrometer to enable smaller samples to be used and speed up the discovery process. Through collaboration with OpenEye we have developed the ability to execute virtual screens of high areas of chemical space. We are able to screen this virtual chemical space in minutes to search for molecules that do not exist today and rapidly identify novel compounds with activity at target proteins. This represents a 10⁶ fold increase in capability since 2015. To synthesise these compounds, we are investing in automated miniaturised chemistry synthesis techniques and machine learning to inform the best molecules to progress further. To complement these new methods for hit identification we are developing a fully automated DMTA cycle. The cycle of chemistry design and synthesis, followed by biological testing and data analysis (DMTA) currently takes around eight weeks. We have initiated a project involving machine learning algorithms aimed at fully automating this cycle to reduce this time to five hours.

Organs on a Chip

Microphysiological systems (MPS) are miniaturised models that combine engineering and biology to generate organ function *in vitro* to emulate human biology at the smallest acceptable scale. MPS models enable scientists to link organs together and discover key factors involved in organ cross-talk that drive particular disease phenotypes – generating data with a high likelihood of clinical translation and offering a real alternative to the use of animals in drug discovery. Our team is collaborating with some of the leading experts in the world at TissUse, Emulate, Harvard and Vanderbilt Universities.

Pre-clinical Biosensors

To enhance the impact of current online data monitoring, our teams have been exploring the possibilities within the rich data source provided by sensor technology and wearable devices. Incorporating biosensor technology into our pre-clinical studies will allow us to change current practice, improve translation and safety read-outs, while reducing the number of animal studies. Current technology allows measuring the body’s vital signs using health patches but our team recognises the true value for pre-clinical monitoring lies with invasive biosensor technology. In the future, developing pre-clinical sensors that monitor drug exposure and biomarkers of safety and efficacy will have the potential for clinical use – providing online biosensors for patients, and hence changing the status quo for patient care.

iDecide

iDecide is a clinical informatics research and development framework enabling early and better decision-making in clinical studies. In collaboration with the Manchester Cancer Research Centre (MCRC), iDecide is designed to integrate, maintain and assess data during an ongoing study utilising real time feedback from patients. Leveraging this patient-centric information in a timely manner enables appropriate adjustment to clinical trial design, saving resources and time while helping us administer the right dose, of the right drug to the right patient.

Digital IMED

The wealth of ‘big data’ in healthcare is revolutionising our approach to research and development. We are already seeing how the next generation of medicines are being shaped by our ability to capture, interpret and apply data. Combining insight from clinical health records with large-scale genomics data is enabling scientists to better predict disease outcomes in the clinic. Our team has been investigating the possibility to connect multiple data stacks from anywhere and of any type, from proprietary data to real world evidence, even social media platforms. This data stack would truly allow us to map 360 degree views of patient journeys and gain understanding of the interplay between ‘nature’ (from genetic information) and ‘nurture’ (environmental data e.g. smartphone/sensor data) to make breakthroughs in science and ultimately patient care.



IMED Events 2016





astrazeneca.com

