Delivering the next wave of scientific innovation

Innovative Medicines and Early Development Biotech Unit

2017 – A year in review
New modalities

In our aspiration to transform disease, we recognise the need to target the novel biology we uncover, and as our understanding of molecular mechanisms advances, our modalities are also becoming more diverse. We are opening up a new world of therapeutics beyond small molecules, focused on the molecular machinery of cells.

Modified mRNA therapy, depicted in the image, is an example of an exciting new modality which enables tissue specific production of a target protein from a clinical grade mRNA transcript. By 2017, the IMED portfolio was enhanced by collaborative work on seven modalities as well as small molecules: modified mRNA, antisense oligonucleotides (ASOs), oligonucleotide conjugates, bicyclic peptides, proteolysis targeting chimeras (PROTACs), therapeutic proteins and Anticalin® molecules. This ever-growing diversity is helping AstraZeneca to pioneer new approaches to drug discovery.
Introduction

The next wave of scientific innovation: An introduction from Mene Pangalos

As I reflect on the transformation we have made in the IMED Biotech Unit over the past seven years, 2017 was an inflection point for me. The end of one chapter and the beginning of another. We are now in the best position we have ever been to enable the translation of innovative science into medicines.

We published our second SR framework publication in Nature Reviews Drug Discovery in January 2018, detailing how we have achieved greater than five-fold increase in our success rates since 2012 from pre-clinical development to Phase III completion – from four per cent to 19 per cent against an industry average that remains around four to five per cent. This has been achieved by embedding the SR framework into everything we do, and at the same time establishing an open, collaborative, ‘truth seeking’ culture with scientific rigor at its heart.

We focussed investment across our core therapeutic areas. This has brought several new medicines to patients such as osimertinib, olaparib, acalabrutinib, ticagrelor, lokelma and evabactam with several potential new medicines in Phase III or under registration. At the same time we have broadened our drug modalities, so we could follow the biology. Our work goes beyond small molecules, with about 30 per cent of our programmes now using new modalities, a testament to our trying to make every target druggable. Modalities such as modified RNA and antisense oligonucleotides are already in clinical development. In partnership with Moderna, we were granted the Phase IIa clinical trial application for AZD8601, a modified RNA for vascular endothelial growth factor A (VEGF-A) to explore cardiac regeneration in patients undergoing coronary artery bypass graft surgery with moderately impaired systolic function. In immunology, and in partnership with Janssen Therapeutics, AZD1960, our antisense oligonucleotide signal transducer and activator of transcription 3 (STAT3) moved into Phase III clinical trials, and is being evaluated for anti-tumour activity in combination with our PD-L1 inhibitor, following completion of Phase Ib. Also in 2017, we forged new partnerships with APT Therapeutics, accessing their therapeutic protein platform; with Pieris to develop novel inhaled drugs that leverage Pieris’ Anticalin™ platform, and with Bicycle Therapeutics in support of respiratory and cardiovascular diseases to develop a new class of therapeutics based on its proprietary bicyclic peptide product platform.

Looking more broadly at our clinical progress, in 2017 eight new molecular entities (NMEs) transitioned from across our therapy areas and a further eight non-NMEs transitioned in oncology, expanding the number of novel combination studies ongoing. We continued to fuel our pre-clinical and Phase I pipeline with exciting new molecules against targets notoriously difficult to drug, such as MCL1 and KRAS in oncology. Our aim is to be able to design a chemical lead for any novel biological target.

Our biotech-style operating model gives us access to the best science, both internal and external, and we are open to exploring new and different kinds of collaborations. In 2017, we entered into key partnerships with Imperial College, the Crick Institute, and the Medical Research Council - Laboratory of Molecular Biology (MRC-LMB), to further our understanding of the underlying biology of disease, with the intent to publish all output in journals of the highest impact. Specifically with Imperial College, one collaboration consists of supporting a Joint Research Fellowship programme and the second creates a Joint Respiratory Hub where our scientists will work side-by-side with Imperial scientists. With the MRC-LMB Blue Sky programme, we have funded 22 research projects. One breakthrough project, published in Science Advances, has applied cutting-edge cryo-electron microscopy to uncover novel structures of ataxia-telangiectasia mutated, a key protein in DNA damage response for IMED Oncology.

In 2017, IMED continued to pioneer new approaches to open innovation, enabling our scientists to share their ideas more freely and collaborate on projects with external scientists. The IMED Open Innovation portal allows external researchers to access the full range of open innovation programmes. By the end of 2017, our teams had reviewed more than 500 proposals for new drug projects. Of these, 26 have progressed as far as clinical trials, while more than 150 are in the pre-clinical stage.

To reflect the broad range of cutting-edge technologies used in IMED, including molecular diagnostics, tissue diagnostics, next generation sequencing and point of care diagnostics, we took the decision to move from Personalised Healthcare to Precision Medicine and Genomics and renamed the function as Genomics and renamed the function as Genomics and renamed the function as Genomics and renamed the function as Genomics.

2017 was a defining year for AstraZeneca. It was a year in which our IMED Biotech Unit flourished and continued to drive research and development productivity. The diversity of our early pipeline is pushing the boundaries of science, delivering the next wave of innovation beyond small molecules, and strengthening our position as a thought leader in precision medicine and genomics. Our continued success and growth is driven by our agile and entrepreneurial culture, our network of partnerships and the extraordinary people who make up our workforce, all of whom are committed to delivering our science to patients.

Pascal Soriot, CEO AstraZeneca

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

I am immensely proud of our scientific leadership and our ability to follow the science.

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

Delivering the next wave of scientific innovation
5R framework: A four-fold increase in research and development productivity over five years

Following a major review of our research and development strategy in 2010, we created a 5R framework to guide how we discover and develop new drug candidates. Looking at our productivity and success rates over the past five years we can now see a transformation in our productivity – enabling us to increase our chances of turning science into medicine.

A recent analysis, published in Nature Reviews Drug Discovery explains how our 5R framework (right target, right patient, right tissue, right safety, right commercial potential) has helped guide successful, efficient drug discovery and development. In five years, we have achieved a four-fold improvement in the proportion of pipeline molecules advancing from pre-clinical investigation to completion of Phase III clinical trials – from four per cent to 19 per cent. This improvement moves AstraZeneca well above the average success rates of six per cent for small molecules in the 2013-2015 timeframe (Data sourced from CMR International’s 2016 Global Research and Development Performance Metrics Programme).

The 5R framework has become embedded into the way we work in the IMED Biotech Unit, and its success is based on improvements across our research and development operation. At the heart of this transformation has been our change in culture. We have established a collaborative ‘truth seeking’ culture where science thrives. A stimulating culture, where we ask the ‘killer questions’ and rigorously test our hypotheses. A culture, which has enabled us to improve the quality of the drug candidates we take forward into pre-clinical studies and into clinical trials.

In a high risk industry with a well documented decline in productivity, I am proud to see the impact of our 5R framework on the pipeline. There is still much room for improvement but we expect that our continued focus on scientific rigor and collaboration, precision medicine and other emerging technologies will further enhance our capability for translating science into innovative medicines for the patients who need them.”

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

In research and early development, teams need to understand the key questions that will position this programme competitively from the perspective of differentiation relative to future standard of care. Experiments in the laboratory and the clinic need to set efficacy and tolerability benchmarks using appropriate comparators. By the time a project reaches a Phase III investment decision, we are committed to ensuring that a thorough commercial assessment has been made, with clarity around the patient population, the unmet medical need, reimbursement versus standard of care, payer criteria for global reimbursement, competitive environment and sales projections.

Right Target

By implementing a stronger focus on biological rationale and understanding of the target, we have markedly reduced the number of projects in our discovery portfolio. We have expanded the classes of drug targets that we are investigating and doubled our ‘hit to lead’ success rate from 23 per cent to 48 per cent. Our expansion into new modalities beyond small molecules has enabled us to work on more novel drug targets, many of which were previously considered undruggable (e.g. KRAS).

Right Tissue

We are increasingly using biomarkers to confirm that our compounds are engaging with desired targets and are active in the right tissues. This is because evidence of target engagement or proof of mechanism is key to improving the probability of project success. We are carrying out research to clearly demonstrate that a candidate drug is engaging the target at a predefined and quantitative level, with a functional effect. By improving our pre-clinical models for measuring the pharmacokinetics, pharmacodynamics, absorption, distribution, metabolism and excretion of our molecules, we are enhancing candidate selection and have improved dose-setting and exposure predictions in the clinic by 18 per cent.

Right Safety

Through changes to the way we assess safety, we can now identify early pre-clinical safety signals and integrate in vitro and in vivo data for quantitative risk assessment of future human use. This includes exploring the physiological role of a target in health and disease, and performing in silico and in vivo safety assays on molecules with potential for lead generation to understand their possible impact on key organs. Additional in vitro and in vivo assays across species are carried out as projects move closer to candidate selection, including microtissue and human organoid tests, in order to gain clearer insights into potential toxicity than previously possible. Following the introduction of our right safety focus, there was a greater than four-fold decrease in our pre-clinical safety attrition rate.

Right Patient

At inception of a drug discovery project, we work on defining ways of stratifying patients to identify those most likely to benefit from treatment. Across our pipeline, projects with a strong focus on patient selection were more likely to move into the next phase in development — 62 per cent for those with patient versus 44 per cent with no selection strategy. This facilitates timely development of biomarkers to identify the ‘right patient’ for treatment and, where appropriate, development of companion diagnostics.

Right Commercial potential

In research and early development, teams need to understand the key questions that will position this programme competitively from the perspective of differentiation relative to future standard of care. Experiments in the laboratory and the clinic need to set efficacy and tolerability benchmarks using appropriate comparators. By the time a project reaches a Phase III investment decision, we are committed to ensuring that a thorough commercial assessment has been made, with clarity around the patient population, the unmet medical need, reimbursement versus standard of care, payer criteria for global reimbursement, competitive environment and sales projections.

In conclusion, AstraZeneca is working hard to improve the quality of its drug candidates by implementing a 5R framework, which has enabled us to achieve a four-fold increase in research and development productivity over the past five years. The transformation of our productivity is enabling us to increase our chances of turning science into medicine.
"2017 was a pivotal year for Oncology, with important data readouts for osimertinib, olaparib, durvalumab and acalabrutinib. We made exciting progress with combinations: olaparib with other agents from our DNA damage response (DDR) portfolio, savolitinib with osimertinib, and AZD9150, our antisense oligonucleotide (ASO) signal transducer and activator of transcription 3 (STAT3) inhibitor, with durvalumab. In addition, we moved our cell death portfolio into the clinic. Translational science has been critical to these developments and is helping to ensure we treat patients who are most likely to benefit from our innovative approaches."

Susan Galbraith, Vice President, Head of IMED Oncology
During 2017, IMED Oncology made substantial advances, delivering six investigational new drugs (INDs) and providing wide ranging translational support for clinical programmes. We delivered combination data including savolitinib with osimertinib, and AZD9150 with durvalumab.

With acalabrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, we have the potential of a backbone therapy for B-cell driven cancers with which to combine our cell death portfolio agents and with the aim of establishing a strong franchise in haematology. We are evaluating new combination partners with blood cancers, with three new projects entering the clinic in 2017-18 – AZD5991, inhibitor of myeloid cell leukemia 1 (MCL1), AZD4573, a cyclin dependent kinase (CDK9) inhibitor and AZD0466, a B-cell lymphoma 2/extra large (BCL2/xL) nanoparticle – targeting complementary aspects of cell death mechanisms.

In women's cancers, we continue to focus on the role of the estrogen receptor (ER) in breast cancer and the multiple ways it can be degraded, advancing our mechanistic understanding with enhanced patient derived xenograft (PDX) model capabilities, and supporting label extensions for our selective ER degrader (SERD) fulvestrant.

In 2017, our other DDR agents targeting WEE1, ataxia telangiectasia and Rad3-related protein (ATR) and ataxia telangiectasia mutated (ATM) progressed in the clinic, and systematic research has been carried out to improve understanding of the mechanism of resistance to poly ADP-ribose polymerase (PARP) inhibition in different cancer types with a focus on PDX models. Furthermore, our partnership with Merck aimed to deepen, broaden and extend responses to olaparib in new patient populations, and to develop a better understanding of resistance in the clinic.

Our immunotherapy portfolio has expanded, with developments in three clinical programmes and extended pre-clinical capabilities and new targets. We are using a broad biomarker platform to predict sensitivity to agents targeting the immune myeloid cells in tumours and to explore further combinations from our DDR and immunotherapy portfolios.

In 2017, IMED scientists Ray Finlay, Richard Ward and Darren Cross received the Malcolm Campbell Award for ‘excellence in medicinal chemistry’ relating to the pioneering research that led to the discovery of osimertinib. The prestigious award is awarded biennially for ‘excellence in medicinal chemistry’ and is one of the key drivers of the cell death portfolio and is integrally involved in shaping and developing the Haematology Franchise through the collaboration with Astra.

People spotlight

Andrew Pape, Vice President Strategy Oncology
Andrew Pape joined AstraZeneca in 2017. His oncology expertise and wealth of experience in the pharmaceutical industry are a great contribution to IMED Oncology. Andrew is a member of the IMED Oncology Leadership Team and plays a key role in the direction of oncology strategy at an enterprise level and within IMED. Andrew also leads the Strategy Group, a team of scientific experts with responsibility for collaborations, alliances and partnerships.

The group engages with leading scientific institutions and clinical centres across the globe, in addition to the biotech community. With Andrew’s lead, the team foster and establish relationships which are essential to our continued immersion in innovative science and the delivery of novel medicines to cancer patients.

Andrew trained as a chemist and has a PhD from University of Cambridge. He was previously a team leader in medicinal chemistry at Alderley Park, before moving to Basel in 2009. He has re-joined AstraZeneca from Novartis where he was Global Head of Oncology having led multiple drug discovery programmes from pre-clinical research to early clinical development.

Wenlin Shao, Project leader
Wenlin Shao is a director and global project leader in IMED Oncology. Prior to joining AstraZeneca in 2016, Wenlin was a project and group leader at Novartis Oncology having led multiple drug discovery programmes from pre-clinical research to early clinical development.

Wenlin is currently leading several oncology projects including in 2017 the successful delivery of candidate drug AZD4573 (ZDK9) for its first time in man study. In addition, Wenlin is one of the key drivers of the cell death portfolio and is integrally involved in shaping and developing the Haematology Franchise through the collaboration with Astra.

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

Highlights

We set out to

Deliver the most effective anti-hormonal therapies for patients with hormone receptor positive breast cancer

AstraZeneca continued to develop our industry leading portfolio of endocrine therapies with the aim to treat patients with hormone receptor positive (HR+) breast cancer. The development of our next generation oral SERD, AZD5446, has had the first patients evaluated in a ‘window of opportunity’, pre-surgical clinical trial. This innovative trial is comparing head-to-head the degree of ER degradation induced by AZD9495 and fulvestrant. This is testing the hypothesis that the improved pharmacodynamic cover potentially afforded by an orally bioavailable SERD will translate into more complete target engagement. We pioneered this approach during the development of fulvestrant, where the increase in dose from 250 mg to 500 mg resulted in more ER degradation.

In pre-clinical research, we are building a panel of HR+ breast cancer patient derived xenograft (PDO), utilising models developed within AstraZeneca and with academic collaborators and contract research organisations. We are partnering with Champions to develop new PDO models from patients progressing on current standard of care therapies. We are also investigating alternative modes of action to cause ER degradation as potential future therapeutic options.

Accelerate progress in key strategic DDR areas and maximise the potential of our agents in the clinic

We accelerated development of key DDR assets in the clinic, with the addition of DDR-DDR combinations to multiple basket trials. Significant progress has been made in defining robust doses for combinations of AZD1775 (WEE1 inhibitor), and selumetinib, and our blood brain barrier penetrating AZD1385 (ATM inhibitor) which was dosed in the first healthy volunteer. Through tumour profiling, evidence of DDR associated immunogenicity in the clinic led to the development of novel DDR/immuno-oncology (IO) combinations, with promising early data from clinical trials.

We established teams dedicated to building our pre-clinical capability, to increase mechanistic understanding of our DDR agents, and, with investment in technology to measure replication dynamics, to facilitate better understanding of replication stress in cancer and the targeting of the replication stress response. Development of syngeneic models has enabled pre-clinical assessment of DDR/IO combinations, and we are building a panel of PDO models with DDR mutational profiles for pre-clinical and co-clinical trial studies. Emerging data from external collaborations, using PDO models will guide differentiation of DDR inhibitor combinations.

The accelerated programme with AZD1778 (ATR inhibitor), and selumetinib resulted in important insights of dose and schedule, with Phase II trials initiated in both gastric and breast cancer. The VIOLETTE multi-centre clinical study, designed to investigate AZD1778 versus AZD1775 in combination with selumetinib in breast cancer, was initiated in 2017, with tolerability data expected in 2018. In addition to providing proof of concept regarding the potential of DDR inhibitors in combination with selumetinib, the study, which includes patients with homologous recombination repair (HRR) mutations including BRCAm, as well as HR proficient cancers, is expected to deliver key data on patient selection strategies for these two DDR-DDR combinations.

Our global strategic collaboration agreement with Merck to co-develop and co-commercialise selumetinib provides an opportunity to evaluate the potential for selumetinib combinations across multiple tumour types. We have already had productive discussions on trial design and translational endpoints and aim to accelerate development of selumetinib and selumetinib.

We set out to

Progress savolitinib, our potent and highly selective small molecule inhibitor of the c-Met receptor tyrosine kinase in combination with osimertinib

We progressed evaluation of savolitinib in collaboration with our Global Medicines Development (GMD) colleagues, by continuing enrolment in a clinical study in c-MET driven EGFR mutation positive non-small cell lung cancer (NSCLC), combining savolitinib with osimertinib in the TATTON trial and completing enrolment with gefitinib in a trial in China. Initiation of these studies was based on strong science highlighting the co-dependence on both c-MET and EGFR in some cancers and the potential for combining inhibitors targeting both of these receptor tyrosine kinases in a subset of patients with lung cancer. Clinical data were presented at the World Congress on Lung Cancer in Japan in 2017. A Phase III investment decision was made in 2018 for c-MET driven papillary renal cell cancer (PRCC). Initiation of the Phase III trial in PRCC occurred in 2017, with enrolment ongoing. Savolitinib mono-therapy continues to be explored in Phase I/II studies in other cancers, including stomach, kidney and lung, and in combination with durvalumab, a programmed death-ligand 1 (PD-L1) antibody, in kidney cancer.

Complement and broaden our industry leading oncology portfolio as a partner of choice

Together with our colleagues in IMED Scientific Partnerships and Alliances, we successfully partnered and licensed innovative opportunities that are key to the industry leading portfolio we have today. The programmes below are all in clinical trials to evaluate their potential:

- AZD9150: a first-in-class, ASO inhibitor of STAT3, was licensed from Ionis Pharmaceuticals, and is evaluated for anti-tumour activity in combination with durvalumab.

- Savolitinib: a highly selective small molecule inhibitor of c-MET, partnered with Hutchison Pharma, is being evaluated in c-MET-driven cancers. It is currently in a confirmatory Phase III trial in PRCC, and is also being evaluated in a Phase II trial in patients with a certain type of lung cancer. AZD1775: a novel small molecule inhibitor of WEE1 kinase was licensed from Merck and is currently being evaluated in Phase II trials as part of our industry leading DDR pipeline.

We are also creating opportunities to assess the full potential of our oncology portfolio through new external partnerships. Drazil Pharmaceuticals was recently established through a joint venture between AstraZeneca and the China State Development and Investment Corporation (SDIC). Through this venture we are able to leverage the capabilities of AstraZeneca’s Innovation Centre China (ICC) unit to create value from existing and new portfolio projects across disease areas. IMED Oncology contributed AZD4945 (Janus kinase 1 (JAK1) inhibitor), to the joint venture and we expect the initiation of clinical trials in patients with lung cancer during 2018.

Expand and progress our portfolio of small molecule immuno-oncology agents and increase our ability to model tumour immunobiology

We progressed three clinical programmes, AZD20150 (STAT3 inhibitor), AZD5695 (chemokine receptor 2 (CCR2) antagonist), and AZD4455, (adenosine A2A receptor (A2AR) antagonist). The study of AZD20150 and durvalumab in metastatic head and neck cancer has enrolled the target patient cohort and interim data were presented at the annual congress of the European Society for Medical Oncology (ESMO) in 2017. We have initiated a Phase II study to evaluate AZD5695 in combination with durvalumab in metastatic pancreatic cancer, and Phase II monotherapy and combinations studies with durvalumab. In addition, we successfully transferred multiple pre-clinical projects through key investment decisions and we added several additional new targets for potential therapies for lymphoid and myeloid cancers to our early discovery portfolio.

We developed a suite of in vitro and in vivo models that enable the impact of specific molecules on key drivers of the immune system to be assessed. This includes investigating innovative ways of generating mouse genetic models of cancer and exploring the interaction between DNA damage and the immune system, via paired biopsies from the AZD9150 programme, with changes in tumour microenvironment. This is giving us fresh insights related to the STAT3 combination with durvalumab. Furthermore, as part of a Cancer Research UK Grand Challenge team to map tumours in unprecedented detail, which we hope will improve our understanding of cancer, allowing us to identify new and better ways to diagnose and treat the disease.
Defining treatment of haematological malignancies with a new class of medicines

Recent advances in understanding of the pathogenomic signalling pathways of haematological malignancies are transforming the way we are addressing these challenging diseases, which currently account for more than 10 per cent of all cancer deaths.

We are prioritising development of combinations of this BTK inhibitor with promising compounds from our exciting oncology pipeline. These combinations provide the opportunity to strengthen responses in diseases where some other BTK inhibitors have already been approved, such as chronic lymphocytic leukaemia (CLL), and establish their potential role in settings, such as diffuse large B cell lymphoma (DLBCL) where monotherapy data have been less impressive.

In 2017, we initiated a study in DLBCL combining acalabrutinib with 17-DMAG (a dual TORC1/2 inhibitor) based on the promising pre-clinical data, and will evaluate the initial clinical benefit in a DLBCL all-comer population exploring both continuous and intermittent dosing.

Another study is exploring the dosing of acalabrutinib with AZD6738 (ATR inhibitor), which has previously shown potential in tumours that are deficient for ATM function.

A class of drug targets that is of particular interest in haematology is the ‘cell death’ group. We are designing compounds which are intended to antagonise these pro-survival proteins (BCL2 family) which tumours up-regulate to avoid apoptosis. The class has been validated clinically through the approval of venetoclax (BCL2 inhibitor) in CLL, and AstraZeneca is evaluating a BCL2/XL dual inhibitor which has the potential to follow suit. MCL1 is another member of this family of proteins that tumours use to avoid cell death, and is being targeted directly by AZD5991 which disturbs the protein-protein interaction between MCL1 and pro-death effectors. A complementary approach is being developed with AZD4573 (CDK9 inhibitor), which provides an indirect method of inhibiting both MCL1 and MCV. These three ‘cell death’ agents are being evaluated clinically with a strong focus on haematological disease. This is based on extensive cell panel screening and the activity seen in pre-clinical combination studies with various agents, including acalabrutinib.

The breadth of our haematology pipeline presents a unique opportunity to use master protocols to rapidly evaluate the numerous monotherapy and combination opportunities in key diseases such as DLBCL, acute myelogenous leukaemia (AML), MCL and follicular lymphoma (FL). PRISM is such a study, evaluating three to five treatment arms per annum in a highly characterised population of DLBCL patients. Investigator interest has been very strong and the study design should allow more rapid and efficient evaluation of combinations in this difficult disease where high quality genomic information is going to be critical in identifying responder populations.

Tumours are complex tissues that have microenvironments comprised of multiple cell types besides malignant tumour cells. A tumour may be infiltrated by immune cells recruited by malignant cells. The tumour takes on the normal immune function of these cells to counteract the patient’s ability to mount an immune response. In some cases, this prevents IO drugs, from benefitting the patient.

STAT3 is a transcriptional factor that is crucial to the function of several types of immune cells, and aberrant signalling has been shown to lead to immunosuppression in several cancers. AZD9150 is an ASO that targets STAT3 mRNA, leading to the depletion of STAT3 protein and a reduction in signals through the STAT3 pathway. In 2013-2014, we performed a translational science analysis of tumour tissues collected from patients with late stage lymphoma from a monotherapy study with AZD9150. These analyses revealed that AZD9150 targeted STAT3 in several cell types of the tumour microenvironment, including immune cells. In addition, gene expression profiling showed that in patients treated with AZD9150, the tumour microenvironment was altered in a way that may make it likely to respond to PD-1/PD-L1 drugs. In parallel, clinical biomarker studies showed the effects of STAT3 blockade, in combination with PD-L1 blockade in several disease models. These clinical and pre-clinical mechanistic studies, led us to hypothesise that treating patients with anti-PD-1/PD-L1 drugs in combination with AZD9150 could overcome immune suppression in the tumours and potentially lead to improved patient outcomes.

In 2014, we initiated a Phase II study (named SCORES) investigating the combination of AZD9150 and durvalumab in patients with metastatic head and neck cancer who may or may not have received prior immunotherapy. These proof of concept data were presented at the ESMO congress in 2017 and generated a lot of positive interest. The programme is expanding quickly to other disease types to more broadly evaluate the concept of blocking multiple checkpoints to overcome immune suppression from the tumour microenvironment.

The field of immuno-oncology (IO) is contributing to the evolving treatment possibilities for patients with later stage cancer. The FDA has issued a number of approvals in recent years for the class of agents known as PD-1/PD-L1 checkpoint blocking antibodies. This new class of drugs, which includes durvalumab, engages the immune system to induce durable tumour responses, in a subset of patients. However, approximately 75 per cent of patients with responsive types of disease do not derive durable benefit from PD-1/PD-L1 blocking antibodies, and there is a continuing unmet need for treatment.

### Oncology pipeline

#### Pre-clinical
- AZD0346 / ERK
- AZD0466 / Bcl2-xl
- AZD7848 / OXR1
- AZD3458 / PI3Kγ

#### Phase I
- AZD4573 / CDK9
- AZD811 / AURN
- AZD0165 / ATM
- AZD7865 / Kras
- AZD5153 / BRD4
- AZD5991 / MCL1
- AZD1390 / ATM-BBB
- AZD9496 / SERD

#### Phase II
- AZD1775 / WEE1
- AZD1158 / ATM
- AZD9150 / STAT3
- AZD0069 / CCR2
- AZD3166 / PD1L
- AZD4357 / A2AR
- AZD4547 / FGFR
- AZD6738 / ATR
- AZD4785 / KRAS
- AZD5069 / CXCR2
- AZD8186 / PI3Kβ
- AZD5363 / AKT
- AZD9496 / SERD

#### Phase III / LCM
- selumetinib / MET
- olaparib / PARP
- erlotinib / EGFR
- acalabrutinib / BTK
- sunitinib / MET
- fulvestrant / ER antagonist

Pipeline correct as of Q4 2017, not including MedImmune programmes.
A selection of key collaborations in 2017

1. University of Cambridge, UK
We are working with Steven Jackson on in vivo screens to investigate resistance to DDR inhibitors in order to identify genetic components in ATM-deficient cells that drive the sensitivity and resistance. Depending on the resistance profile to the different inhibitors observed, rational combinations may be tested to provide synergistic effects or to overcome resistance.

2. Vanderbilt University School of Medicine, USA
Dr. Cortez’s laboratory uses the IPOND technique they developed that provides mass spectrometry characterisation of protein changes at DNA replication forks. This is achieved by treating cancer cell lines with DDR inhibitors such as ATFR1, WEE1 and olaparib, and observing the level of replication stress following treatment. The goal is to gain insights into the use of different combinations of DDR agents and identify the genetic backgrounds where these approaches are most impactful.

3. University of Pittsburgh, USA
Chris Bakkenist is working to establish the syngeneic mouse model of lung cancer.

4. University of Oxford, UK
We are working with Anderson Ryan to evaluate modulators of cell death pathways with potential clinical translation.

5. MD Anderson Cancer Center, USA
With John Heymach, we are evaluating DDR inhibitors and IO agents in preclinical models of KRAS-mutant lung, head and neck cancer.

6. Beatson Institute, UK
Together with Owen Sansom, we are studying the impact of novel therapeutics on the tumour microenvironment in genetically engineered models of colorectal and pancreatic cancer.

7. Dana-Farber Cancer Institute, USA
David Weinstock is carrying out pre-clinical work to evaluate modulators of cell death pathways in T-cell lymphoma and other haematological cancer types being used to identify new indications and molecular markers for our novel agents.

8. Institute for Cancer Research, UK
Christopher Lord is using combination CRISPR screens to identify novel genetic determinants of tumour response to DDR inhibitors. This work may identify patient selection hypotheses and insights into mechanisms of action.

9. University of Cambridge, UK
The Carlos Castelo collaboration investigates the use of patient derived breast tumour models to understand the pathways and biomarkers involved in the response to novel therapies. A number of novel, large scale analysis techniques have been used for these studies, including RNA sequencing and mass cytometry (cytometry by Time of Flight, CyTOF).

10. Samsung Medical Centre, South Korea
Jeeyun Lee and Keunchi Park are Principal Investigators of the Phase II VICTORY and SUKSES umbrella clinical studies in gastric cancer and small cell lung cancer, designed to enable signal seeking in molecularly-selected patients. Emerging clinical and translational science data is facilitating better definition of molecular subtypes, mechanisms of resistance and exploration of specific responder/non-responder patients.

11. Morck & Company, Inc., USA
We combine resources and work collaboratively with Morck, with the aim of producing new clinical trial proposals. The partnership enables the efficient production of studies which would not otherwise be as readily feasible, by capitalising on the skills and expertise of both AstraZeneca and Morck.

Key publications in 2017

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“2017 was a year of significant change for IMED Respiratory Inflammation and Autoimmunity (RIA) as we built an organisation fit to deliver on our ambition of transformative therapies aiming for disease modification and cure in respiratory disease. With our research moving beyond traditional small molecules to new modalities, we are establishing IMED RIA as a recognised scientific leader in the field of respiratory research.”

Maria Belvisi, Vice President and Head of IMED Respiratory, Inflammation and Autoimmunity
In 2017, we restructured our IMED RIA organisation to focus our efforts on three scientific pillars: lung epithelium, lung immunity and lung regeneration to tackle the underlying causes of chronic lung diseases. This new direction builds on our strong portfolio and experience in respiratory medicine, including recently benralizumab (IL-5R mAb), tezepelumab (TSLP mAb) and PT010 (LABA/LAMA/ICS).

Our respiratory strategy

To realise our ambition of disease modification and cure in respiratory disease, we focus on three core themes: lung epithelium, lung immunity and lung regeneration. This continued scientific focus aims to achieve breakthrough innovation and establish world-class capabilities in respiratory disease to enable IMED RIA as scientific leaders in this field.

To realise our ambition of disease modification and cure in respiratory disease, we focus on three core themes: lung epithelium, lung immunity and lung regeneration. This continued scientific focus aims to achieve 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.

For the estimated 300 million people worldwide who have asthma, there is a continuing need for advances in therapy, especially for those whose symptoms cannot be controlled by today’s medicines.

AZD1402 is a first-in-class, inhaled Anticalin® protein developed for patients with inadequately controlled, moderate to severe asthma. It is designed with the aim to offer improved efficacy and tolerability compared to injectable biologics by using convenient and familiar inhalation delivery. AZD1402 is directed against the alpha subunit of the human IL-4 and IL-13 receptors and thereby blocks signalling of both IL-4 and IL-13, two of the signature cytokines driving inflammation in asthma.

IL-4Rα is a validated target based on clinical Phase III data for subcutaneously dosed dupilumab. We believe that AZD1402 may bring similar benefit to patients, with the convenience of inhalation rather than injection.

AZD1402 is the first of five inhaled Anticalin® proteins whose development has been made possible by our recently completed agreement with Pieris Pharmaceuticals Inc. The Anticalin® proteins are biengineered by Pieris to interact with antibody-like precision and potency at drug targets that would normally be intractable to traditional small molecule receptor blockers. This collaboration extends our ability to potentially deliver unique, new inhaled medicines to people with a range of respiratory diseases.

In 2017, it was agreed to move forward with AZD1402 as a candidate drug, less than two months after the completion of the agreement with Pieris Pharmaceuticals. The Phase I programme sponsored by Pieris Pharmaceuticals was initiated and the project achieved first dose in man in 2017 with the aim of establishing proof of mechanism in a cohort of patients.

The partnership between AstraZeneca and Pieris for inhaled Anticalin® proteins in respiratory diseases was nominated for ‘Best Partnership Alliance’ in the 2017 Scrip Awards.
Strengthen and progress our respiratory portfolio aligned to our three scientific pillars of lung epithelium, lung immunity and lung regeneration

We set out to

We delivered

To build our portfolio, six new projects were nominated in line with our new strategy, all with a clear respiratory focus.

We took the first inhaled Anticalin® treatment into man. AZD1942 (inhaled IL-4Rα antagonist), developed in collaboration with Pieris Pharmaceuticals achieved first dose in Phase I.

We progressed our clinical portfolio in a number of areas, including initiation of a proof of mechanism study with AZD5694, inhaled EtaC inhibitor, in patients with cystic fibrosis.

Abediterol (bronchodilator – related orphan nuclear receptor gamma, ROH1, inhibitor) showed in a Phase I study, the ability to inhibit interleukin – 17 (IL-17) production in blood from healthy volunteers.

Abediterol completed a study in patients with asthma which investigated the effects of ultra-low, and were subsequently highlighted in the ERS meeting summary in Lancet Respiratory Medicine.

This achievement confirmed that the combination was stable and that no unexpected drug-drug interactions occurred. AZD7594 Phase IIa study with Abediterol was dosed for the first time in man in a dry powder inhaler (DPI) and Aerosphere ® platform consists of engineered proteins which can bind with antibody-like precision to drug targets. They are small, robust and easy to purify, offering the potential of direct delivery to the lung via inhalation.

We progressed our clinical portfolio in a number of areas, including initiation of a proof of mechanism study with Abediterol to understand the biological effect. This enables more functionally selective targets to be addressed.

We used a combination of free energy perturbation (FEP) and hydrogen-deuterium exchange (HDX) techniques to build our understanding of the protein dynamics in several of our early projects.

Our studies have delivered unprecedented knowledge of differential targeting of lung tissues by inhaled medicines, compared to systemic drug delivery. We hope that this will enable us to design precision inhaled medicines that target specific lung sub-structures and will facilitate faster drug discovery and delivery of optimised medicines to the right patients.

To further develop and explore the application of HDX-MS, RIA, hosted the first global symposium in 2017 focusing solely on HDX-MS, attracting world scientists colleagues. The Lung-Sim platform is being used successfully to predict pre-clinical and clinical data for different formulations administered with different devices, and has the potential to address challenges when ‘bridging’ between different devices and formulations in late stage clinical development.

We progressed our bronchodilators in monotherapy or combination in Phase I and Phase II studies.

We successfully progressed two of our bronchodilators in monotherapy or combination in Phase I and Phase II studies.

At the beginning of 2017, a Phase IIa, a repeat-dose study of AZD8871 was conducted in patients with COPD, investigating two doses of AZD8871 and placebo. Results support further development and an additional Phase IIa study is now planned. Results of Phase I single-dose investigations in asthma and COPD were presented at the European Respiratory Society (ERS) congress in 2017. AZD7594, an inhaled selective glucocorticoid receptor modulator (SGRMR) is now ready for Phase III studies. In 2017, AZD7594 was dosed for the first time in man in a dry powder inhaler (DPI) fixed-dose combination with the beta-2 [β2] adrenergic antagonist bronchodilator, abediterol. The achievement confirmed that the combination was stable and that no unexpected drug-drug interactions occurred. AZD7594 Phase IIa data were also presented at the ERS congress in 2017, and were subsequently highlighted in the ERS meeting summary in Lancet Respiratory Medicine.

Abediterol completed a study in patients with asthma which investigated the effects of ultra-low, single doses administered via two different inhalers, Gardiner® DPI and AerospHERE® pressurized metered dose inhaler (pMDI). Both devices gave similar results, indicating that abediterol could be delivered by either device.

We progressed our inhaled bronchodilator combinations

We successfully progressed two of our bronchodilators in monotherapy or combination in Phase I and Phase II studies.

We progressed our clinical portfolio in a number of areas, including initiation of a proof of mechanism study with Abediterol to understand the biological effect. This enables more functionally selective targets to be addressed.

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To further develop and explore the application of HDX-MS, RIA, hosted the first global symposium in 2017 focusing solely on HDX-MS, attracting world leading experts in the field.

We expanded our inhaled drug opportunities in new modalities beyond small molecules

We invested in two novel platform technologies with the potential to deliver therapeutics to the lung through our collaborations with Pieris Pharmaceuticals Inc. and Ethris GmbH.

Our collaboration with Pieris Pharmaceuticals enables us to leverage the Pieris Anticalin® technology. The proprietary Anticalin® platform consists of engineered proteins which can bind with antibody-like precision to drug targets. They are small, robust and easy to purify, offering the potential of direct delivery to the lung via inhalation.

Our collaboration with Ethris GmbH, a leader in messenger RNA (mRNA) based therapeutics, gives us exclusive access to their proprietary stabilized non-immunogenic mRNA (SNPmRNA) technology and formulations for development of new therapies to treat asthma, COPD and idiopathic pulmonary fibrosis (IPF). mRNA therapies deliver genetic instructions to cells to produce selected proteins to help prevent or fight diseases. Ethris’ proprietary mRNA technologies can be targeted to the lungs to replace, inhibit or increase proteins that are involved in respiratory disease pathology.

We have made progress in our collaboration with Bicycle Therapeutics to target protein-protein interactions not usually addressed by a traditional small molecule chemistry approach. Early screening has generated several peptide sequences with promising properties with respect to binding affinity.

In addition, we are harnessing clustered regularly interspaced short palindromic repeats (CRISPR) gene editing tools as a therapeutic approach for defined patient groups with COPD.

We understand the spatial distribution of inhaled drug and response

We set out to

We delivered

The human lung is a complex organ composed of multiple types of cell layered through an estimated 24 ‘generations’ of airway branches from the trachea to the periphery. To improve understanding of how best to optimise delivery of inhaled medicines in different locations of the lung, and minimise unwanted tissue exposure, we used state of the art imaging to explore targeting of lung epithelial and sub epithelial cells and trafficking immune cells. Using high resolution mass spectrometry and RNAscope® technology, coupled with tissue and blood sampling techniques, we were able to determine drug concentrations and effects during lung exposure, in small areas of tissue, with high resolution.

Our studies have delivered unprecedented knowledge of differential targeting of lung tissues by inhaled medicines, compared to systemic drug delivery. We hope that this will enable us to design precision inhaled medicines that target specific lung sub-structures and will facilitate faster drug discovery and delivery of optimised medicines to the right patients.

Alongside this research, we are benefiting from the application of Lung-Sim, an innovative physiologically based pharmacokinetic prediction tool developed by our Pharmaceutical Sciences colleagues. The Lung-Sim platform is being used successfully to predict pre-clinical and clinical data for different formulations administered with different devices, and has the potential to address challenges when ‘bridging’ between different devices and formulations in late stage clinical development.

We utilise the combination of cutting edge computational and experimental techniques to progress projects

We set out to

We delivered

We used a combination of free energy perturbation (FEP) and hydrogen-deuterium exchange (HDX) techniques to build our understanding of the protein dynamics in several of our early projects.

This has been fruitful because it has given us necessary insights into how protein dynamics influence pharmacodynamic readouts so that we can prioritise which new compounds should be synthesised.

FEP is based on statistical mechanics which calculate the free energy involved in transforming one molecule into another. The difference in free energy between a ligand and a reference compound is calculated, both in solution and when bound to the protein, resulting in a predicted free energy difference.

Combining HDX with mass spectrometry (HDX-MS) allows us to study the conformation and dynamics of proteins and determine the impact of binding on different classes of protein compound to understand the biological effect. This enables more functionally selective targets to be addressed.

To further develop and explore the application of HDX-MS, AstraZeneca Gothenburg, led by IMED R&D, hosted the first global symposium in 2017 focusing solely on HDX-MS, attracting world leading experts in the field.
**Therapy area progress**

**Respiratory, Inflammation and Autoimmunity**

Differentiated pre-clinical efficacy of a novel inhaled PI3Kδ inhibitor developed for patients with steroid-resistant asthma

People with asthma typically have eosinophilic inflammation in their lungs driven by activation of immune cells called helper T2 (Th2) cells and are generally responsive to inhaled anti-inflammatory steroids treatment. However, there is growing evidence that some patients have a mixture of activated T-cell types, including Th1, Th2 and Th17, which attract both eosinophils and neutrophils into their lungs, and cause an inflammatory response and symptoms that are refractory to both inhaled and oral steroid treatment. This mixed T-cell type of asthma is seen primarily in mixed granulocytic asthma (MGA) but also in other some other asthma phenotypes.

Inhaled phosphatidylinositol 3-kinase gamma and delta (PI3Kγδ) inhibitors are being developed to impact multiple inflammatory steroid treatment. This mixed T-cell type of asthma is seen primarily in mixed granulocytic asthma (MGA) but also in some other asthma phenotypes.

Inhaled phosphatidylinositol 3-kinase gamma and delta (PI3Kγδ) inhibitors are being developed to impact multiple pathways of airway inflammation driven by Th2, Th1, and Th17 cells, with potential to address steroid-refractory asthma.

Inhalation delivery aims to maximise local effects, while minimising systemic side effects. Through our collaboration with U-BIOPRED, we are identifying PI3Kδ/Cδ gene signatures to optimise treatment through a precision medicine approach. Following the nomination of our PI3Kδ inhibitor, AZD8154, as a candidate drug at the end of 2016, we have focussed on two key challenges in 2017: predicting free drug concentration within the lung, and being able to demonstrate pharmacodynamic differentiation in vivo and in vitro.

To address the first challenge, we are adopting a unique in-house developed physiologically based pharmacokinetic (PBPK) inhalation model, to describe inhaled drug disposition and regional free concentrations in order to predict free concentrations after inhalation delivery of AZD8154.

To address the second challenge, we are investigating the importance of dual inhibition of both PI3Kδ and PI3Kγ compared to inhibition of PI3Kδ alone. The collaboration with Professor Hanshiro (University of Newcastle, Australia) gave us access to his novel pre-clinical model of steroid insensitive airway inflammation and hypersensitivity, caused by allergy or respiratory infection. The project team is using this model to compare the effects of AZD8154 with a competitor molecule that is selective only for PI3Kδ. These data strengthen the inhaled PI3Kδ project as we can now model the behavior of AZD8154 in the lung to support a therapeutic dose prediction. Furthermore, we are building confidence that this dual PI3Kδ/δ inhibitor approach is a potential way forward for patients with mixed T-cell severe asthma.

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**Key publications in 2017**

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<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Author</th>
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**Nature Reviews Drug Discovery**

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<th>Title</th>
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<tr>
<td>Directing evolution: the next revolution in drug discovery?</td>
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<tr>
<td>Davis A, Valeur E, Poorsa A.</td>
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**American Journal of Respiratory and Critical Care Medicine**

<table>
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<tr>
<th>Title</th>
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<tr>
<td>XEN-D0501, a novel transient receptor potential vanilloid 1 antagonist, does not reduce cough in patients with refractory cough</td>
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**Clinical Pharmacology and Therapeutics**

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<th>Title</th>
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<tr>
<td>First-in-human study with the inhaled TJP1 oliginucleotide against AZD1419 results in on-target interferon responses in the lung, and is safe and well-tolerated</td>
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**Journal of Medicinal Chemistry**

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<tr>
<td>Design and synthesis of soluble and cell-permeable PI3Kδ inhibitors for long-acting inhaled administration</td>
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**Journal of Medicinal Chemistry**

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<tr>
<td>Design of a chemical probe for the Bromodomains and PHD-Finger-containing (BRPF) family of proteins</td>
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**Journal of Medicinal Chemistry**

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<td>Selective non-steroidal glucocorticoid receptor modulators for the inhaled treatment of pulmonary diseases</td>
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**Pharmacology & Therapeutics**

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<td>Patient stratification and the unmet need in asthma</td>
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**CPT: Pharmaceutometrics & Systems Pharmacology**

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<tr>
<td>Translational model to predict pulmonary pharmacokinetics and efficacy in man for inhaled bronchodilators</td>
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**PLoS One**

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<td>Altered regulation and expression of genes by BET family of proteins in COPD patients</td>
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### Therapy area progress: Respiratory, Inflammation and Autoimmunity

**A selection of key collaborations in 2017**

| 1. | Pieris Pharmaceuticals Inc, US | In 2017, we signed a multi-target collaboration with Pieris Pharmaceuticals, Inc. to develop novel inhaled drugs that leverage Pieris’ Anticalin® platform. The proprietary Anticalin® platform is engineered proteins which behave like antibodies by binding to sites on proteins and small molecules. Anticalin® proteins are small, robust and easy to purify, and can be delivered into the lung via inhalation. |
| 2. | Ethris GmbH, Germany | In 2017, together with Medimmune we announced a five-year strategic collaboration with Ethris GmbH, a leader in messenger RNA (mRNA)-based therapeutics. The focus will be on developing new stabilised non-immunogenic mRNA (SNIM®) therapies for respiratory diseases. The collaboration will give us exclusive access to Ethris’ proprietary SNIM®RNA technology and formulations to develop new targets for investigation in the areas of asthma, COPD and PF. |
| 3. | Bicycle Therapeutics, UK | Our collaboration with Bicycle Therapeutics, signed in 2016, is progressing successfully. The aim of the work is to identify and develop bicyclic proteins to treat cardiovascular, metabolic, and respiratory disease. The early screening efforts in our respiratory project have generated several peptide sequences with promising binding affinity related properties. |
| 4. | Imperial College London, UK | A collaboration with Imperial College London (ICL) to establish a Respiratory Pharmacology Hub at the ICL campus in London was signed in 2017. The aim of the hub is to strengthen and synergise the respiratory pharmacology capabilities within IMED RIA with those at Imperial College by having IMED RIA colleagues working side by side with Imperial College scientists. By building on the strengths of both organisations with fully integrated teams, we aim to accelerate ground-breaking research into the development of new medicines to help address unmet treatment needs in respiratory disease. |
| 5. | Karolinska Institutet, Sweden | Our collaboration with Professor Anders Lindén from Karolinska Institutet and Karolinska University Hospital aims to characterise bacterial colonization in relation to alterations of immune signalling by IL-26 and Tn17 cells in the lungs of smokers with and without COPD and /or chronic bronchitis. |
| 6. | University of Southampton, UK | In 2017, we signed an additional agreement with the University of Southampton to develop a novel in vivo imaging method to visualise lung inflammation in COPD patients. The goal of the project is to identify the many facets of immune and inflammatory biology in lung disease and relate this to the pulmonary anatomy, in line with our scientific ambition to modify and cure respiratory disease focusing on lung epithelium, lung immunity and lung regeneration. |
| 7. | Wallensten Centre for Molecular and Translational Medicine, Sweden | The Wallensten Centre for Molecular and Translational Medicine (WCMTM) situated at the University of Gothenburg continues to build. One of the objectives together with IMED RIA is to enhance the scientific collaboration in the field of respiratory and inflammatory diseases in the Gothenburg region and the overall goal is to regain Sweden’s position as a world-leader in molecular medicine. We have already established a respiratory presence in the WCMTM and recruited a respiratory epigeneticist. The recruitment of other key senior scientists is ongoing both in the respiratory and cardiovascular and metabolic area. |
| 8. | Innovative Medicines Initiative U-BIOPRED (Unbiased Biomarkers in PREDiction of respiratory disease outcomes) | The aim of this consortium is to personalise severe asthma diagnosis and treatment by creating ‘handprints’ that identify sub-phenotypes of asthma by a system medicine design. Anonymised meta-data has been collected from pediatric and adult cohorts including demographic, clinical, transcriptomic, proteomic, lipidomic, genomic and metabolic data. We have identified novel severe asthma phenotypes, based on complex biological networks. This identified novel disease drivers such as interacting Type-2 and non-Type-2 pathways. This is a breakthrough in asthma patient stratification with the potential to revolutionise current therapeutic approaches. |
| 9. | University of Lund, Sweden | We support the PhD scholarship of UM Hedström together with Lund University and Gunilla Westergren-Thorson, the Dean of the Medical Faculty. The aim is to study the effects of extracellular matrix signaling in lung repair and regeneration in chronic pulmonary disease. We are focussing on the interactions between extracellular matrix and airway epithelial cells by repopulating bronchial scaffolds derived from COPD patients and healthy smokers with normal and COPD airway epithelial cells. |
| 10. | Fraunhofer Institute for Toxicology and Experimental Medicine, Germany | The aim of our collaboration with Professor Antje Prasse is to understand what pathways drive fibrotic repair in idiopathic pulmonary fibrosis versus inefficient repair in emphysematous COPD. We are using Prasse’s differential basal cell biology phenotypic assay to assess emerging lung regeneration targets. This novel in vitro model will be used to determine the impact of small molecules on disease cell phenotypes, providing human patient validation for emerging targets. |

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<th>RIA pipeline</th>
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<tr>
<td><strong>Pre-clinical</strong></td>
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<tr>
<td>AZD8154 / PI3Kgd</td>
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<td><strong>Phase I</strong></td>
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<tr>
<td>AZD1402 / IL4 / Anticalin®</td>
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<td>AZD5634 / ENAC</td>
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<td>AZD6967 / eCSGRM</td>
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<td>AZD6284 / RORq</td>
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<tr>
<td><strong>Phase IIa</strong></td>
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<td>AZD7994 / iCSGRM</td>
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<td>AZD1419 / TL1B</td>
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<td>AZD0871 / MABA</td>
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<td>abediterol / LABA</td>
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<tr>
<td>AZD7986 / DPP1 (multisite with grant option)</td>
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<tr>
<td><strong>Phase IIb</strong></td>
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<tr>
<td>PT010 / Triple MDI (asthma)</td>
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<td>PT027 / ashina</td>
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<td><strong>Phase III / LCM</strong></td>
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<td>PT010 / Triple MDI (in COPD)</td>
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Pipeline correct as of Q4 2017, not including Medimmune programmes.
Cardiovascular, Renal and Metabolism

“In 2017, IMED Cardiovascular, Renal and Metabolism (CVRM) made great progress with our clinical pipeline including rapidly moving two promising projects, AZD5718 and verinurad, into Phase IIa clinical trials, and advancing AZD8601 ready for Phase IIa start. At the same time, we continued to build a strong discovery portfolio with an exciting mix of various therapeutic modalities. We are expecting a stimulating and rewarding 2018.

Regina Fritsche-Danielson, Vice President, IMED Cardiovascular, Renal and Metabolism
IMED CVRM is focussed on discovering and developing novel drug candidates with the aim to improve the lives of patients with long term debilitating cardiovascular, renal and metabolic diseases, including heart failure, diabetes, non-alcoholic steatohepatitis (NASH) and chronic kidney disease.

In early 2017, positive readouts from critical pre-clinical studies, combined with strong leadership, enabled us to move AZD8601, our vascular endothelial growth factor A (VEGF-A) modified mRNA, into a first in man, Phase I clinical trial. AZD8601 is the first ever modified mRNA to be developed for a cardiovascular indication, and a strong and exciting candidate within our new modalities platform. Following a Phase I study, AZD8601 progressed and is now ready for the start of Phase II clinical trials, an achievement we are very proud of.

In parallel, we continue to build a strong discovery portfolio with a broad mix of modalities. Our nomination of new candidate drugs and repositioning of AZD9807 place us in an exciting position to develop medicines which may be of benefit in the treatment of patients with cardiovascular, renal and metabolic diseases.

In collaboration with our partners at TissUse, and colleagues in Drug Safety and Metabolism, we developed a human microfluidic two-organ chip model to study the interplay between pancreatic and liver cells. In this miniature system, compartmentalised cultures of human pancreatic islet microtissues and liver spheroids are interconnected with microfluidic channels where cross-talk based on insulin and glucose regulation emulates systemic interaction. The established co-culture is robust, maintaining functional responses for two weeks. The science behind these miniature models combining engineering and biology was recently published, and showcases the power of our cross functional and collaborative culture. The models have the potential to improve early validation of drug targets in diabetes and identification and testing of novel therapies. They also provide an opportunity for elucidating factors involved in organ cross-talk and offer a real substitute for animal models.

Progress our research on hepatocyte-pancreatic islet cross talk using micro physiological systems

We identified AZD3366 (APT102) recombinant apocytochrome as a unique drug candidate, which we are now developing together with our business and research partner, APT Therapeutics. During the next two years, we will work with APT to evaluate the compound in clinical trials in patients with ST elevation myocardial infarction (STEMI) and acute ischaemic stroke (AIS). AZD3366 has a unique mode of action that provides a differentiated opportunity compared to current standard of care. Moreover, it has the potential for a rapid onset of antithrombotic and tissue protective effects without bleeding. If these properties are verified in the clinic, the protective effect of AZD3366 in the hyperacute phase of STEMI and AIS may offer a bridge to existing, long-term antithrombotic treatment.

Demonstrate scientific leadership

We completed a Phase I clinical trial for AZD5718 (FLAP inhibitor), in development for the treatment of coronary artery disease, showing promising data in healthy volunteers.

We also progressed verinurad into Phase II trials in patients with chronic kidney disease and we are excited to work on the development of this compound in this area of large unmet medical need.

To bring virtual screening to the next level

We developed a virtual screening tool based on the previous success of OpenEye Scientific Software’s FastRocs. The new tool, FastVS, has increased scale, speed and usability and puts virtual screening hit lists from any available molecular database at the fingertips of our scientists. This new tool was developed through a collaboration between computational chemists at IMED CVRM and the team at OpenEye Scientific Software. It reduces the time to search and score entries in our library of two million compounds from hours to seconds.

We set out to

Showcase strong scientific leadership for our small molecule heart failure pipeline

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Identify opportunities to further build our presence in acute coronary syndrome

We achieved our first publications in major peer-reviewed journals, of which 46 were in high quality and seven in high impact journals.

A key highlight was our publication in Cell, which came from our long-term collaboration with Professor Domenico Accili at Columbia University Medical Centre who, earlier in 2017, was awarded the Banting medal for ‘outstanding, long-term contributions to the understanding, treatment or prevention of diabetes’. This publication demonstrated novel mechanisms whereby insulin regulates liver glucose and lipid metabolism via the transcription factor FOXO1, raising the possibility of preventing diabetes. This publication demonstrated novel mechanisms whereby insulin regulates liver glucose and lipid metabolism via the transcription factor FOXO1, raising the possibility of developing selective modulators of unliganded transcription factors to dial out adverse effects of insulin sensitizers.

We presented significant results from our industry-leading pipeline, at key conferences in 2017, showcasing the impressive advances of our discovery and clinical stage programmes. These included meetings of the European Society of Cardiology (ESC), European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA), American Chemical Society (ACS), American Heart Association (AHA), American Society of Nephrology (ASN) and Oligonucleotide Therapeutic Society.

We continued to strengthen our engagement with universities, by initiating joint PhD and post-doctoral opportunities. These initiatives benefit from the combination of scientific and leadership experience from industry and academia. Also in 2017, Associate Principal Scientist, Dr. Sepideh Sarmazdeh, was appointed Adjunct Professor in Molecular Biology at the University of Skövde and Principal Scientist, Dr. Jerome Boucher, was appointed Adjunct Senior Lecturer in Molecular and Clinical Medicine, at University of Gothenburg, and started a research laboratory at the newly established Wallenberg Centre for Molecular and Translational Medicine.

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A key highlight was our publication in Cell, which came from our long-term collaboration with Professor Domenico Accili at Columbia University Medical Centre who, earlier in 2017, was awarded the Banting medal for ‘outstanding, long-term contributions to the understanding, treatment or prevention of diabetes’. This publication demonstrated novel mechanisms whereby insulin regulates liver glucose and lipid metabolism via the transcription factor FOXO1, raising the possibility of developing selective modulators of unliganded transcription factors to dial out adverse effects of insulin sensitizers.

We presented significant results from our industry-leading pipeline, at key conferences in 2017, showcasing the impressive advances of our discovery and clinical stage programmes. These included meetings of the European Society of Cardiology (ESC), European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA), American Chemical Society (ACS), American Heart Association (AHA), American Society of Nephrology (ASN) and Oligonucleotide Therapeutic Society.

We continued to strengthen our engagement with universities, by initiating joint PhD and post-doctoral opportunities. These initiatives benefit from the combination of scientific and leadership experience from industry and academia. Also in 2017, Associate Principal Scientist, Dr. Sepideh Sarmazdeh, was appointed Adjunct Professor in Molecular Biology at the University of Skövde and Principal Scientist, Dr. Jerome Boucher, was appointed Adjunct Senior Lecturer in Molecular and Clinical Medicine, at University of Gothenburg, and started a research laboratory at the newly established Wallenberg Centre for Molecular and Translational Medicine.

To bring virtual screening to the next level

We developed a virtual screening tool based on the previous success of OpenEye Scientific Software’s FastRocs. The new tool, FastVS, has increased scale, speed and usability and puts virtual screening hit lists from any available molecular database at the fingertips of our scientists. This new tool was developed through a collaboration between computational chemists at IMED CVRM and the team at OpenEye Scientific Software. It reduces the time to search and score entries in our library of two million compounds from hours to seconds.
Exploring the boundaries of heart failure care with AZD8601 – the world’s first modified mRNA therapeutic being developed for a cardiovascular indication

Heart failure is among the leading causes of death due to cardiovascular disease. As no current treatment can reverse damage to the heart muscle, the prognosis is worse than for many cancers. The global prevalence of cardiovascular disease is predicted to increase every year, due to the expansion of the aging population and other influences of modern life. Thus, there is an urgent need for novel therapeutic approaches to reduce the burden of heart failure for patients and society.

Today, there are several surgical, interventional and medical approaches to treat patients after a heart attack to reduce mortality and morbidity. However, no therapy so far has been able to repair or regenerate the damaged heart to treat or reverse heart failure.

In 2017, our cardiac regeneration programme received a regulatory approval for a Phase IIa trial to explore this new approach in patients with heart failure who are undergoing coronary artery bypass surgery. AZD8601 is being developed by our scientists in close partnership with colleagues at Moderna Therapeutics, who pioneer in mRNA medicines, and provided us with the technology to enhance production of a key protein, VEGF-A, in the heart, as a potential treatment approach to heart failure patients. This modified mRNA-based therapy is an innovative, evolving treatment concept that can be used to enable therapeutic production of proteins. This concept is opening up new treatment approaches to heart failure.

VEGF-A is an exciting target, because it has been shown to play a critical role in the regulation of new blood vessel formation and has a pro-survival effect on vascular, endothelial, and cardiac cells. It also enhances the proliferation of epicardial derived progenitor cells, inducing a fate switch towards endothelial lineage.

AZD8601 is being evaluated for potential application in diseases that cannot be addressed with existing treatments and represents an advance in the development of biologic therapies.

AZD8601 is the first ever modified mRNA programme evaluated in a cardiovascular indication. The compound has been designed to initiate VEGF-A protein expression from a clinical grade mRNA transcript, resulting in the local production of human VEGF-A.

The Phase I clinical trial was a major milestone for the project and for the advancement of mRNA medicines overall. While there have been previous clinical trials of mRNA-based prophylactic vaccines, AZD8601 is the first mRNA therapeutic evaluated for a cardiovascular indication. With AZD8601, we broke new ground advancing the project ready for Phase IIa start in the beginning of 2018. We believe that AZD8601 holds the potential to make a significant difference to the future care of patients with ischemic vascular disease. The progress of the project marks a critical milestone for the IMED CVRM strategy and brings us even closer to one of our goals: to discover and develop therapeutics that will deliver life-changing regenerative treatments to patients with heart failure.

Key publications in 2017

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In 2017, we received a regulatory approval for a Phase IIa trial to explore in patients with heart failure who are undergoing coronary artery bypass surgery.
Delivering drugs with precision – specific and selective targeting of pancreatic β-cells for the treatment of diabetes

The global burden of Type 2 diabetes is increasing worldwide and it is of considerable concern to patients, and at public health level, owing to the significant direct costs of healthcare and indirect costs of lost productivity. Successful treatment of Type 2 diabetes therefore needs a constant supply of novel innovations, with the ultimate aim of curing the disease.

A hallmark of Type 2 diabetes is insulin resistance and loss of insulin producing β-cells in the islets of Langerhans of the pancreas. There are no approved therapies that reverse loss of functional pancreatic β-cell mass, the primary defect leading to disease progression in Type 2 diabetes. There is therefore a substantial unmet medical need for treatment.

Antisense oligonucleotides (ASOs) offer great promise as β-cell regenerative treatments because they can be used to switch off expression of genes linked to β-cell loss. However, β-cells are resistant to ASO uptake and systemic administration does not get ASOs close enough to the cells. Thus, inability to selectively deliver antisense (or other) therapies to β-cells is a substantial barrier to the development of innovative and safe treatments for Type 2 diabetes.

To address this challenge, scientists from IMED CVRM, Discovery Sciences, and Drug Safety and Metabolism established a creative, fast-moving open innovation collaboration with Ionis Pharmaceuticals. The work was funded on the hypothesis that cell specific targeted delivery and increased uptake of ASOs can be achieved by attaching an ASO to a high-affinity ligand for a receptor which is enriched on β-cells, and has the ability to internalise. This principle has previously been successfully demonstrated by Ionis using GalNAc conjugation to enhance ASO uptake in hepatocytes via internalisation of the asialoglycoprotein receptor.

The concept was successfully demonstrated using a glucagon-like peptide 1 receptor (GLP1R) peptide agonist, to deliver ASOs to pancreatic β-cells. GLP1R is expressed on pancreatic β-cells, and internalises upon ligand binding. In this way, the team were able to switch off mRNA expression in both in vitro cell systems, and in pancreatic islet cells in vivo.

We believe that the breakthrough achievement has the potential to transform therapy for Type 2 diabetes. Together with our key collaborator, Ionis, we have established a novel technology platform and are now in a position to take the lead in the development of targeted delivery of therapeutic cargo specifically to pancreatic β-cells.

With this new knowledge we have developed the ability to pharmacologically modulate targets previously not amenable to classical small molecules. This work brings us closer to one of our goals – to discover and develop therapies that can restore β-cell function and potentially cure Type 2 diabetes. The platform is a cross functional, inter-disciplinary approach that brings together expertise from drug discovery, biotechnology, and biology to achieve this ambitious goal.

Shalini Andersson
Senior Director and Head of Drug Metabolism and Pharmacokinetics

Shalini is, in addition to her role as Department Head, leading the targeted drug delivery platform. The platform is a cross functional effort where Shalini's long-term experience and strong leadership capabilities have been essential for the rapid success of the programme. Shalini is also leading the open innovation collaboration with Ionis Pharmaceuticals and is Project Lead for subcutaneous delivery of modified RNA to man. Prior to her current role, Shalini held several leadership roles within medicinal chemistry including Head of Enabling Technologies and Head of Lead Optimisation focused on developing world class platforms for design, synthesis, purification and analysis of small molecules for drug projects. Shalini received her PhD at the University of Linkoping where she also holds an Associate Professorship in organic and analytical chemistry. She joined AstraZeneca in 1997. She is the author or co-author of over 35 peer reviewed articles, two book chapters and four patents.

Jeremie Boucher
Principal Scientist, Bioscience Diabetology

Jeremie joined AstraZeneca in 2014, from the renowned Joslin Diabetes Center at Harvard Medical School.

He brings over 15 years of experience in adipose tissue biology and diabetes. He has published 45 scientific articles in journals including Nature Medicine, Nature Communications, Cell Metabolism, Science Translational Medicine, JCI and PNAS. As part of IMED CVRM Diabetology, Jeremie coordinates early drug discovery efforts and leads projects related to adipose tissue biology, drives several strategic academic collaborations and contributes to the Bioscience Diabetes leadership team. In 2017, Jeremie was appointed Adjunct Senior Lecturer at Gothenburg University, and started a research laboratory at the newly established Wallenberg Center for Molecular and Translational Medicine. His research focuses on characterising the molecular changes occurring during brown adipose tissue formation, with the ambition to discover novel targets for the treatment of metabolic diseases.

Imaging the latest progress in CVRM therapies and programmes
A selection of key collaborations in 2017

1. Moderna Therapeutics, US

The collaboration with Moderna aims to discover and develop mRNA therapeutics for the treatment of cardiovascular, metabolic and renal diseases and cancer. AZD8601 VEGF-A which is an investigational mRNA-based therapy, was the first project to enter clinical development, and has successfully completed clinical Phase I study. The collaboration has also led to the development of a lipid nanoparticle delivery system that can be utilised in man for subcutaneous administration and repeated dosing.

2. IONIS Pharmaceuticals, US

This strategic collaboration is focussed on discovery and development of ASO therapies for cardiovascular, metabolic and renal diseases. The development of new, targeted delivery approaches for oligonucleotide therapeutics which give access to disease relevant tissues is ongoing, and the collaboration has successfully delivered its first candidate drug.

3. Integrated Cardio Metabolic Centre, Sweden

A collaboration with Professor Winston Shim on human inducible pluripotent stem cells (iPS) derived cardiomyocytes for disease modelling with the aim to phenotype mutations that play a role in heart failure. We will use different modalities including CRISPR methodologies to reverse deficits in this innovative “patient-in-a-dish” model.

4. National Heart Centre Singapore, Singapore

A collaboration with Professor Bin Zhou, we are studying the contribution of resident cardiac progenitor cells to new cardiomyocyte formation under normal and pathological conditions. The collaboration has recently generated four high impact publications with IMED CVRM scientist as co-authors.

5. Renal Pre-Competitive Consortium

(University of Michigan, Eli Lilly, Gilead and Novo Nordisk)

Through this collaboration, IMED and Medimmune scientists have access to a world-leading source of patient intrarenal transcriptomic data and animal models to advance understanding of molecular drivers of chronic kidney disease and identify potential new first in class targets and therapies.

6. Shanghai Institute for Biological Sciences, China

In collaboration with Professor Bin Zhou, we are studying the contribution of resident cardiac progenitor cells to new cardiomyocyte formation directly into the academic environment at Max Planck institute, led by Professor Herbert Waldmann. Researchers from industry and academia work side-by-side to address challenging therapeutic targets through novel strategies.

7. Max Planck Institute, Institute of Molecular Physiology, Germany

This new “satellite unit” embeds AstraZeneca scientists directly into the academic environment at Max Planck institute, led by Professor Herbert Waldmann. Researchers from industry and academia work side-by-side to address challenging therapeutic targets through novel strategies.

8. Wallenberg Centre for Molecular and Translational Medicine, Sweden

Through this collaboration, IMED and Medimmune scientists have access to a world-leading source of patient intrarenal transcriptomic data and animal models to advance understanding of molecular drivers of chronic kidney disease and identify potential new first in class targets and therapies.

9. University of Queensland, Australia

The collaboration with Professor Elisabeth Gillam, is focussed on developing novel engineered thermostable cytochrome P450 enzymes with improved stability and solvent tolerance. These enzymes can catalyse a wide range of P450 metabolic pathways and are being explored for emerging applications in synthetic biology.

10. University of Gothenburg, Sweden

Human genetic studies have identified molecular mechanisms and therapeutic targets for the prevention and treatment of non-alcoholic fatty liver disease (NAFLD). In our collaboration with Professor Stafano Romano at the University of Gothenburg, we are exploring novel cell and animal models to direct future drug development.

11. Bicycle Therapeutics, UK

The collaboration with Bicycle Therapeutics is aimed at the identification and development of bicyclic peptides to treat respiratory, cardiovascular, renal and metabolic diseases. The Bicycle® platform provides an exciting opportunity to screen a vast number of highly constrained bicyclic peptides to then be optimised towards disease-relevant targets.

12. University of Michigan, US

We entered a new collaboration with University of Michigan to identify new therapeutic targets for the treatment of chronic kidney diseases for which there are currently no effective treatments. Within the four-year agreement our teams will jointly conduct chemistry and drug discovery research using novel pre-clinical disease models and phenotypic screens.

This collaboration represents a new level of cooperation between the University of Michigan and an industry partner to significantly improve the treatment and outcome for patients with chronic kidney disease. New therapies for patients are waiting to be discovered among the vast amount of information now available. I’m confident this is an effective route to get better medicines to people with failing kidneys.”

Steve Kunkel, Ph.D., Senior Associate Dean for Research at the University of Michigan Medical School Office of Research
“We have continued to drive significant advances in the science of neurodegenerative diseases, epilepsy and pain at IMED Neuroscience, thanks to our innovative ways of working, including mutually beneficial collaborations with key academic institutions and developments within our own team of world-class talent. By combining outstanding scientific expertise and unique skills in drug discovery and development, we are intent on transforming latest science into novel, life changing medicines.”

Iain Chessell, Vice President, IMED Neuroscience
Our small, entrepreneurial IMED Neuroscience group is responding to breaking science by rapidly capitalising on new opportunities, aiming to deliver a portfolio of first and best-in-class medicines.

Our IMED Neuroscience organisation is progressing our unique portfolio of small molecule and biologic therapies, exploiting breaking science in new modalities, such as proteolysis targeting chimeras (PROTACs) and antibody-drug conjugates, and utilising artificial intelligence (AI) and machine learning to identify the best molecules to meet the exacting demands of central nervous system (CNS) therapeutics.

As a small, focussed and agile group, we respond to new discoveries as they emerge, and that pathologically relevant ɑ-synuclein aggregates can propagate between cells connected regions of the brain. In experimental studies, we have demonstrated that MEDI1341 dose-dependently and robustly suppresses free ɑ-synuclein levels in brain interstitial fluid and cerebrospinal fluid, demonstrating that MEDI1341 can enter the brain and sequester extracellular ɑ-synuclein aggregates. These findings have helped to validate the development of antibody-based drug approaches that target extracellular ɑ-synuclein for the treatment of Parkinson’s disease.

MEDI1341 is a high affinity ɑ-synuclein-specific, fully human IgG1 monoclonal antibody that specifically binds to the C-terminal region of human ɑ-synuclein. It is engineered for reduced effector function by virtue of a triple mutation modifying treatments for Parkinson’s is slow Parkinson’s disease progression. There are currently available that can prevent aggregation of ɑ-synuclein. Finally, pre-clinical safety toxicology studies have been completed with MEDI1341 and no safety findings were observed in animals.

We believe that MEDI1341 is an exciting highly differentiated novel candidate drug that can sequester extracellular ɑ-synuclein and modify the underlying disease process of Parkinson’s disease; planned Phase I clinical studies will provide critical insight into the pharmacodynamics effects of MEDI1341. In 2017, we took a strategic decision to enter a collaborative agreement with Takeda Pharmaceuticals to jointly develop and commercialise MEDI1341, a compound we hope has the potential to be a world class asset, while at the same time sharing the known risks and costs of developing neuroscience drug programmes. In this collaboration, we will oversee all of the Phase I clinical studies, after which Takeda will take the lead on further development activities.

Could MEDI1341 halt the spread of Parkinson’s disease?

At the end of 2017, MEDI1341, our high affinity ɑ-synuclein monoclonal antibody, entered the first clinical trials to explore its potential as a disease modifying drug for Parkinson’s disease, an age-related neurodegenerative disorder that affects approximately 10 million people worldwide. Despite significant progress in understanding disease mechanisms and substantial drug discovery-related efforts over recent years, no medicines are currently available that can prevent or slow Parkinson’s disease progression. Thus, the development of disease-modifying treatments for Parkinson’s is an important unmet clinical need.

ɑ-synuclein is a protein, found in large amounts in the brain, that has a tendency to form clumps (aggregates) and has been implicated as a cause of Parkinson’s disease. For example, ɑ-synuclein aggregates are the major constituent of Lewy bodies and Lewy neurites, which are pathological insoluble inclusions found inside the brain cells of people with Parkinson’s disease. In addition, missense mutations and multiplications in the ɑ-synuclein gene cause familial genetic forms of Parkinson’s disease. Post-mortem histopathological studies indicate that the progressive neurodegeneration observed in Parkinson’s may result from the spread or propagation of ɑ-synuclein ‘Lewy’ pathology between neuroanatomically connected regions of the brain. In support of this theory, recently published experimental studies have demonstrated that pathologically relevant ɑ-synuclein aggregates can propagate between cells in culture via an extracellular phase, and pathological ɑ-synuclein aggregates can spread throughout the brain in mouse models of Parkinson’s disease. In these experimental models, it has been shown that administration of antibodies directed against ɑ-synuclein can block its uptake into cells and prevent its spread, as well as clearing ɑ-synuclein aggregates. These findings have helped to validate the development of antibody-based drug approaches that target extracellular ɑ-synuclein for the treatment of Parkinson’s disease.

As a small, focussed and agile group, we have invested in projects targeting alpha (α)-synuclein and tau, proteins involved in Parkinson’s disease and Alzheimer’s disease, respectively, and brought forward development of molecules such as MEDI1341 (ɑ-synuclein antibody).

We are excited to have entered a partnership with Takeda to jointly develop MEDI1341 for Parkinson’s disease. We have continued our ongoing collaboration with Eli Lilly and Company with MEDI1814, a unique amyloid-beta 42 (Aβ42) selective antibody which targets pathological proteins in Alzheimer’s disease. This complements our collaboration on lanabecestat, our oral, potent, small molecule beta (β) secretase (BACE) inhibitor in Phase III.

We have documented our scientific progress and findings in a number of high impact and high quality scientific papers. Our consistent commitment to high quality science has led to a strong portfolio with the potential to provide the next wave of revenue generation for AstraZeneca, and positively affect the lives of those living with neurodegenerative diseases, chronic pain, or psychiatric conditions.
Highlights

We set out to

We delivered

Progress development of new medicines for neurodegenerative diseases

In addition to continuing our Phase III studies of lanecozastat in collaboration with Eli Lilly and Company, we have completed our Phase I study of MED3181A. Here, we have generated data showing selective abrogation of Aβ 1-42 in the cerebrospinal fluid of patients with Alzheimer’s disease, and look forward to continued progress within the framework of our co-development agreement, also with Eli Lilly and Company.

In 2017, we announced a new co-development agreement with Takeda to progress MEDI1341, a monoclonal antibody targeting α-synuclein for the treatment of Parkinson’s disease.

Progress our chronic pain pipeline

MEDI7352, our nerve growth factor/tumour necrosis factor bispecific molecule, will soon complete the single ascending dose portion of a first time in human study in patients with painful osteoarthritic knees of the knee. Multiple ascending dose cohorts are ongoing. Early data shows predicted pharmacokinetic properties as well as target engagement. Partnering activities have been initiated with a number of parties, moving quickly to confidential discussions.

In addition, we have made great progress with our pre-clinical portfolio, delivering a new molecule for entry into clinical development in 2018. We have also progressed assets in discovery in order to provide sustainability for our portfolio.

Nurture our collaborations and partnerships

In addition to forging a new collaboration with Takeda for co-development of MEDI1341, we continue to collaborate with the best scientists worldwide. Our collaboration with Tufts University, through the AstraZeneca-Tufts Laboratory for Basic and Translational Neuroscience, continues to deliver critical data to support exciting programs in both neurodegeneration and epilepsy, leading to publication of a series of impactful scientific papers.

Our collaborations with Trinity College Dublin and Brigham and Women’s Hospital, Boston, continue to develop assays and provide data to help us understand the impact of key proteins involved in neurodegenerative diseases on important underlying mechanisms of cognition.

In 2017, we continued to work with the Target ALS Foundation, which provides a framework for the world’s leading researchers in amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) to coordinate research. ALS is a neurodegenerative disorder which causes progressive paralysis and is usually fatal within three to five years after diagnosis. We were privileged to receive grant funding from Target ALS and ALS Finding A Cure (ALSAC) to accelerate a collaboration with Penn University, Stanford University and the Gladstone Institute on finding small molecules which could reverse cellular pathologies of key ALS linked proteins.

We started a number of exciting new early discovery collaborations in 2017, in partnership with colleagues in Discovery Sciences. Highlights include entering collaborations with Professor Richard Wada Martens (University of Oxford) and Baci Pharma (Finningham, MA) on Parkinson’s disease and the Alzheimer’s Research UK Drug Discovery Institute at University College London on Huntington’s disease.

Demonstrate scientific leadership

We published the first reported crystal structure of protease activated receptor 2 (PAR2) in Nature. This receptor plays a key role in inflammation and is considered a highly desirable drug target for treatment of osteoarthritic pain. The research, which was carried out in collaboration with Hepanis, XChrm and Discovery Sciences, describes three distinct and previously unknown antagonist binding sites on PAR2.

Our work on triggering receptor expressed on myeloid cells 2 (TREM2), in collaboration with the University of Cambridge, culminated in the identification of the site at which TREM2 is cleaved extracellularly, and this was published in EMBO Molecular Medicine.

With the AstraZeneca-Tufts laboratory, we have continued to pioneer research into the function of potassium-chloride transporter member 2 (KCC2), which is considered a key target in the search for new treatments for epilepsy. This work culminated in a paper in Nature Neuroscience on KCC2 pharmacology and a review in Trends in Neuroscience which clearly outlines the rationale for KCC2 as a drug target.

In addition to forging a new collaboration with Takeda to progress MEDI1341, a monoclonal antibody targeting α-synuclein for the treatment of Parkinson’s disease.
Therapy area progress

Neuroscience

A selection of key collaborations in 2017

1. Massachusetts General Hospital, US
   This collaboration with Berg aims to validate novel targets for treatment of Parkinson’s disease identified through Berg’s AX platform known as “Interomimetic Biology.” The method employs human patient biosamples to identify disease targets, and the goal is to screen AstaZeneica small molecules against specific targets and to follow up hits derived from these screens.

2. Pharmacos, US
   Our collaboration with Professor Stephen McMahon investigates the role of inflammatory mediators such as nerve growth factor and nerve growth factor inhibitors in pathways central to chronic pain states. The work focusses on potential additive or synergistic effects due to interactions between these and other mediators. The studies are helping to elucidate the mechanism of existing clinical candidates and the potential to contribute new targets to the portfolio.

3. Trinity College Dublin, Ireland
   In 2016, we announced a collaboration with Trinity College Dublin and Trinity College, Cambridge, MA, US. Our collaboration with Trinity College Dublin and Trinity Women’s Hospital, Cambridge MA, investigates the toxic species of aggregating proteins found in brain samples of patients with Alzheimer’s disease. Using biochemical and in vitro electrophysiological approaches we aim to understand how these proteins interact with neurons to disrupt synaptic communication. The collaboration also supports the development of translational assays to profile key disease proteins in patient cerebrospinal fluid.

4. Tufts University, US
   The team of 10 scientists continued to focus on targets related to neurodegeneration, epilepsy and neurodevelopmental disorders. The team thrives in the academic environment of Tufts with the support of key AstaZeneica scientists on the ground. Highlights from 2017 include providing data sets which led to a critical project transition and the publication of a number of excellent papers in journals such as PNAS, JBC and Nature Medicine.

5. Takeda, Japan
   In 2017, we entered into an agreement with Takeda for joint development and commercialisation of ME DIH3141, an α-synuclein antibody with high affinity and selectivity and reduced effector function. Phase I trials started at the end of 2017 to investigate the potential of the compound as a disease-modifying treatment for Parkinson’s disease. AstaZeneica will oversee the Phase I development and Takeda will lead future clinical development activities.

6. King’s College, UK
   Our collaboration with Professor Stephen McMahon investigates the toxic species of aggregating proteins found in brain samples of patients with Alzheimer’s disease. Using biochemical and in vitro electrophysiological approaches we aim to understand how these proteins interact with neurons to disrupt synaptic communication. The collaboration also supports the development of translational assays to profile key disease proteins in patient cerebrospinal fluid.

7. Eli Lilly & Company (Lilly), US
   In 2016, we announced a collaboration with Lilly to co-develop MEDI1814, an antibody selective for Aβ42, which is currently in Phase I trials as a potential disease-modifying treatment for Alzheimer’s disease. This agreement builds on the small molecule CLP257 does not modify the activity of the K+-Cl- co-transporter KCC2 but reduces the dwell time of the H157Y variant. The collaboration also supports the development of translational assays to profile key disease proteins in patient cerebrospinal fluid.

Key publications in 2017

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<tr>
<td><strong>Trends in Neurosciences</strong></td>
<td>Seizing control of KCC2: A new therapeutic target for epilepsy</td>
<td>Moore Y, McInley M, Brandon N, Deeb T, Moss S.</td>
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<td><strong>PLoS One</strong></td>
<td>Truncation of the TAR DNA-binding protein 43 is not a prerequisite for cytopathic reactivation, and is suppressed by caspase inhibition and by introduction of the 4609 sequence variant</td>
<td>Wibbt H, Wescottel S, Deling L, Jacobsen S, Deeb T, Dunlop J, Brandon NJ, Moss S.</td>
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<td><strong>Nature</strong></td>
<td>Biomarker of extracellular matrix remodeling C1M and pro-inflammatory cytokine IL-6 are related to synovitis and pain in end-stage knee osteoarthritis patients</td>
<td>Razzoli MR, Prudhom CS, Herkranse K, Tan K, Karsten R, Dutley A, Cheesell I, Korstad MA, Bay-Jensen AC, Crema MG, Guermier A.</td>
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<td><strong>PNAS USA</strong></td>
<td>Exiribin modulates the efficacy of fast synaptic inhibition by decreasing the dwell time of γ-aminobutyric acid type A receptors at inhibitory synapses</td>
<td>Muihraynie J, Canadelli R, Cantaut-Belair Y, Deeb T, Svanadze D, Pongapalas M, Triller A, Maguire, Brandon N, Moss S.</td>
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<td><strong>Pain</strong></td>
<td>Central inhibition of granulocyte macrophage colony-stimulating factor is antagonistic in experimental neuropathic pain</td>
<td>Nicoli LSC, Thornton P, Hatcher JT, Glover CP, Webster CI, Burrell M, Jones CA, Sleeman M, Blackmon A, Cheesell I.</td>
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Artificial intelligence and machine learning: revolutionising drug development

Artificial intelligence (AI) is revolutionising all stages of drug discovery and development from drug design to pivotal clinical trials – and beyond. With deep learning, machines are starting to mimic the activity of human neurons in the brain – to create, in effect, an artificial ‘neural network.’ We are taking an AI approach to a growing number of assays deployed during the drug discovery phases, reducing costs and speeding up the supply of data to our scientists. We are also using AI to help us analyse and interpret huge amounts of data from imaging studies of pathological samples and from biomarker research, to match the right drug to the right patient. In our clinical trials, AI is enabling us to continuously monitor incoming safety data and alert our scientists to safety signals that need attention.

By integrating the latest AI advances into all our drug development programmes, we are helping our scientists to harness the power of ‘big data’ to deliver potentially life-changing medicines to patients most likely to benefit.

The energy, motivation and enthusiasm at DMTA Hackweek was phenomenal – we worked relentlessly every day and evening for the entire week. It looked almost impossible to build an automated DMTA platform from scratch within one week but we did it. There is a lot of work ahead of us but this is the first step on the path to fully leveraging the capabilities of emerging laboratory automation technology and machine learning."
Michael Kossenjans, Head of iLAB, Gothenburg
Quantum computing: Speeding up structural chemistry to find the molecule that matters

Establishing the chemical 3D-structure of potential new medicines is a key element of drug discovery and development because size and shape matter. They affect many different characteristics, including interactivity to biological systems and the way molecules pack together to form materials needed for successful formulation. Yet, rather like a parachutist who needs to make multiple jumps into the Swiss mountains to find the deepest valley, we have to look at many options to evaluate all possible shapes of molecules to find the low energy conformations we need to optimise our medicines.

The emerging field of quantum computing has the potential to make a dramatic impact on how we approach this problem. A quantum computer can simultaneously explore all the possible conformations of our compounds and, given suitable criteria, converge on the best possible option in a single operation. By tuning the criteria, it is possible to locate a range of high-quality solutions. In the near-term, quantum computing is limited in the amount of information it can process, and we still have to do some post-evaluation analysis on the solutions it offers, using existing accurate methods on standard computers. The future application of machine learning is expected to take quantum computing to the next level. Our current hybrid approach looks set to bring the most relevant solutions within our grasp and help us make the best choices of chemical structure.

Using AI to liberate our IMED scientists

In discovery, we are also applying AI to make existing processes more efficient, and to turn data into knowledge. We are using AI to reliably predict the results of routine assays, such as human plasma protein binding (hPPB) tests, to liberate our scientists and give them more time to focus their passion for science on problems that will give AstraZeneca an even greater competitive edge.

The hPPB assay, developed in Drug Safety and Metabolism, is used to help us understand how a potential drug molecule is distributed within a patient. We are working with world-leading partners to use the latest advances in AI to predict the results with a high degree of confidence.

We are currently assessing the utility of AI for safety screens, protein production, image analysis and the design of clustered regularly interspaced short palindromic repeats (CRISPR) gene editing. In the months and years ahead, we expect to use AI to transform any area in the discovery process where we collect data and turn that data into knowledge.

In 2017, a testament to the success of machine derived efficiency was the development of a virtual screening tool FastQ. The new “Google-like” web-based tool, developed in collaboration with OpenEye Scientific Software, reduces the time to search and score entries in numerous large molecular databases, from hours to seconds, optimising the process of drug discovery.

Big data analysis helps move traditional pathology into the 21st century

In a science-driven environment, the ability to rapidly identify and learn from signals and patterns in the data we generate is key to building knowledge and influencing future scientific direction and discovery. To achieve this, we need to access and integrate our large and diverse data sets in a usable format.

In the past, evaluation of comprehensive gene expression, protein and metabolic data from an individual organ was hampered by our limited computational capacity for data analysis. For the first time, Al is making it possible to tackle ‘big data’ and analyse all these endpoints and their spatial relationship to each other.

We are using mass spectrometry imaging (MSI) to spatially map molecules to their cellular localisation in biological samples and sections of tissue, such as those taken for pathology assessment. This comprehensive data-rich spatial information is a fantastic opportunity to link the tissue microenvironment with drug localisation, efficacy and safety. However, existing data mining approaches place great demands on computer systems and we are limited to analysing small, single data sets. To address this we have developed new computational algorithms that enable accurate and efficient segmentation of large amounts of MSI data to improve our capacity to learn across multiple endpoints, as described in our recent publication in Analytical Chemistry.

This has enhanced our capacity to accurately quantify molecular changes in tissue and organ specific regions and mine data for increasingly complex spatial relationships. Critical to our success was the close collaboration between researchers in Drug Safety and Metabolism and external experts in computer and pathological sciences.

Looking ahead, we plan to combine deep learning algorithms with image analysis to accelerate evaluation of animal models of chronic kidney disease, generating more robust data for downstream multispectral image analysis. This will increase the speed of confidence, reproducibility and productivity of data and allow the integrated multimodal image models to detect biological relationships and consequences. In 2017, our scientists worked with Cancer Research UK’s (CRUK) Grand Challenge Team for Tissue: from Images to Genes – a deep learning approach to tissue genomics. This has the potential to take pathology – one of the most traditional and discipline-specific – firmly into the 21st century and beyond.

Harnessing AI to connect the right drug to the right patient

Tissue biomarkers are increasingly used to match the right drug to the right patient. However, current technology involves manual scoring of images by pathologists – a process that is subjective, time consuming and complex. To overcome this challenge we turned to AI, and developed a novel deep learning algorithm to automatically score tissue biomarkers using a process called digital pathology.

In a proof-of-concept study of 71 patient tumour samples, we showed that AI can automatically score a human epithelial growth factor receptor 2 (HER2), a well-established biomarker in breast cancer. The algorithm also identified samples at risk of misdiagnosis, demonstrating its potential to make tissue biomarker scoring faster, simpler and more precise.

In 2017, we presented this exciting work at two world leading scientific congresses and published it in Scientific Reports.

We are continuing to use the latest science to lead the way in similar advances, through collaborations with the best academic partners. Using a combination of cloud computing and the latest graphics processing unit (GPU) hardware, we intend to make automated analysis of digital pathology images a high throughput process, and to incorporate Al algorithms into the development of diagnostics tests. We aim to use the power of Al to affect patients’ lives, match targeted medicines even more precisely to those most likely to benefit.

Watcher complements REACT 4, another iDecide tool, which collates and visualises safety, efficacy and biomarker data from Phase I and Phase IIa trials and is currently deployed in over 140 studies at AstraZeneca. REACT 4 enables clinical interpretation on-demand and depends on the system being actively used. However, Watcher’s continuous monitoring allows insights and notifications to be generated when a signal emanates, without manual intervention.

In the future, we plan to enhance Watcher with clinical rulesets and machine learning to augment and extend its current functionality. These developments will enable it to be brought into the patient’s home in conjunction with point-of-care devices, further empowering our patients to self-monitor while participating in our clinical trials.
IMED functions

Discovery Sciences

“2017 was a bumper year for Discovery Sciences, with substantial growth in the discovery pipeline, and new modalities entering the portfolio. Our discovery technology platforms, clustered regularly interspaced short palindromic repeats (CRISPR) editing, cryo electron microscopy (cryo-EM), cellular thermal shift assay (CETSA), acoustic mass-spectrometry (MS), and virtual screening are reaching maturity. Externalisation has been used to great effect to drive our science forward with a variety of really high calibre partners.”

Mike Snowden, Vice President, Discovery Sciences

CRISPR (clustered regularly interspaced palindromic repeats) gene editing tool
**Discovery Sciences**

In Discovery Sciences, we are routinely using the latest technologies, including genome editing, CETSA and cryo-EM, to transform our understanding of cell biology and revolutionise the way we generate, test and enhance new leads for tomorrow’s medicines.

**Taking CETSA to a new level for confirming target engagement**

AstraZeneca is gaining new insights into the mechanisms of action of its pipeline drugs, thanks to the successful application of CETSA, including in areas beyond those for which the technology was originally designed.

Through a strategic research collaboration with Pelago Biosciences, we have been using CETSA to robustly monitor interactions between drugs and their intended targets in physiological relevant systems. CETSA is designed to measure drug-target engagement in cells or tissues by monitoring changes in thermal stability of proteins upon ligand binding, and was developed as a small-molecule label-free technology for soluble proteins.

However, in Discovery Sciences, we have now successfully applied CETSA to study proteins that span membranes where classical biophysical methods were not feasible. We used an innovative detergent-based, in-cell approach to understand how new molecules, identified through high throughput screening, interact with the 12-pass-transmembrane ion channel.

We have also successfully used classic CETSA to advance understanding of challenging proteins, such as protease activated receptor 2 (PAR2), monocarboxylate transporter 4 (MCT4), sarco/endoplasmic reticulum Ca2+-ATPase (SERCA2A), and the cyclin dependent kinase 9 (CDK9) project to benchmark and fully implement the technology in-house. The results from these CDK9 CETSA-MS experiments together with a comparative analysis with chemical-proteomic studies are being summarised in a scientific manuscript.

**At almost every stage of the discovery process, the integration and consolidation of new technologies is enabling us to work faster and more efficiently, with better use of resources and less waste.**

The everyday application of CRISPR means that we are building expertise in the field of precise genome editing and have made excellent progress in model systems. We routinely supply cell lines through the Medical Research Council (MRC)/AstraZeneca UK Centre for Lead Discovery, underlining the value of this unique cornerstone for academic and industrial drug discovery projects.

By using the latest biochemical and biophysical techniques, we are gaining mechanistic insights to enable the selection of the most appropriate molecules to progress as candidates. With CETSA, we have confirmed target engagement of lead molecules in cells or ex vivo including engagement with the membrane ion channels. Using a number of mass spectrometric techniques, we have expanded our proteomic capabilities to discover novel drug targets following readouts from phenotypic screens which identify substances that alter the phenotype of a cell in a desired manner.

Machine learning is becoming an integral component of the way we screen targets in silico and design novel molecules. Through automated processes, investigations are performed and repeated, with results used to inform and refine subsequent tests. Indeed, machine learning is beginning to replace some of our drug metabolism and pharmacokinetics (DMPK) assays, making the process smarter and more efficient.

As we prepare for our exciting move to the Cambridge Biomedical Campus, the arrival of cutting-edge automation platforms is enabling us to perform high throughput screens with external partners through the Medical Research Council (MRC)/AstraZeneca UK Centre for Lead Discovery, underlining the value of this unique cornerstone for academic and industrial drug discovery projects.

People spotlight

Amir Taheri-Ghahfarokhi, Post-Doctoral Fellow

Amir is a post-doctoral fellow in the Translational Genomic department, working in the CRISPRP team. An outstanding scientist, he was awarded his PhD from Ferdowsi University in Iran. Amir developed and patented the RamNet system which enables insertion deletion enrichment for CRISPR knock-out assays, which he used for the first proof of concept of arrayed screening in AstraZeneca. Amir developed a novel computational platform called Rational Indel Meta-analysis (RIMA) that enables an in-depth comprehensive analysis of Cas9 induced genetic alterations. RIMA sheds light on the Cas9 nuclease activity and repair mechanisms in mammalian cells. Amir has been listed as co-inventor in two AstraZeneca-CRISPR patent applications.

Chris Phillips, Associate Director

Chris joined AstraZeneca in 2012 from Pfizer, and is working as an Associate Director in the Protein Structure group. His scientific career started in Oxford with a DPhil in crystallography, after which he became an industry-funded research scientist and developed a passion for drug discovery. Chris is an expert in the application of structural biology to drug discovery, from target selection to structure based drug design (SBDD) which uses experimental three dimensional, atomic resolution structures of drug target proteins in the design of drug candidate molecules. Chris leads the UK structural biology team, a group primarily focussed on the SBDD of our early-stage innovative oncology portfolio and is building AstraZeneca’s capability in cryo-EM.

Paola Castaldi, Associate Director

Paola joined AstraZeneca in 2013 as an Associate Principal Scientist in the Chemical Biology Team with expertise in phenotypic drug discovery target identification and mechanism of action studies from SaroT Oncology in Cambridge, UK. Since then Paola’s responsibilities have evolved, and she is currently the head of the Chemical Biology team with a focus on the application of cutting-edge technologies for target identification and validation, target engagement, and off-target determination. Paola played a key role in the CETSA Granite collaboration with Pelago Biosciences by being a member of the Joint Research Committee and ensuring effective know-how transfer and full implementation of the CETSA classic and CETSA MS in-house. Recently Paola led the inception and organisation of the first ‘Chemical Biology in the Hub’ symposium in Boston where examples of impactful CETSA applications were highlighted in the context of several stages of the drug discovery process.
Discovering experiences

IMED functions

Discovery Sciences

Introduction

Therapy area progress

Highlights

We set out to

Create a human secretome library to discover new biology

We delivered

In partnership with the Royal Institute of Technology in Stockholm, we expressed and purified 1,400 human secreted proteins. This “secretome” library consists of known signaling proteins, including growth factors, cytokines, and regenerative factors, together with novel proteins predicted to have signaling activity. The proteins are tested in primary, and uterine cell models of disease to identify new pathways and targets for disease modulation. We completely screens to identify targets that modulate the stabilization of regulatory T cells, the differentiation of pancreatic beta (β) cells, the activation of kidney fibroblasts, and the proliferation of cardiac progenitor cells.

Confirm target engagement using classic CETSA

In collaboration with Pelago Bioscience, we are applying CETSA to study the binding of compounds to proteins in cells and tissues. We combine CETSA with Western Blot to demonstrate target binding in cells, the first use of this method to study compound binding to membrane spanning on channels and G-protein coupled receptors. High throughput CETSA was destroyed to characterise the antagonistic receptor ligand mechanism of action, and CETSA-MS was established to measure compound binding to thousands of proteins in a single experiment. The technique is being applied to demonstrate the selectivity profile of lead compounds in tissue samples from in vivo efficacy, and safety studies in animals.

Use acoustic mass spectrometry to screen targets in high throughput screening mode

We used a prototype acoustic MS screening system and demonstrated its remarkable robustness by supporting multiple high throughput screening (HTS) campaigns. A full collection screen (2.2 million samples) was processed, and we identified both known and novel inhibitors of a de-acetylase target. In addition, the technology delivered hits for a methyltransferase project from a sample screen (1.5 million samples) to generate tool compounds. Through knowledge sharing, AstraZeneca is giving collaborators access to this world-leading technology and a campaign to support Cancer Research UK will start early in 2018. As a label free primary screening platform it is highly cost effective, and produces fewer artefacts, thus reducing both biases at the end rates, and time from hit to lead identification.

Reformat the AstraZeneca compound screening collection

We recognised the need for an upgrade in the compound screening set used in HTS hit discovery, and set out to rebuild it. By changing our work patterns, machine maintenance and IT systems, we transferred two million compounds from the Primary Liquid Store (PLS) at our Alderley Park site to 384-well screening plates. Four million individual compound dispensers were then used to create duplicate 1336-well screening plates, providing a compound set for use in HTS. We completed the entire work package in record time of nine months.

Use machine learning to improve our assay screening process

Working with world-leading academics, we have exploited recent advances in machine learning to understand the quality of our individual predictions for compound activities in drug metabolism and pharmacokinetics (DMPK) and safety. These predictions are transforming the way we bring compounds through the lead optimisation process. They have reduced the number of compounds screened in an outburst DMPK assay, by almost 40 per cent and improved prioritisation in safety screening, giving our scientists relevant data quicker, supporting data-driven decision making, and saving cost.

Using cryo-EM to gain new insights in structural biology

2017 saw us firmly establish cryo-EM within Discovery Sciences and publish our first research in the field in Science Advances - a groundbreaking study in which we describe, for the first time, the structure and activation mechanism of human ataxia-telangiectasia mutated (ATM), a key trigger protein in the DNA damage response (DDR) and a prime therapeutic target in cancer.

Cryo-EM is revolutionising structural biology, allowing scientists to determine the structure of complex multicomponent cellular machines and many integral membrane proteins at near-atomic resolutions, something that has typically proved impossible in the past. Cambridge provides an unmatched environment for studying cryo-EM and we are fortunate to collaborate with scientists at the MRC Laboratory of Molecular Biology (MRC-LMB) who are pioneers in the field. We warmly congratulate the LMB’s Richard Henderson for being awarded the 2017 Nobel Prize in Chemistry for his groundbreaking contributions to cryo-EM. With Richard’s help, AstraZeneca, along with four industry partners, the University of Cambridge, the leading microscope manufacturer, FEI, and the MRC-LMB have formed a unique consortium enabling routine access to state of the art equipment and world-leading expertise.

With cryo-EM, we have produced images of ATM showing exquisite structural detail, enabling us to demonstrate that ATM acts as a molecular switch. In the ‘on’ state the active site of the ATM dimer is open and able to bind substrate, while in the off state, ‘the closed dimer’, the active site is blocked. Activators and inhibitors of ATM may work by altering the equilibrium between the open and closed populations of ATM. With our research, we have thus provided a new framework for understanding ATM biology. As ATM is the key initiator protein of the cellular response to DNA double-strand breaks, our discoveries have exciting implications for DDR research and the development of innovative cancer medicines within IMED Oncology.

Our cryo-EM research into ATM was carried out as part of our Blue Sky programme with the MRC, through which we jointly assess collaborative, innovative, early stage research proposals for support. Plans are in place to build on our investment and expand the consortium by adding an additional high-resolution microscope to the facility next year. Our cryo-EM project portfolio is growing, and we are having success with epigenetic targets and making good initial progress with integral membrane proteins, a particular challenge for the structural biologist.
A selection of key collaborations in 2017

1. Labcyte and Waters acoustic mass Spectrometry collaboration, US
   A research and development collaboration between Labcyte, Waters and AstraZeneca, which has delivered the world’s first acoustic mass spectrometer. The application is currently in use in AstraZeneca in HTS and structure activity relationship (SAR) research. Waters and AstraZeneca will commercialise the hardware and make the technology available to other Pharma.

2. Brooks and Labcyte acoustic sample tube collaboration, US
   The Brooks and Labcyte collaboration will deliver the world’s first direct acoustic dispensing technology to solve protein structures using the world’s leading technology provider, FEI Cambridge Pharmaceutical Cryo-EM, a collaboration between Labcyte, Waters and AstraZeneca, has delivered the world’s first acoustic mass spectrometry readout.

3. Massachusetts General Hospital, US
   Our collaboration with the world-leading laboratory of Massachusetts General hospital is extensive beyond collaborative projects, including joint symposia, visiting speakers, and Medimmune. The scientific exchange of LMB groups, and scientists across IMED with Imperial College London. The Innovation fund will support projects until 2021.

4. University of Cambridge, UK
   A research collaboration to identify new epigenetic targets and compounds for respiratory diseases.

5. Cambridge Pharmaceutical Cryo-EM Consortium, UK
   AstraZeneca is part of a four pharma consortium that partners with the technology provider, FEI (now part of Thermo Fisher) and the University of Cambridge to solve protein structures using cryo-EM. The facility is housed in the University’s Nanoscience department.

6. Petago Biosciences, Sweden
   A research collaboration focused on the application and extension of Petago’s CETSAS technology. We investigate target engagement in cellular systems and s.vn samples using classic, Western Blot based CETSAS with extended mass spectrometry readout.

7. Royal Institute of Technology (KTH), Sweden
   The objective of this collaboration is to produce and screen all human secreted proteins. This exciting research uses phenotypic screens to unravel new biology leading to new targets for drug discovery. To date we have screened 700 screened proteins in several assay systems.

8. Pelago Biosciences (now part of Thermo Fisher) and the University of Cambridge, UK
   Pelago’s CETSAS technology is being used to develop a novel high-throughput screening platform for the identification of new molecules for drug targets.

9. Imperial College London, UK
   In 2017 AstraZeneca initiated two collaborations with Imperial College London. The Innovation fund provides funding for smaller research projects of interest, focusing on “translational” research. The co-funded projects typically run for up to nine months at Imperial College with support from AstraZeneca where necessary, and aim to generate data to support future grants and funding proposals. In addition to the Innovation Fund, AstraZeneca co-sponsors up to two research fellowships for up to two years at the LMB, and visiting AstraZeneca typically supporting a postdoc for up to three years at the LMB, and visiting AstraZeneca laboratories. There are 28 active projects covering a wide range of disease biology and novel methodologies, involving ~40 per cent of LMB groups, and scientists across IMED and Medimmune. The scientific exchange is extensive beyond collaborative projects, including joint symposia, visiting speakers, attendance of LMB seminars, open innovation projects, technical training and hiring of excellent young scientists.

10. Medical Research Council Laboratory of Molecular Biology (MRC-LMB), UK
   The Blue Sky fund supports collaborative research between scientists at the world-leading MRC-LMB, and AstraZeneca and MedImmune commitment to explore the biology of disease. The fund will support projects until 2021. Two calls for proposals are held each year, typically supporting a postdoc for up to three years at the LMB, and visiting AstraZeneca laboratories. There are 28 active projects covering a wide range of disease biology and novel methodologies, involving ~40 per cent of LMB groups, and scientists across IMED and Medimmune. The scientific exchange is extensive beyond collaborative projects, including joint symposia, visiting speakers, attendance of LMB seminars, open innovation projects, technical training and hiring of excellent young scientists.

Key publications in 2017

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<td>Nature Reviews Drug Discovery</td>
<td>DNA-encoded chemistry: access to new and larger small molecule libraries</td>
<td>Goodnow R, Dumélec C, Kwek AD</td>
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<td>Nature Communications</td>
<td>Mapping the sugar dependency for natural generation of a DNA-RNA hybrid-guided Cas9 endonuclease</td>
<td>Rueda FC, Bleda M, Naevton MD, Goeppele A2, Cuerno ME, Garzon E, Krifke F, Raas J, Wrigley JD, Rueda D, Taylor SM</td>
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Drug Safety and Metabolism

“Throughout 2017, we made significant progress in impacting on the selection and delivery of safer medicines for patients through application of our science, passion and expertise. We enhanced scientific innovation – investing in novel technology platforms and expanding our collaborations. We also advanced our access to data for better data mining and prediction of safety. Project support has excelled with the delivery of novel, tailored studies that apply the best science specific to project needs.”

Stefan Platz, Vice President, Global Drug Safety and Metabolism
In 2017, Drug Safety and Metabolism (DSM) demonstrated valuable expertise through delivery of innovative safety studies across all phases of AstraZeneca’s portfolio from discovery through development and into life cycle management (LCM). This was exemplified by combining the power of disease models with toxicological assessments, successfully supporting future clinical progression of AZD8601 (vascular endothelial growth factor A, VEGF-A, modified mRNA) and FDA regulatory needs for dapagliflozin in the treatment of patients with Type 2 diabetes.

Our newly founded Centres of Excellence for Microphysiological Systems (MPS) and New Modalities have made considerable progress. For MPS, we have expanded our portfolio of investigative models, including development of a multi-organ chip, linking the heart and liver together. In New Modalities, we have advanced our mechanistic understanding of the immune response triggered with subcutaneous dosing of modified mRNA formulations. Additionally, we have been collaborating with world leading scientists to define the best tools and robust safety strategies to assess the impact of off- and off-target action genome editing.

Collaboration is key to our success and in 2017, we continued to combine our strengths and resources with the expertise and knowledge of our partners to drive the future of safety science. We are an instrumental partner in the Cambridge Alliance for Medicine Safety (CAMS), aimed at improving predictive accuracy of experimental safety models and mechanistic understanding of toxicity. Generating knowledge from our data is extremely powerful, and in 2017, we developed standardised electronic mapping and scripting processes for extraction of more than 4,000 historic pre-clinical safety studies. This has laid the foundations for global data access and paved the way for ‘big data’ mining and analysis.

Liver sinusoidal endothelial cells image within Emulate’s liver-chip

Clay Scott, Associate Director
Discovery Safety
Clay Scott leads the DSM Discovery Safety team in Boston. He has a PhD in Pharmacology from Southwestern Medical Center, Dallas, Texas. Gastrointestinal adverse effects are particularly common with oncology medicines and although detected pre-clinically in dogs, in vivo models for optimising gastrointestinal safety in early drug discovery are lacking. The Boston team collaborated with Merck to develop an assay using human 3D gastrointestinal microtissues that has high predictive capacity for clinical diarrhoea. The assay mirrored clinical gastrointestinal toxicity reported with our WEE1 DDR inhibitor and is being used alongside predictive modelling to evaluate different clinical dose schedules for improved tolerability. The team also collaborated with John Wikswo, Vanderbilt University, to develop a novel microfluidics device to dynamically regulate drug concentrations in cell-based assays to mimic in vivo drug exposures. The instrument is being used to evaluate the impact of pharmacokinetic parameters on both efficacy and safety endpoints.

Amy Pointon, Associate Director
Cardiovascular Target Organ Strategy Lead
Amy Pointon leads the Cardiovascular (CVS) in vivo group in Safety and ADME Translational Sciences. Amy gained her PhD at the University of Leicester investigating mechanisms of doxorubicin cardiotoxicity. As our CVS target organ strategy lead the focus in 2017 has been to establish novel 3D cardiac microtissues and develop live cell imaging based assays to assess structural CVS and contractility safety risks. Using the cardiac microtissues, we have an ongoing collaboration focusing on metabolomics to facilitate understanding of molecular events, biomarkers and translation of structural CVS adverse outcome pathways. In addition, quantitative translational modelling has been applied to in vitro CVS data to predict the likelihood and certainty of clinical ECG interval changes. This approach has been applied to a number of oncology projects allowing project teams to make quantitative decisions on compound progression.

Ann Doherty, Director of Genetic Toxicology
Ann Doherty leads the Genetic Toxicology Group in Discovery Safety. Ann gained her PhD in genetic toxicology from Swansea University. The genetic toxicology team are developing novel assays to increase our understanding of genotoxicity and drug induced DNA damage. In 2017 a novel industry-leading in vitro high content imaging assay was developed and implemented. The ‘MEGA Screen’ (Multi End Point Genotoxicity Assessment Screen), provides parallel measurement of multiple endpoints that aid mechanistic understanding of micronucleus origin, either clastogenic (chromosome break) or aneugenic (chromosome loss), detect nucleic fragmentation, condensation, and cell cycle block. The current industry standard is the in vitro micronucleus mammalian assay which has limited mechanistic capability and very low throughput (1-2 compounds). In comparison, the MEGA screen transforms our ability for high-throughput early detection of molecular initiating events that lead to genotoxic risk. In 2017 we screened ~300 compounds with successful impact on ~30 projects in early discovery. Development of the high content assay was achieved in collaboration between DSM and Discovery Sciences, a fantastic result of close working relationships within our Cambridge laboratories.

Based on a cross-industry survey using 2016 data, IMED had the lowest project attrition in first time in man enabling toxicology studies at 0 per cent vs. a peer company average of 13 per cent.

IMED has the best reporting times for four-week GLP toxicity studies with a 44 per cent difference vs. the average peer company reporting times (as measured in weeks).

People spotlight
Developability to guide dose and scheduling for DNA damage response inhibitor mono- and combination therapies

Our safety capability has expanded to effectively assess DNA damage response (DDR) inhibitor formulations across in vivo, MPS and in vitro models. We are evaluating a number of state-of-the-art bone marrow MPS technologies for future application in the DDR space. Utilising our knowledge of in vivo haematotoxicity kinetics, tissue distribution and elimination, we advanced our understanding and revealed insight into mechanisms of clinical haematotoxicity of poly ADP-ribose polymerase (PARP) inhibitors.

Additionally, as DDR agents can cause gastrointestinal toxicity, we explored an in vivo human gastrointestinal microtissue model of diarrhoea. The system is stable for more than 40 days and supports repeated non-invasive measurement to accurately model onset and recovery of WEE1 inhibitor induced diarrhoea.

Our collaboration with Professor John Wikswo, at Vanderbilt University, focused on his novel multiwell ‘microformulator’ technology to mimic in vivo drug exposure profiles in in vitro cell-based assays. We successfully demonstrated the ability of the microformulator to reproduce drug exposure profiles in cell-free systems. This work will enable in vitro assessment of favourable pharmacokinetic profiles for DDR inhibitors as monotherapies and in combinations.

Increase the number of organ systems that can be represented by a microbiophysiological model

In partnership with Hoppe, we connected a human stem cell/heart chip to a metabolically competent human liver chip to investigate parent compound and metabolite-induced cardiotoxicity—something that can currently only be done in vivo animal models. The model correctly detected cardiotoxicity caused by the formation of a toxic metabolite from a proprietary small molecule and showed the disappearance of cardiotoxicity in two different drugs that were metabolised to non-cardiotoxic metabolites. These responses were reversed with the inclusion of a CYP450 inhibitor. Using a modelling and simulation approach, the data from the MPS model were able to predict in vivo outcomes in animals.

Demonstrate leadership in safety assessment of new modalities

In the modified hPMA model, understanding physiological and immunological responses to subcutaneous injection was key in 2017. Mechanistic in vivo work identified the potential for innate pattern recognition receptors to interact with mRNA formulations to drive unwanted inflammatory effects that limit dose. These observations are guiding efforts to develop more advanced formulations to address this safety issue.

Another key area was the investigation of strategies to boost intracellular mRNA translation and protein production. We identified key pathways in the cell stress response that limit protein production in vitro and demonstrated that blockade of such pathways can boost cellular protein production by up to 100 per cent. Follow-up work to circumvent these limiting factors with the goal of reducing overall hPMA dose required for efficacy is ongoing.

In a first for IMED, we conducted a complex disease-relevant, three-month toxicological assessment of AZD8601 (VEGF-A modified mRNA), to support Phase II clinical progression in patients undergoing coronary-artery bypass graft. This pre-clinical study (injected intramuscular injection of AZD8601 i.p. pigs following experimental myocardial ischaemia). We led the safety assessment of AZD8601 in this animal model, which also showed improvements in cardiac function. This study was a critical component in the application to initiate a Phase II trial.

Lay the foundations for using artificial intelligence in pathology

Artificial intelligence (AI) is increasingly used for pattern recognition across many areas, and in 2017, DSM contributed to a publication in Science Reports on the use of AI for interpreting results of immunohistochemistry staining in clinical samples. The study showed good agreement between diagnosis generated by pathologists, AI using machine learning and AI using deep learning. However, resolution of equivocal cases was enhanced by application of AI, and deep learning was superior to other forms of AI.

AI highlighted 12 cases where the diagnosis by computer and pathologists diverged. On reviewing the cases, the pathologist decided to change the diagnosis in eight cases. A comparison between machine learning (involving random forests and support vector machine) and deep learning (involving convolutional neural networks) revealed the higher overall accuracy of deep learning. We held an internal workshop on the use of AI for histological image assessment with collaborators from the National Physics Laboratory, Imperial College London, and Cancer Research UK. As part of this, two post-doctoral proposals were approved and initiated, for development of deep learning algorithms for diagnosing kidney pathology, and multimodal data integration tools for hyperspectral imaging.

Highlights

We set out to We delivered

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Enhance access to pre-clinical safety data through centralisation in the PreDICT database

DSM extended access to pre-clinical safety data generated on drug candidates for AstraZeneca scientists, by capitalising on a previous collaboration with Translate that produced leading data mining tools, PreDICT, for capturing in vivo animal efficacy data. We performed complex mapping to align the data model in PreDICT with the recently implemented FDA Standard for Exchange of Non-Clinical Data (SEND). Standardising the way studies are described will facilitate the mining and analysis of the database and provide faster and safer access to pre-clinical data for our scientists. By combining our safety and efficacy data, we will provide a ‘one-stop-shop’ for all pre-clinical in vivo data across AstraZeneca which will enable us to harness our knowledge to greatest effect.

Harnessing the power of big data from pre-clinical safety studies: leveraging the SEND framework

In order to address the opportunities around big data and machine learning, DSM initiated a safety data science project in 2017. The aim being to create a central machine readable data warehouse that allows scientists to locate, compile and analyse safety data from both our current and comprehensive legacy studies. Capitalising on the FDA SEND framework, we transformed our historic data through an extensive mapping process and built an automated process to load this and future studies into the PreDICT database. This process is now complete and the necessary modifications to PreDICT are underway. We signed a collaboration agreement with Instern to provide an automated method of retrieving legacy data from more than 4,000 studies and loading these into PreDICT.

We are confident that, by establishing an industry-leading, comprehensive, accessible ‘warehouse’ of data from current pre-clinical safety studies, and those conducted over the last 30 years, DSM is setting the stage for scientists across AstraZeneca to unleash the true potential of our data.

Upon completion, we will continue to load new internal and external studies into our data warehouse which will constitute in excess of 15 million data points and measurements. By integrating our pre-clinical data with data from AstraZeneca’s clinical warehouses and our broader human genome initiative, we hope to more accurately assess the relevance of pre-clinical observations to outcomes observed in clinical trials.

Linking genomic, pre-clinical and clinical information in this way presents us with unique abilities to mine our vast data resources across the length and breadth of our discovery and development portfolios. Using SEND for hypothesis generation, we will have the opportunity to find links between events in the clinic and pre-clinical observations – down to in vitro responses – to increase our understanding of early safety signals and improve our ability to select safer drug candidates.
A selection of key collaborations in 2017

1. Harvard University, US
   In collaboration with Professor Don Ingber, we are developing a novel bone marrow model to investigate on target haematoxicity for oncology projects.

2. Medical Research Council (MRC) Toxicology Unit, UK
   We are exploring the toxicity pathways induced by cellular delivery of modified nucleotides in collaboration with Professor Anne Willis.

3. CN Bio Innovations, UK
   Together we are combining MPS models of fatty liver disease and non-alcoholic steatohepatitis with computational systems biology to enable drug repurposing or repositioning.

4. Genoskin, France
   We are investigating the ex vivo skin model in collaboration with Dr Pascal Descargues, to explore inflammatory responses induced by skin model in ex vivo Genoskin, France.

5. University of Uppsala, Sweden
   In collaboration with Professor Per E Andersson we are aiming to improve qualitative and quantitative, high spatial resolution mass spectrometry imaging techniques to enable highest spatial resolution detection of biomarkers and drugs in tissues.

6. University of Leiden, Netherlands
   With Professor Piet Hein van der Graaf we are exploring the development of mathematical models of pharmacokinetic/pharmacodynamic relationships that incorporate mechanisms of feedback and tolerance to support optimisation of dose and scheduling of oncology drugs.

7. University of Cambridge, UK
   With Dr Hendrik W van Veen we are exploring the molecular mechanisms of inhibition of the bile salt export pump, which plays a role in drug-induced liver injury.

8. University of Cambridge, UK
   We are an instrumental partner in the pre-competitive consortium CAMS, with Glaeser/Similina, MRC Toxicology Unit and University of Cambridge, aiming to improve predictive accuracy of experimental safety models and mechanistic understanding of toxicity across the industry.

9. University of Birmingham, UK
   In collaboration with Professor Mark Van't Hof, we are applying metabolomics to facilitate discovery of key events contributing to structural cardiotoxicity adverse outcome pathways.

10. University of Cambridge, UK
    We are exploring the toxicity pathways induced by cellular delivery of modified nucleotides in collaboration with Dr Pascal Descargues, to explore inflammatory responses induced by skin model in ex vivo Genoskin, France.

Key publications in 2017

**Publications**

**Nature Reviews Drug Discovery**
- Legacy data sharing to improve drug safety assessment: the eTDR project

**Nature Reviews Drug Discovery**
- Impact of a five-dimensional framework on R&D productivity at AstraZeneca

**Science Translational Medicine**
- Targeting KRAS-dependent tumours with AZD4785, a high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS

**CPT: Pharmacoanalytics & Systems Pharmacology**
- Translational modelling of drug-induced myostatusepression to predict clinical platelet changes, risk of thrombocytopenia and exploration of effect of pre-treatment myostatusepression for AZD3153, a selective BRD4 inhibitor
  - Author: Collina TA, Hatemans E, Yates J, van der Meer, Moncal M, Mettel J, JT

**Toxicological Sciences**
- Deconvoluting kinase inhibitor induced cardiotoxicity

**Annual Review of Pharmacology and Toxicology**
- Application of microphysiological systems to enhance safety assessment in drug discovery

**Archives of Toxicology**
- Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury

**Clinical Pharmacology and Therapeutics**
- Systems pharmacology modeling of drug-induced hypothyroidism: Differentiating hepatotoxicity and inhibition of enzymes/transporters

**Toxicology and Applied Pharmacology**
- A semi-quantitative translational pharmacology approach to understand the relationship of in vitro ENTP1 inhibition to the clinical incidence of dyspnoea and bronchospasm
  - Author: Roomans M, Robero L, Stoner I

**Pharmacology & Therapeutics**
- Towards better models and mechanistic biomarkers for drug-induced gastrointestinal injury

**Regulatory Toxicology and Pharmacology**
- Current nonclinical testing paradigms in support of safe clinical trials: An IQ Consortium Dcudile perspective
  - Author: Butler DR, Guizzi-Peck A, Hartlie, J, Bogganryr M, MS, Mill X, Daniel D, Mortimer-Cassian E, Al Decel M, Greene N, Da George JJ
**IMED functions**

**Early Clinical Development**

“Our core strategic pillars are delivering innovative clinical studies, integrating data to inform research and development, and accelerating human target validation. Focussing on these, we helped deliver eight first time in man Phase I studies, 16 Phase II starts and one transition to Phase III for the IMED Biotech Unit.”

Professor Stephen Rennard, Vice President and Head of Early Clinical Development

Investigation of protein expression in a positive control tissue core on a tissue microarray slide containing non-small cell lung cancer
In 2017, Early Clinical Development (ECD) not only delivered our portfolio, but started our new clinical trial delivery model, which will place us closer to our patients and clinical collaborators while reducing costs and timelines.

Scientifically, we used advanced modelling to facilitate portfolio delivery, implemented novel clinical designs and developed new clinical outcome measures; accomplishments which are reflected in our publications. Importantly, ECD remains a great place to work and our employees have taken advantage of a wealth of development opportunities.

Clinical trials are facing many challenges, including increasingly complex studies, difficulties in patient recruitment, high volumes of paperwork for investigators and more complex analytical approaches.

To address these challenges, in ECD we are using adaptive study designs for early trials, adopting biomarker-guided patient selection, and have developed state-of-the-art tools for data gathering, real-time visualisation and analysis. We are also collaborating with world-leading scientists to advance drug development in our key therapeutic areas.

Adaptive designs in the majority of our clinical studies allow us to get to the right dose quicker, and get more patients to that dose sooner.

In 2017, we published a paper in Lancet Respiratory Medicine about our work on a novel clinical trial endpoint for use in asthma trials, which should help to accelerate clinical development of new therapies. Following this advance in asthma trial design we are working on a similar composite endpoint for COPD trials.

Occurrence of severe asthma exacerbations is used to evaluate the effectiveness of asthma management, but severe asthma exacerbations are rare events. As a result, the large, lengthy trials needed to assess the effect of novel drugs on exacerbation rates are undertaken late in clinical development programmes. To bring this process forward in smaller, shorter studies, we aimed to establish a composite endpoint which captured clinically relevant deteriorations, incorporating diary events, combined with severe exacerbations. By creating this composite outcome, called composite exacerbation (CompEx), we can now design shorter clinical trials with fewer patients to evaluate severe exacerbations.

Data from 12 asthma trials were used to construct and test CompEx. With data from five trials, we established a series of diary events to assess trends. For the development phase, we evaluated different combinations of variables and deterioration criteria, selected the most robust algorithm to define a diary event for the composite outcome, and then defined CompEx as first occurrence of a diary event or a severe exacerbation. We assessed the performance of CompEx in seven trials. This novel endpoint accurately measured severe exacerbation rates with a substantially smaller number of patients, in less than half the time of previous severe exacerbation studies.

Importantly, CompEx, which was initiated by AstraZeneca, was completed through a collaboration with GlaxoSmithKline, demonstrating both the generalisability of the tool and our commitment to advancing the treatment of our patients through collaborations in non-competitive areas.

After this important work in clinical endpoints for asthma, we pursued a similar ambition in COPD. The result – CompEx COPD – has the potential to allow smaller patient numbers and trial duration of three months, promoting agile progression through clinical development. Incorporating clinically relevant deteriorations, traditional exacerbations and study drop-outs, makes CompEx for COPD a very clinically relevant endpoint. CompEx is now being used as an exploratory endpoint in ongoing COPD clinical studies.

Novel composite endpoint reduces sample size and trial duration

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**Highlights**

**Drive progression across the pipeline portfolio**

We continue to deliver across the AstraZeneca portfolio. We have demonstrated our commitment to scientific progress with 140 publications, 12 of which have been in high impact journals and 54 in high quality journals.

We led early clinical developments in our main therapy areas, with first-dose milestones across our portfolio and contributions to one transition to Phase III.

We delivered 16 Phase II studies including seven new molecular entities (NMEs). These included AZD8601 (vascular endothelial growth factor A, VEGF-A, modified mRNA) team used microdialysis to measure local VEGF-A protein production in vivo following modified mRNA treatment in patients. The results demonstrated that AZD8601 produces VEGF-A protein in the human skin after single intradermal administration. AZD3681 is now planned to start a Phase IIa study in patients undergoing coronary artery bypass surgery.

**Extend and enhance innovative study designs across the core therapeutic areas**

We delivered industry leading innovative approaches to study design, incorporating novel methodologies for guiding appropriate dosing and other decision making in a broad range of clinical trial programmes.

In oncology, we collaborated with the Karolinska Institute to confirm adenosine A2a receptor (A2aR) target occupancy using non-human position-emission tomography imaging. We used this imaging, and a model of human A2aR occupancy, to guide a dose reduction for the next patient cohort. We are also increasingly using umbrella studies in immuno-oncology (IO) which assign patients with the same type of cancer to different study arms based on their individual mutations.

In IMED Cardiovascular, Renal and Metabolism (CVRM) the AZD8601 (vascular endothelial growth factor A, VEGF-A, modified mRNA) team used microdialysis to measure local VEGF-A protein production in vivo following modified mRNA treatment in patients. The results demonstrated that AZD8601 produces VEGF-A protein in the human skin after single intradermal administration. AZD3681 is now planned to start a Phase IIa study in patients undergoing coronary artery bypass surgery.

**Integrate data to inform research and development**

Our Quantitative Clinical Pharmacology (QCP) group is highly skilled in advanced modelling and simulation. Modelling and simulation and data integration allow us to understand dose-exposure-response, which is used to inform decision making and improve efficiency in early clinical trials. Our QCP group has applied modelling and simulation to assess clinical outcomes and extend clinical trial results to special populations. These types of analyses are embedded in the early clinical development decision making process.

Specifically in 2017 our QCP group has supported regulatory approval in Europe of the orally disintegrating tablet of lorcaglatin (oral PPAR agonist) providing a complementary study design to show that the new formulation is comparable with the conventional immediate-release tablet. In patients with leptinomerginaii diabetes, we have used sophisticated analysis of clinical change in longitudinal tumour size to support inclusion of osimertinib in Phase IIIa trials such as FLAURA. Our QCP team performed quantitative exposure response (effect and efficacy) analysis in high agility to support the regulatory submission of the FLAURA study.

**We set out to**

- Extend and enhance innovative study designs across the core therapeutic areas

**We delivered**

- Industry leading innovative approaches to study design, incorporating novel methodologies for guiding appropriate dosing and other decision making in a broad range of clinical trial programmes.

**Accelerate human target validation**

The development of safe, effective medicines depends on thorough validation of human drug targets. The Clinical Discovery Unit (CDU) has developed a human target validation (HTV) strategy encompassing the entire product lifecycle, which can be applied retroactively to advanced clinical programmes to determine the validity of metrics. It can also be applied prospectively to pre- and early-clinical programmes to inform key decisions.

In 2017, we established collaborations with leading academic to further validate potential drug targets. With researchers at the University of Cambridge, we are working to understand the physiological role(s) of peroxisome proliferator-activated receptor alpha (PPARα), a critical regulator of hepatic lipid metabolism. Through collaborations at the Karolinska Institute in Stockholm, we are learning more about characterising patients with heart failure with preserved ejection fraction (HFpEF) and exploring genomics and metabolomics in patients with Type 2 diabetes.

Our approach to HTV enables us to further our understanding of disease and effectively address targets at multiple levels of validation. For example, in oncology we dosed our first patient with AZD2465 (selective estrogen receptor degrader) in a window of opportunity (WoO) study for patients with breast cancer who were about to have surgery to remove their tumour. These studies provide invaluable PK and PD data. In cardiovascular disease, we designed patient-reported outcomes measurement system (PROMIS), a world first in non-interventional clinical studies, to characterise patients with HFpEF with imaging and molecular biomarkers, paving the way for more precise patient stratification.

**Nurture leadership behaviours consistent with our values**

ECD follows the science. Not only have we published in competitive peer-reviewed scientific journals, our ComPEx tool enables the design of shorter clinical trials with fewer patients, making asthma trials more efficient.

ECD also puts patients first. This is particularly important for early clinical trials, which is where science meets the patient, and is ECD’s remit. Our BigDecide clinical informatics research and development framework and PROACT give the patient a voice, enabling them to become an effective ‘co-scientist’.

Our scientific leadership helps us to win, our quantitative clinical pharmacology team delivered an ethnically sensitive analysis for osimertinib which was critical for the rapid journey from submission to approval by the China FDA.

In-line with AstraZeneca values, ECD is committed to doing the right thing. For our employees, this means a proactive programme to foster career development that includes a variety of training opportunities, such as the possibility of gaining experience in other parts of the AstraZeneca enterprise.

Our entrepreneurial spirit is embedded in our transformative new study delivery model and projects, such as iBSCAY, an innovative Phase II umbrella study platform. This is the first multi-drug study combining immunotherapy and small molecule targeted therapies for evaluation in metastatic bladder cancer.

**We set out to**

- ECD strives to deliver an environment where science thrives

**We delivered**

- Collaborating for science innovation

**Delivering the next wave of scientific innovation**
IMED functions
Early Clinical Development

Technological advances make clinical trials smarter, faster and more cost-effective

Clinical trials are becoming ever more complex and expensive to perform, with growing risk of delay in bringing medicines to patients. ECD is at the forefront of advancing early phase clinical trials. We are making them smarter, faster and more cost-effective, with the hope that patients can benefit from advances in medical science as quickly and safely as possible.

iDecide

We are innovating in the use of real-time data capture to enable more efficient and effective decision making. In addition, we are collaborating with leaders in information technology and artificial intelligence (AI) to explore if we can fundamentally change the way clinical trials are performed.

iDecide is our cutting edge clinical informatics research and development framework that facilitates rapid interpretation of results, accelerates early identification of safety and efficacy signals, and improves understanding of the patient experience. The iDecide programme is being delivered through the Digital Experimental Cancer Medicine Team (digitalECMT) based at The Christie and Cancer Research UK (CRUK) Manchester Institute, and currently has three key components: REACT, PROACT and Watcher. REACT collates raw efficacy and signals, and improves understanding related to the trials they are working on. REACT is currently being used in over 140 studies (213,000 patients) of investigational medicines in early and late stage development, and PROACT is increasingly being incorporated into Phase I studies.

Additionally, one of our key objectives is to engage patients as co-scientists and this has been achieved through our Digital Patient Design Lab, which has been successfully established in the National Institute for Health Research (NIHR) Manchester Clinical Research Facility at The Christie NHS Foundation Trust. This lab is now delivering important new patient-centred clinical trials, where the team have daily interactions with patients.

2017 saw Carrick Therapeutics enrol patients on to our new secure cloud platform hosted by Microsoft Azure. This has been a sea-change enabling external access to REACT for collaborations with third parties. It also has given REACT and our other systems full machine learning capabilities.

Covance Laboratory Partnership

The industry leading Covance Laboratory Partnership was formed in 2016 to bridge science and operations. Amongst innovations in 2017, the partnership allowed centralised ELISA testing to be used for the first time in a Phase III double-blind, paediatric study (HESTIA 3). In a Phase I study, an exploratory test for vasoconstrictor-stimulated phosphoprotein (VASP) was identified, but a new solution was needed for the scale up to a Phase III multicentre double-blind paediatric study. However, the short analyte stability window and the remoteness of site locations with poor transportation infrastructure raised significant logistical issues.

The Covance logistics team determined that we needed to improve the analyte stability window to accommodate sample shipping turnaround times. With Covance, we explored two different technologies – flow-cytometry and enzyme-linked immunosorbent assay (ELISA). Both use antibodies that have a tag to measure proteins, but flow-cytometry requires complex machinery and lasers, while ELISAs are simpler as they use an enzyme that changes colour when there is a protein target. We collaborated to find scientific and logistical solutions to stabilise samples for shipment to a centralised testing laboratory, with successful implementation on an ELISA platform. This marks the first time a centralised ELISA assay measuring VASP activity is being implemented in a double-blind multicentre Phase III study in children.

People spotlight

Hani Gabra, Chief Physician Scientist

In 2017, Hani Gabra joined AstraZeneca as Chief Physician Scientist and became a member of the ECD leadership team. He is currently the Medical Science Director for AZD0156 within our DNA damage response (DDR) portfolio. Hani joined AstraZeneca from Imperial College London where he was Professor and Head of Medical Oncology at Imperial College Healthcare and Director of the Ovarian Cancer Action Research Centre within the Institute of Reproductive and Developmental Biology. He is a Fellow of the Royal College of Physicians of both Edinburgh and London. Previously, Hani was Cancer Research UK Clinical Scientist and Consultant Medical Oncologist at the Cancer Research UK Edinburgh Oncology Unit. Hani has 95 peer reviewed publications including nine in high impact journals, Nature, Nature Reviews Cancer, Nature Genetics, Lancet and Journal of Clinical Oncology. He has participated at over 50 international conferences since 2015, serves on five oncology related editorial boards (including the American Journal of Cancer Research) and holds eight patents in cancer research and technology. At Imperial, his research focus included the role of tumour suppressor genes in ovarian cancer.

Wolfram Brugger, Senior Medical Director

Wolfram Brugger is a haematologist/medical oncologist specialising in blood stem cell research and cellular Therapies (autologous transplantation, dendritic cell based immunotherapies). He joined AstraZeneca from academia as a Senior Medical Director in the Oncology Translational Medicine Unit in 2016. Wolfram is the medical lead of AZD2811 (aurora B nanoparticle), AZD4573 (cyclin dependent kinase inhibitor), AZD4055 (lucase kinase 1 inhibitor) and AZD8186 (PI3Kα inhibitor). His expertise in leukaemias/lymphomas has been valuable in the clinical development of AZD4573 in collaboration with the Boston ale and Astra. In addition, Wolfram serves as the Medical Science Director of the HUDSON umbrella study in non small cell lung cancer (NSCLC) and is involved in developing potentially new immunotherapies for chronic obstructive pulmonary disease (COPD) patients with scientists from the Clinical Discovery Unit and the IMED R&D team. Previously, Wolfram has participated in numerous Phase I – III trials and authored 169 peer reviewed articles in journals, including Nature Medicine, NEJM, Lancet, Lancet Oncology, Journal of Clinical Oncology, Blood and Leukemia. His H-index is 52 with more than 10,500 citations.

Natalie Fishburn, Head of Study Operations

In 2017, Natalie Fishburn became Head of Study Operations and a member of the ECD leadership team. Natalie joined ECD from an international assignment as Head of Clinical Operations in Japan, where she has led organisational change to drive productivity improvements in monitoring. Natalie has also been Site Management and Monitoring Director for AstraZeneca Australia and Site Management and Monitoring Cluster Director for Germany, Austria and Switzerland. Natalie obtained a BSc Honours in Neurophysiology and Anatomy at University of New South Wales in 1997.

Natalie will be taking on a leading role in delivering key changes to our Study Operations practice as we move towards a model working much more closely with sites and investigators.
### Key publications in 2017

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<tr>
<th>Publication</th>
<th>Title</th>
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<tr>
<td>Nature Genetics</td>
<td>Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis</td>
<td>Holde BD, de Jong K, Lamontagne M, Bossie Y, Remond St, Hardin M, Cho MH et al</td>
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<tr>
<td>Journal of the National Cancer Institute</td>
<td>Durable control of metastatic AKT1-mutant WHO grade I meningothelial meningioma by the AKT inhibitor, AZD9383</td>
<td>Weiler M, Roh P, Salm F, Blunhacht I, Schulmelt B, Rushing EJ, Regl L, Lindemann JP, von Diering A</td>
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A selection of key collaborations in 2017

1. University of Cambridge, UK
   Together with clinical investigators from the university, we are researching the physiological role(s) of PPARα, a critical regulator of hepatic lipid metabolism, through deep-phenotyping of humans with loss-of-function PPARα gene mutations. Through a joint ECD and Bioscience sponsored postdoctoral position with Professor Gillian Griffiths at the Cambridge Institute for Medical Research, we are investigating the potential effects of small molecules on cytokotic T cell function. In addition a clinical PhD studentship is evaluating PK-PD on cytotoxic T cell function. Through a joint ECD and Bioscience sponsored postdoctoral position with Professor Anders Jeppsson will characterise coronary artery bypass graft patients and link tissue regenerative capacity to improvement of artery bypass graft patients and link tissue regenerative capacity to improvement of arterial function.

2. University of Georgia, US
   A collaboration with Dr. Melissa Hallow to develop a mechanistic systems pharmacology model of the kidney and apply it to the late phase diabetes portfolio. The model has been integrated as a business as usual activity and is used extensively to support decisions including the dapagliflozin heart failure and chronic kidney disease outcomes studies and the DAPA-HF mechanistic study. The model is now being used for sodium-glucose co-transporter-3 (SGLT3) class differentiation and applied to other diabetes drugs such as exenatide and saxaglitin.

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4. Newcastle University and Cancer Research UK and the University of Manchester, UK
   Omacetaxine is the focus of a five-year collaboration between IMED, CRIK’s Manchester Institute, The Christie, and the University of Manchester. We are uniting the world-class scientific and clinical expertise of these institutions with the unique contributions of participating patients to deliver personalised healthcare in the Experimental Cancer Medicine Centre at The Christie and in other IMED collaborating institutions.

5. Warwick University, UK
   We support the doctoral training programme in the Department of Engineering under the supervision of Dr Mike Chappell. The first PhD student started in 2017 and is working on the integration of multiple high-dimensional genomic data types for survival and outcome prediction.

6. University of Gothenburg, Sweden
   This clinical research collaboration with the department of cardiology is focused on patient characterisation and imaging biomarker validation. A collaboration with Professor Anders Jeppsson will characterise coronary artery bypass graft patients and link tissue regenerative capacity to improvement of arterial function.

7. Karolinska Institute, Stockholm, Sweden
   Our collaboration with Professor Lars Lund is focused on understanding and characterising HFpEF patients. The SciLifeLab project Zewat aims to map the epigenome (including noncoding RNA such as micro RNA and transcripts, as well as the metabolome in skeletal muscle and from Type 2 diabetic patients and healthy subjects – in the basal state and in response to relevant interventions: i.e. glucose, insulin or physical activity.

8. Covance Laboratory Strategic Partnership, US
   Our Clinical Laboratories partnership benefits both investigators and patients through simplified processes including enhanced use of sample tracking, an online Investigator Portal and dedicated resources. As a single clinical laboratory provider, Covance collaborates with study teams in ECD and Global Medicine Development and scientists in the scientific functions in Precision Medicine and Genomics. AstaZeneca Clinical Biomedical Science and Translational Science to deliver end-to-end clinical laboratory services in clinical studies.

9. Sarah Cannon Research Institute (SCRI), US
   The ECD SCRI collaboration is an oncology alliance with a partner who has both extensive patient treatment (300+ first time in patient studies) and clinical delivery expertise in early stage oncology. SCRI assists IMED with shaping and delivering both individual studies and development programmes by bringing a wider awareness of how patients are treated and other clinical development trends in the field of oncology.

10. Acerta, US
    The acquisition of a majority stake in Acerta Pharma has enabled a collaboration between ECD and an early stage research and development group (aRED) with the aim to continue discovery activities within Acerta and also plan and execute clinical trial programmes. This establishes in-house expertise in haematological cancers and complements strategic use of immunotherapy in both haematological and solid malignancies.
Pharmaceutical Sciences

“Pharmaceutical Sciences continued to grow in 2017, building a new cross functional team in intracellular drug delivery, attracting world class talent, and initiating exciting collaborations. It was a phenomenal year, with novel modalities such as oligonucleotides, modified mRNAs and nanoparticles driving scientific leadership across the AstraZeneca portfolio.”

Anders Holmén, Vice President, Pharmaceutical Sciences
In 2017, Pharmaceutical Sciences continued to develop innovative drug delivery solutions, analytical methods and synthetic routes to enable rapid progression of the AstraZeneca pipeline. We grew in size to approximately 200 people, with a global presence in Boston, San Francisco, Cambridge, Macclesfield and Gothenburg.

We built a cross-functional intracellular drug delivery team and forged new collaborations with leading academic institutions such as the Karolinska Institute in Stockholm and the Max Planck Institute in Dresden. We attracted outstanding experts in drug delivery, analytical chemistry and molecular biology to join Pharmaceutical Sciences. In addition, we increased our use of theoretical methods for solid state prediction for our small molecule portfolio with the creation of a ‘Virtual Crystallisation Lab’. This will provide a stronger scientific rationale for selection and assessment of appropriate forms for our new medicines. It is already enabling us to reduce the number of experiments required to find the best form and increase the quality of our solid state risk assessments.

Another state-of-the-art predictive tool that we developed is a physiologically based pharmacokinetic (PBPK) model called Lung-Sim. This has significantly improved the prediction of drug dose deposition in the lung and plasma exposure and is being used to adjust formulation and dose for the first pre-clinical in vivo studies. For clinical studies, Lung-Sim is used to ‘bridge’ use of different devices and formulations throughout the development programme, and we are now embarking on an exciting journey in the field of inhalation biopharmaceutics, focussed on modified mRNAs and Anticalin® proteins alongside the small molecule portfolio in IMED RIA.
IMED functions
Pharmaceutical Sciences

Highlights

We set out to	We delivered

Collaborate across industry and academia to secure an investment of 8.5 million USD to improve the delivery of RNA-based therapies

We spearheaded a consortium called FoRmulaEx, consisting of five companies (AstraZeneca, Camurus, EVOX, GSD and Vironova) and three universities (Chalmers University of Technology, University of Gothenburg and Karolinska Institutet) to advance mechanistic insights into how nucleotide-based drugs enter cells and are processed before reaching their targets. In 2017, it was announced that the consortium will receive a total investment of 8.5 million USD over six to eight years from the Swedish Foundation for Strategic Research (SSF) to generate an ecosystem of researchers and industry addressing the challenge of RNA-based drug delivery.

FoRmulaEx’s Industrial Research Centre (IRC) will focus on rational design of new formulations that gain inspiration from nature’s use of extracellular vesicles (EVs) and exosomes (EVs with endocytic origin) to transport nucleotides such as RNA. Critical molecular and cellular factors for successful uptake and efficacy will be elucidated and this project aims to develop innovative drug vehicles that are efficacious and safe for clinical use, thereby contributing game-changing opportunities for disease treatment.

Be an industry leading separation science laboratory

In Pharmaceutical Sciences, we have leading separation science laboratories, not only delivering pure compounds, from small molecules up to large peptides, but also influencing the progress of the AstraZeneca portfolio by smart utilisation of chromatography methods. This has been primarily achieved using sustainable supercritical fluid chromatography (based on recycled CO2) instead of petroleum based solvents.

The first ever microgram-scale preparative instrumentation was successfully installed and applied in the automated Design-Make-Test-Analyse cycle (DMTAc), allowing for mass spectrometry triggered fraction collection. This enables the chemistry requirement to be scaled down with potential for large efficiency gains.

By sharing our expertise in separation science globally we were instrumental in getting our major contract research organisation for chemistry (Pharmaron) to cut their purification time for reactions for GMP manufacture.

We established a new team within Pharmaceutical Sciences to focus on addressing the challenges of delivering macromolecules into cells. This has included the recruitment of new scientific leadership positions in cell biology.

The challenges of delivering macromolecules are multifaceted and include novel excipient design and synthesis, manufacture of carrier systems and understanding biological mechanisms of cellular uptake/transferring. The Intracellular Delivery Team therefore worked holistically, in partnership with colleagues in Pharmaceutical Sciences and IMED functions, to form a multidisciplinary team which is uniquely positioned to tackle these challenges.

The team brings together scientists with expertise in chemistry, formulation and bioclinics and is focused on advancing our scientific understanding of intracellular delivery for new modalities such as modified mRNA and antisense oligonucleotides. The activities in the team will result in better research tools, new formulations and novel delivery approaches which will enable and enhance therapeutic programmes where intracellular delivery of macromolecules is needed.

Establish an analytical tool package for nucleotide based therapies

We successfully established an analytical tool package for our nucleotide based therapy projects, including development, implementation and validation of analytical methods to a Good Manufacturing Process (GMP) level. This key achievement has had direct impact on the progression of our oligonucleotide and mRNA projects, enabling clinical development via in-house delivery of key analytical data. The continued extension of this important capability will prepare us to meet future portfolio demand and become scientific leaders in the field.

Oligonucleotides and mRNA are highly complex large molecules and characterisation of these types of modalities is therefore challenging, requiring advanced analytical tools and highly trained scientists. Although there are some similarities between these two modalities, there are also distinct differences with respect to size and regulatory and characterisation requirements.

We developed the use of continuous flow reactors to optimise scale-up and yield of drug substances, and reduce impurities, ready for early phase clinical trials.

In 2017, we used high temperature (175°C) and high pressure (15 bar) continuous flow chemistry for laboratory scale production of AZD5634 (inhaled epithelial sodium channel, ENAC, inhibitor), under investigation in patients with cystic fibrosis. This process was then transferred to the continuous flow reactor in the Large Scale Lab (LSL), thus allowing production to GMP in-house design of an air-cooled manifold allowed for collection of the flow reactor output at less than 50°C.

FoRmulaEx’s Industrial Research Centre (IRC) will focus on rational design of new formulations that gain inspiration from nature’s use of extracellular vesicles (EVs) and exosomes (EVs with endocytic origin) to transport nucleotides such as RNA. Critical molecular and cellular factors for successful uptake and efficacy will be elucidated and this project aims to develop innovative drug vehicles that are efficacious and safe for clinical use, thereby contributing game-changing opportunities for disease treatment.

We achieved timely and efficient deliveries of pure material for toxicology studies by integration with a major contract research organisation for chemistry (Pharmaron) to cut their purification time for reactions for GMP manufacture.

For the early phase GMP manufacture of AZD3229, a two stage process, at two different temperatures, was developed and scaled-up for continuous flow to avoid the isolation of hazardous amines. The process is monitored and controlled through use of Process Analytical Technology (PAT) (Fourier-transform infrared (FT-IR) and Raman spectroscopy). The use of a continuous flow reactor can provide some key advantages over standard, agitated batch reactors. They allow access to reactions and conditions that cannot safely be scaled-up in batch reactors, as well as accessing favourable reaction conditions that can increase yield and selectivity and so reduce impurities. Many of these reactions also lend themselves to monitoring using RCR.

Our team at the LSL facility in Macclesfield is highly skilled in the transfer and scale up of these reactions for GMP manufacture.

We capitalised on new opportunities by understanding more about delivering macromolecules into cells

We established a new team within Pharmaceutical Sciences to focus on addressing the challenges of delivering macromolecules into cells. This has included the recruitment of new scientific leadership positions in cell biology.

The challenges of delivering macromolecules are multifaceted and include novel excipient design and synthesis, manufacture of carrier systems and understanding biological mechanisms of cellular uptake/transferring. The Intracellular Delivery Team therefore worked holistically, in partnership with colleagues in Pharmaceutical Sciences and IMED functions, to form a multidisciplinary team which is uniquely positioned to tackle these challenges.

The team brings together scientists with expertise in chemistry, formulation and bioclinics and is focused on advancing our scientific understanding of intracellular delivery for new modalities such as modified mRNA and antisense oligonucleotides. The activities in the team will result in better research tools, new formulations and novel delivery approaches which will enable and enhance therapeutic programmes where intracellular delivery of macromolecules is needed.

In Pharmaceutical Sciences, we have leading separation science laboratories, not only delivering pure compounds, from small molecules up to large peptides, but also influencing the progress of the AstraZeneca portfolio by smart utilisation of chromatography methods. This has been primarily achieved using sustainable supercritical fluid chromatography (based on recycled CO2) instead of petroleum based solvents.

The first ever microgram-scale preparative instrumentation was successfully installed and applied in the automated Design-Make-Test-Analyse cycle (DMTAc), allowing for mass spectrometry triggered fraction collection. This enables the chemistry requirement to be scaled down with potential for large efficiency gains.

By sharing our expertise in separation science globally we were instrumental in getting our major contract research organisation for chemistry (Pharmaron) to cut their purification time for reactions for GMP manufacture.

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Our team at the LSL facility in Macclesfield is highly skilled in the transfer and scale up of these reactions for GMP manufacture.

We developed the use of continuous flow reactors to optimise scale-up and yield of drug substances, and reduce impurities, ready for early phase clinical trials.

In 2017, we used high temperature (175°C) and high pressure (15 bar) continuous flow chemistry for laboratory scale production of AZD5634 (inhaled epithelial sodium channel, ENAC, inhibitor), under investigation in patients with cystic fibrosis. This process was then transferred to the continuous flow reactor in the Large Scale Lab (LSL), thus allowing production to GMP in-house design of an air-cooled manifold allowed for collection of the flow reactor output at less than 50°C.

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This in turn will allow us to work with previously undruggable targets, significantly increasing the biological breadth of our portfolio.
Managing hazardous chemistry: successful use of continuous processing in AZD3229 manufacture

It is not every day that we work with potentially explosive chemicals to make new medicines. However, when we were asked to make large quantities of AZD3229, we had to think “outside the box.” We needed to design and establish a manufacturing process which avoided the handling of hazardous, explosive intermediates. For conventional production of AZD3229, synthesis of one of the key building blocks requires the use of azides which are well known for their often highly energetic and toxic properties. We therefore focused on finding conditions where we could handle this hazardous chemistry and develop a safe manufacturing route to this essential building block.

Traditional batch synthesis was not an option as this can lead to accumulation of highly energetic and poisonous reagents with potential for a devastating explosion. To minimise such risks, we instead developed a continuous processing manufacturing method. This meant processing only a small quantity of the hazardous ingredient at any given time, in a continuous manner, allowing for minimal exposure and risk of severe damage. Working in this way facilitated further scale-up because the main factor we needed to consider was time rather than the multiple parameters associated with batch synthesis such as heat-cooling capacity, size and form of batch reactor and agitation efficiency.

To further ensure the safety of our manufacturing process, we considered which analytical method would be the most appropriate for monitoring formation of hazardous components. This would make it possible to adjust reaction parameters appropriately. Traditional analytical methods such as high performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) spectroscopy were not appropriate so, once again, we needed to be innovative. Infrared absorption (IR) spectroscopy is a technique used for analysis of organic and inorganic compounds. Each individual substance absorbs IR at a certain wavelength and this can be used for structure verification. The technique is also sometimes used for quantification of a specific component in a reaction mixture. We found that the hazardous azide components used in this synthesis had well resolved, specific IR-absorption bands which could be used for monitoring relative levels of these azides in the crude reaction mixture.

We developed a two step continuous manufacturing process capable of producing approximately 40g per hour of the key building block. A very small instrument setup was used which could be placed inside ordinary fume hoods, with FT-IR in line monitoring of the hazardous azides in real time. Three peristaltic pumps were used to deliver each of the three reactant solutions which ensured a continuous process with no interruptions. We used the same equipment for scale up and, after 20 hours of processing, more than 700g of the key building block was manufactured.

Using this innovative continuous approach, we were able to deliver the key building block for our drug candidate, AZD3229, safely and in time for the next stage of development, and secured its long term supply for future research.

The results of our work in developing this manufacturing process are available to other scientists through our publication in the international journal, Organic Process Research & Development.
### Key publications in 2017

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Author</th>
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<tr>
<td>Organic Process Research &amp; Development</td>
<td>Development of a safe continuous manufacturing route to 2-(4-isopropyl-1H-1,2,3-Triazol-1-yl)acetic acid</td>
<td>Karlsson S, Cook C, Emiritu H, Fan K, Gillespie P, Mohamed M</td>
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<tr>
<td>Organic Process Research and Development</td>
<td>Development and scale-up of a biocatalytic process to form a chiral sulfoxide</td>
<td>William R F, Gradey, Bradley Astane, Helen Benson, Julie Dementt, Steven McIcson, Keith Mulford, Amy Robertson, Paul Siedlecki, Paula Tomlin, Kevin Iare</td>
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**Polymorph prediction: an invaluable tool in drug development**

Solid chemical structures, including medicines, exist in multiple crystalline forms, called polymorphs, and selecting the right form of a compound for drug development is a key step for all pharmaceutical companies. Suboptimal selection can lead to very costly product redesign late in development or even after launch, and alterations to the chemistry required to make the active pharmaceutical ingredient (API). A good example of the value of this approach relates to AZD7624 (inhaled p38 inhibitor). Initially, AZD7624 was found to exhibit a single Form A, but during the development phase of the API crystallisation process, a new Form S appeared. Experiments showed that Form S is more stable under manufacturing conditions and the crystallisation process needed to be re-designed to produce Form S alone. Any crystallisation process is initiated via solubility measurements and solvent selection. Selecting the right solvent facilitates high yield, form control and negligible or no chemical degradation. By following an experimental approach to solubility measurements, acetone/1-pentanol was found suitable to crystallise Form S using a seeded cooling crystallisation process. In situ PAT monitoring of Form S crystallisation enabled us to make instant decisions to enhance the efficiency of the process. Within two months of its discovery, we successfully made Form S at over 10 kg scale. With this type of challenge in mind, we started a successful collaboration with Cambridge Crystallographic Data Centre in developing innovative tools to evaluate our crystal structures. These tools enable us to interrogate crystal structure databases of small organic molecules, giving us information about crystal structure packing and molecular interactions. By interrogating more than 875,000 crystal structures in our own database and the Cambridge Structure Database, we can now risk assess known solid forms of a designated API to confirm the likelihood of any form being the most stable. This approach showed that AZD7624 Form A was suboptimal and suggested that a more stable form might exist – a conclusion in line with our earlier research on Form S. This process for evaluating crystal structure is being implemented across our entire portfolio. The experience with AZD7624 has also motivated us to develop another tool for polymorph assessment to be used even before a compound is crystallised. Our bespoke method creates crystal structures of organic molecules in silico. Results from this Virtual Crystalisation Laboratory (VCL) can guide experimental work in the physical laboratory. This method has already been used in the selective estrogen receptor degrader (SERD) breast cancer programme to explore the polymorph landscape of our lead compound before sufficient material was available for experimental work. The accelerated timelines did not allow for full experimental exploration, but the theoretical polymorph landscape directed crystallisation of the most appropriate crystalline solid form. In a first for AstraZeneca, we have now successfully predicted the crystal structures of two polymorphs for pipeline molecules before they were produced.

At this point we have an industry leading risk assessment toolbox which allows early identification of suboptimal solid forms so that we can reduce the risk of unwanted, late phase surprises. We can provide a stronger than ever scientific rationale to underpin form selection and assessment, and use fewer experiments to make the right decision. Furthermore, we are planning further development of our VCL with new methods to predict not only the most stable polymorph but also ideal crystallisation conditions. In this way, we can enhance the likelihood of making the right crystalline solid form, with the most desirable crystal morphology.
“I am immensely proud of our progress in 2017. Our new Precision Medicine and Genomics function harnesses the power of genomics to discover new drug targets, and diagnostics to match therapies to patients most likely to benefit. We launched four new diagnostics linked to our medicines, including AstraZeneca’s first FDA-approved test for programmed death-ligand 1 (PD-L1) (diagnostic developed in collaboration with Medimmune), analysed over 200,000 genomes, and announced six new partnerships. We are well placed to build on our science leadership in 2018 and beyond.”

Ruth March, Vice President and Head of Precision Medicine and Genomics
This is a time of unprecedented change in technology and life sciences, with AstraZeneca leading the way in precision medicine and genomics.

Since we introduced a precision medicine approach to research and development in 2009, we have launched 19 diagnostics linked to four of our medicines in three key regions; therapies that target the epidermal growth factor receptor (EGFR), including the T790M resistance mutation, the poly ADP ribose polymerase (PARP) pathway, and the programmed death-ligand 1 (PD-L1) pathway. Approximately 80 per cent of our clinical pipeline now has a precision medicine approach.

Since 2014, we have maintained scientific leadership in precision medicine, being ranked first equal for the number of drugs linked to FDA-approved diagnostic tests [three] and having the most biomarker-related publications (99) in the industry.

In genomics, we have analysed more than 200,000 genomes (including data from internal and external databases) to inform investment decisions in drug discovery. We have completed our first analysis of sequence data from clinical trials in complex disease and are reporting the results at world-leading genomics meetings and in highly-cited journals. We have invested in secure cloud-based data technology, novel statistical science and machine learning. Like all aspects of our research, genomics research is always conducted in the most ethical and responsible way, upholding the highest possible standards of data privacy and security and in line with appropriate consent from donors.

Everything we do is driven by patient need and using a precision medicine approach to match innovative, targeted medicines to patients who are most likely to benefit. We are working with policymakers to bring earlier diagnosis to patients. For example, we contributed to the Life Sciences Strategy in the UK and collaborate closely with US groups such as Friends of Cancer Research.

In addition to building industry-leading science, we have a focus on supporting the commercial business. In 2017, we worked with health authorities to ensure that patients in key markets get access to innovative, targeted therapies. For example, we achieved an industry-first diagnosis turnaround in Japan. We also managed interactions with our diagnostic partners to set an industry record drug submission within 44 days of data availability.

Beyond oncology, our point-of-care diagnostics approach to match innovative, targeted medicines to patients who are most likely to benefit. We are working with policy-makers to bring earlier diagnosis to patients. For example, we contributed to the Life Sciences Strategy in the UK and collaborate closely with US groups such as Friends of Cancer Research.

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People spotlight

Slavé Petrovski, Vice President and Head of Genome Analytics

Slavé Petrovski is internationally recognised for his contributions to the science of genome analytics and variant interpretation and joined PMG in 2017 from the University of Melbourne, Australia. As Head of Genome Analytics within the Centre of Genomics Research (CGR), Slavé helps to drive the scientific direction of the CGR’s research, including the sourcing, development and application of statistically robust analytical frameworks. Slavé has published more than 55 scientific papers in the past five years, with the majority published in highly respected journals (median journal impact factor 10.1). He will apply his expertise in human genetics and informatics to facilitate delivery of novel insight into the biology of disease, evaluate human genetic validation of therapeutic targets and improve patient stratification based on molecular signatures.

Craig Barker, Laboratory Head Tissue Diagnostics

Craig is a recognised scientific diagnostic leader in PD-L1 laboratory testing who joined PMG from Leica Biosystems. He led the science and is co-author on two peer-reviewed manuscripts describing the comparability of multiple PD-L1 diagnostic tests, including the assessment of multiple cut-offs in NSCLC. These highly cited papers inform the clinical community on the utility of commercially available PD-L1 immunohistochemistry (IHC) diagnostic tests, and have been referenced in health authority guidelines in key markets. As a Laboratory Head, Craig leads a group of 14 diagnostic scientists delivering tissue diagnostic testing across the clinical portfolio enabling more than 30 ongoing pivotal clinical studies, and five innovative posters being presented at international meetings in 2017. To advance innovation in diagnostic science, Craig supervises research in artificial intelligence to enhance the use of digital pathology in diagnostic testing, which has the potential to facilitate the diagnosis of cancer in the future.

Magdalena Zajac, Diagnostic Expert

Magdalena Zajac joined PMG from Roche in 2015, bringing a passion for science, a strong desire to develop and a commitment to make a difference to patients. Magdalena is a committed and dedicated diagnostics leader who has driven the first FDA approval of an innovative complementary diagnostic for AstraZeneca. The analysis of PD-L1 expression on tumour and immune cells was key in providing biomarker data to health authorities. Magdalena’s enthusiasm and hard work led the team to successfully deliver this complex PD-L1 diagnostic submission, not only keeping pace with the accelerated timelines, but also managing interactions with our diagnostic partners Ventana and helping the regulatory team to set an industry record drug submission within 44 days of data availability. Magdalena is currently focused on delivering critical data to the clinic to illustrate the importance of the PD-L1 test used in making the right treatment decision for patients, positioning AstraZeneca as a leader in the field of diagnostic development and precision medicine.
IMED functions

Precision Medicine and Genomics

Highlights

**We set out to**

We launched four diagnostic tests with our diagnostic partners, linked to four AstraZeneca drugs in oncology:

- The first of these is Vantana PD-L1 (SP03), an immunohistochemistry test for tumour tissue.
- Secondly, the BRCAla100C from Myriad Genetics detects mutations in the BRCA1 and BRCA2 genes.
- The Rochi Cubist 7700 ESFR test is approved for use based on tumour tissue and plasma samples.
- The FoundationOne CDx next-generation sequencing panel is a diagnostic companion to identify patients who may benefit from treatment with targeted therapies.

We are committed to matching the right patients to medicines in our clinical trials – approximately 30 per cent of our clinical pipeline has a precision medicine approach, compared with 10 per cent in 2009.

**We delivered**

- **Deliver precision medicine to patients**
  - Our first FDA-approved point of care test beyond oncology, the Novo Biomarker Uric Acid Test.
  - We are working with our partners to enable patients with gout to be monitored and treated to target uric acid levels.
  - We are developing the world's first point of care test to stratify patients with asthma into eosinophilic and non-eosinophilic subgroups. Through our partnership with Chelsea Diagnostic Systems, a leading diagnostic point of care company, we will develop the test for regulatory submission in 2018.

- **Bring the benefits of precision medicine to all therapy areas**
  - Using next-generation sequencing (NGS), we are prospectively selecting patients in ten clinical studies with seven AstraZeneca drugs.
  - We are pushing the boundaries of NGS by exploring point of care NGS technology – the MiKron device from Oxford Nanopore is a scientifically portable device that can deliver DNA sequencing in minutes.
  - We are also evaluating NGS from circulating tumour DNA, with Guardian Health and Resolution Biogenics, to provide an alternative for patients who do not have tissue biopsies.

- **Drive new technologies and novel ways of approaching diagnostic testing**
  - We have sequenced over 5,000 genomes from our own clinical trials, including nearly 4,000 whole exomes and more than 1,000 whole genomes, using NGS.
  - We analysed more than 200,000 genomes to evaluate human validation of our targets, which is aligned to increased success rates in pharmaceutical development.
  - We created the Centre of Genomics Research in Cambridge, UK, recruiting some of the brightest minds in genomics, establishing close links with academic centres and investing in cloud-based bioinformatic and statistical analysis capabilities.
  - We also achieved proof of principle for our genomics strategy, including the role of rare variants in common disease. For example, we used exome sequencing and collapsing analysis of samples from a clinical trial in CKD, combined with clinical data, to identify genes known to cause CKD.

- **Transform discovery and development with an integrated genomics approach**
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  - We analysed more than 200,000 genomes to evaluate human validation of our targets, which is aligned to increased success rates in pharmaceutical development.
  - We created the Centre of Genomics Research in Cambridge, UK, recruiting some of the brightest minds in genomics, establishing close links with academic centres and investing in cloud-based bioinformatic and statistical analysis capabilities.

- **Establish leading scientific reputation in diagnostic and genomics science**
  - We have maintained scientific leadership in precision medicine since 2014. We are ranked first equal for the number of drugs linked to FDA-approved diagnostic tests (three) and have the most biotechnology-related publications (99) in the industry.
  - We demonstrated our scientific leadership through three high impact publications and 23 high-quality publications in peer-reviewed journals.

**In focus: Using precision medicine to identify patients most likely to benefit**

**Our company-wide genomics initiative puts genomics at the heart of drug discovery and development, enabling us to identify new targets for medicines and understand which patients are most likely to benefit. Our ambition is to analyse up to two million genomes by 2026, bringing together data from our strategic partnerships and sequencing over 500,000 samples from our own clinical trials.**

Since 2014, we are one of the leaders in FDA approvals of precision medicines linked to companion diagnostics. Recognising the importance of patient stratification has been key to success and our integrated genomics initiative is groundbreaking in terms of scale and scope. Since we made patient stratification a priority, we’ve also achieved many other key “firsts” in diagnostics.

- **Response to treatment in patients with ovarian, prostate, or gastric cancer may be mediated by mutations in multiple genes within the homologous recombination repair (HRR) pathway.**
- **Many patients with these diseases do not have tumour biopsies available for testing, and having a diagnostic test based on circulating tumour DNA (ctDNA) in plasma could increase the number of patients identified who may benefit from PARP inhibition.**

- **The only diagnostic tests currently approved by the US FDA for use with ctDNA are based on a few mutations in a single gene. The HRR gene panel identified by scientists in IMED Oncology Translational Science, based on many years of clinical and biological research, includes many genes and thousands of mutations. This highly complex genetic variation can only be detected by next generation sequencing, for which there is no approved diagnostic ctDNA test.**

- **The cross-functional team, led by scientists in IMED Oncology working with PMG diagnostics experts, carried out a proof of concept study to demonstrate feasibility of a clinical-grade HRR ctDNA NGS panel test in less than one year. The team evaluated and selected ctDNA clinical testing vendors, developed HRR gene ctDNA standards, and completed the analysis of 80 contrived and clinical samples from relevant cancer types.**

- **Results from the study showed success rates from both vendors of over 95 per cent, agreement between data supplied by the two vendors of over 90 per cent, and few false positive results. Most importantly, the per cent agreement between solid tumour and plasma samples for this complex panel was similar to that achieved by FDA-approved single-gene diagnostic tests. The team will continue its promising work in 2018 and beyond to evaluate this diagnostic panel in clinical studies.**

**Combining next-generation sequencing with circulating tumour DNA – an IMED Oncology-led PMG collaboration**

**Chronic kidney disease is a common, devastating disease that affects up to ten per cent of the population. Current treatments are not fully effective, so we are focussing on developing new, innovative medicines to target the causes of the disease, and to find new biomarkers to match the right patients to existing and novel treatments.**

In collaboration with Columbia University, our Centre of Genomics Research conducted its first genomic analysis of CKD patients. This analysis is the largest population-based analysis ever undertaken in CKD and includes the exomes from 1,100 genomic samples from an AstraZeneca clinical trial in patients with end stage renal disease. In this population, 10-15 per cent of patients with CKD were known to have hereditary forms of the disorder. We sequenced the protein coding parts of the genome (exomes) of 3,000 unrelated individuals with CKD and compared these with 9,000 control exomes. We then assessed the rate of identical variants in these sequences using novel statistical methodology based on collapsing analysis. This type of analysis enables us to code each individual within the dataset according to the presence or absence of “qualifying” rare variants in each sequenced gene, taking into account how likely these variants are to affect gene function. The analysis identified three genes known to cause familial renal disease at high-genome-wide significance levels. The strategy was also successful in identifying variants in individuals without a known genetic basis for their disease, and exploring genes not known to be related to the disease mechanisms of CKD.

**Innovative respiratory point-of-care testing – identifying the right patient for the right drug**

Using existing testing methods, it can take weeks to send a patient’s blood sample to a central laboratory to return the results. Point-of-care testing allows healthcare professionals to achieve lab-quality diagnostic results within minutes, rather than weeks or days.

We set ourselves a challenge to create a prototype handheld immunoassay test that could rapidly identify a subset of respiratory patients, in less than 10 minutes.

The ability to identify such patients rapidly and accurately at the point-of-care has the potential to facilitate research into precision medicine in IMED’s respiratory portfolio.

**Achieving proof of principle for genomics in chronic kidney disease**

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### IMED functions

**Collaborating for science innovation**

An environment where science thrives

**Introduction**

**Therapy area progress**

Delivering the next wave of scientific innovation

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### PMG adoption across AstraZeneca pipeline

#### Phase I - 27 New Molecular Entities

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Includes significant fixed dose combination projects, and parallel indications that are in a separate therapeutic area. Individual studies and indications not displayed.

### PMG adoption across AstraZeneca pipeline

#### Phase II and Life Cycle Management - 31 New Molecular Entities

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### PMG adoption across AstraZeneca pipeline

#### Phase III and Life Cycle Management - 20 Entities

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**PMG Not Applicable**

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Pipeline correct as of Q4 2017.
### Key publications in 2017

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### A selection of key collaborations in 2017

1. **Roche Molecular Diagnostics, US**
   - Our collaboration delivered a regulatory approved blood-based diagnostic for cancer patients with the T790M mutation who cannot provide a new tumour tissue biopsy sample.

2. **Roche Tissue Diagnostics, US**
   - This collaboration achieved a FDA approved complementary diagnostic test that measures PD-L1 status to inform physicians, making treatment decisions (diagnostic developed in collaboration with Medimmune).

3. **Foundation Medicine, US**
   - Using next-generation sequencing technology, Foundation Medicine is providing AstraZeneca with an assay to detect multiple classes of genomic alterations across a range of genes involved in homologous recombination repair (HRD).

4. **DNAnexus, US**
   - Working together with DNAnexus, AstraZeneca will leverage their secure cloud-based platform to analyze a massive volume of rare sequencing data rapidly and economically, enabling the processing of samples from thousands of patients per week and the sharing of data easily and safely with collaborators around the world.

5. **FinnGen, Finland**
   - FinnGen is a consortium of academic and Pharmaceutical partners, led by the University of Helsinki. This collaborative research project will produce and analyse genomic data from 500,000 individuals from the Finnish population over six years. This allows AstraZeneca access to a population with a higher than normal frequency of rare genetic variants, with matching clinical data enabled by Finland’s unique integrated health record system.

6. **Regeneron and UK Biobank**
   - Through our new partnership with Regeneron, UK Biobank, and four industry partners, we have obtained rights to gain access to 550,000 exome sequences (protein-coding regions of the genome) from DNA samples from the UK Biobank. This collaboration provides an invaluable resource of paired genomic and clinical data on a large scale, aiding our understanding of the role of genetics in human health.

7. **Institute of Genomics Medicine (IGM), Columbia University**
   - This collaborative genomic initiative enables us to develop novel statistical genome analysis methodology and drive innovation in gene discovery from large whole exome and genome data sets. Large-scale datasets, paired with corresponding patient clinical data, are being generated and analysed in collaboration with experts at the Institute of Genomics Medicine (IGM). Informatics experts at the IGM are also developing a cloud computing framework to support large scale statistical genetic analyses, to be implemented at AstraZeneca.

8. **Chembio Diagnostic Systems, US**
   - Through our partnership with Chembio we are developing a next-generation quantitative lateral-flow point-of-care test to allow rapid patient testing in the primary care or hospital setting.

9. **Myriad Genetics, US**
   - We expanded our companion diagnostic collaboration to support Japanese regulatory approval for the BRCA1/2 analysis in BRCA2 genes.

10. **University of Cambridge, UK**
    - Our collaboration with Professor John Danesh, at The Cardiovascular Epidemiology Unit, University of Cambridge, will allow access to specialised expertise in quantitative genetics and multi-ethnic population genetics, adding diversity to our genomic data.

John Danesh’s expertise includes epidemiology, systems genomics, screening and risk prediction and population genetics.
Expanding our science and platforms beyond small molecules

By 2017, the IMED portfolio progressed across seven new modalities: modified mRNA, antisense oligonucleotides (ASOs), oligonucleotide conjugates, bicyclic peptides, proteolysis targeting chimeras (PROTACs), therapeutic proteins and Anticalin® molecules. By combining our distinctive skills and technologies with those of leaders in highly specialised fields, we worked towards our goal to address the unmet medical needs of patients.

PROTACs – a novel approach to controlling intracellular proteins

Traditional, small molecule drug discovery typically focusses on targeting protein function. PROTACs are a new class of hetero bifunctional molecules, which are able to tag intracellular proteins for degradation by protein complexes, called proteasomes. This novel functionality offers an advantage over small molecules with its improved specificity, and maybe one day, better efficacy – presenting protein degradation as a new paradigm for drug discovery.

The future development of PROTACs presents a unique opportunity to deliver such molecules directly to the site of action for the treatment of diseases, and the potential to target proteins previously not accessible by traditional small molecule approaches. PROTACs stand as an alternative to ASOs and therapeutic peptides for controlling intracellular proteins levels. They may have an advantage in being able to penetrate cell membranes more easily, and owing to their unique catalytic mode of action, the potential to reduce systemic drug exposure.

Ionis: Antisense oligonucleotides – drugging targets that other therapies cannot reach

The great thing about antisense technology is that all targets are druggable; we can target any gene of interest at the RNA level regardless of its molecular function, and reach targets that are not approachable with small molecules or antibodies.”

Brett Monia, COO, Ionis

Five years into our highly productive collaboration with Ionis Pharmaceuticals, a leader in the discovery of mRNA targeting therapies, we have two clinical candidates in oncology (AZD4785, Astra Zeneca-Ionis KRAS inhibitor and AZD9150, ASO STAT3 inhibitor) and a third in pre-clinical development in cardiovascular disease (AZD8233).

Focussed on the development of ASOs, which destroy mRNA involved in creating disease-causing proteins, the collaboration is enabling us to develop drugs with the potential to be more effective than current therapies for cancer and other diseases that are difficult to address with conventional small molecules or antibodies.

AstraZeneca and MedImmune have a long and successful history in small molecule and antibody therapies, so the addition of ASOs to our therapeutic ‘toolbox’ is enabling us to broaden our approach to addressing the unmet needs of patients with some of today’s most serious diseases.

The combination of Ionis’ antisense technology and its new Generation 2.5 chemistry, which increases the potency of its therapeutics, is enabling us to modulate important new targets that have previously proved elusive.

AZD4785 is a Generation 2.5 antisense drug, discovered by Ionis, which is designed to directly target Kirsten rat sarcoma virus (KRAS), one of the most frequently mutated genes in cancer. The KRAS protein is involved in regulating cell division and tumour cell survival, and is therefore an attractive target for cancer therapies. However, no effective inhibitors emerged from 30 years of conventional research effort.

Now this is changing – thanks to the innovative approach of the AstraZeneca-Ionis team in developing AZD4785 to deplete KRAS protein by degrading the mRNA involved in its production. The team demonstrated that this leads to changes in downstream cell signalling and tumour regression in pre-clinical models of lung cancer and the research was published in 2017 in Science Translational Medicine. In 2017, AZD4785, the first drug in clinical development to directly target KRAS, was dosed in patients for the first time, with subsequent safety testing with increasing doses.

Alongside the progress with AZD4785, the AstraZeneca-Ionis team has advanced AZD9150, our ASO STAT3 inhibitor into a Phase II trial in combination with durvalumab, in patients with relapsed metastatic squamous cell carcinoma of the head and neck. Preliminary results were presented at the European Society for Medical Oncology congress in 2017. The progression of AZD4785 into the clinic and AZD9150 into Phase II trials reflects the continued success of the AstraZeneca-Ionis collaboration and the dedication of all the team members to forge ahead with the development of a new modality which holds great promise in a broad range of challenging diseases. With targeted delivery of ASOs, we have the opportunity to extend treatment options for patients that target key disease mechanisms and the potential to reverse progression and improve outcomes.
Moderna: Entering a new era in regenerative research

Since 2013 when AstraZeneca and Moderna Therapeutics announced an exclusive agreement to discover, develop and commercialise pioneering mRNA therapeutics, scientists across the groundbreaking team have relished the open, honest and energetic nature of the fast-moving collaboration.

Focussed on new treatments for cardiovascular, metabolic, renal diseases, and cancer, mRNA is the ‘mediator’ in the process by which genetic information contained in DNA in cells is transferred to make proteins. The beauty of mRNA-based therapy is that it acts locally and transiently. It does not integrate into a person’s genome, as happens with DNA therapy, and make a permanent change. mRNA treatment simply accelerates and improves on what the body does on its own.

The focus of our initial modified mRNA collaboration with Moderna has been vascular endothelial growth factor A (VEGF-A), a protein that stimulates formation of new blood vessels and protects heart muscle cells (cardiomyocytes) from dying. In pre-clinical studies, AZD8601, our VEGF-A modified mRNA, has triggered new blood vessels to grow at the borders of half-dead heart muscle, with accompanying improvements in cardiac function.

Following a successful Phase I clinical trial in patients with Type 2 diabetes, AZD8601 has progressed, and is ready to start the next phase of clinical trials in 2018. AZD8601 will become the first modified mRNA modality to go into a Phase Ila trial in cardiovascular disease. This exciting progress provides a potential pathway for treating patients with heart failure, a debilitating disease, for which current treatments can only provide symptomatic relief and attempt to improve the pumping action of the heart.

The rapid progression of AZD8601 into clinical trials would not have been possible without the combined strengths of the AstraZeneca-Moderna team. Moderna scientists were able to modify and purify modified mRNA so that the body’s immune cells would not attack it, while AstraZeneca’s expertise in drug delivery and cardiovascular medicine has enabled AZD8601 to move into clinical trials.

We also announced a second strategic agreement in the cardiometabolic space, in 2017, to advance a modified mRNA therapeutic encoding for the hormone, relaxin, as potential treatment for heart failure.

Ethris: Developing inhaled mRNA therapies for respiratory diseases

Among our most recent collaborations focussed on novel therapeutic modalities is a five year strategic research partnership with Ethris GmbH, a leader in mRNA-based therapeutics with specific expertise in pulmonary disease.

The collaboration aims to develop new stabilised non-immunogenic messenger RNA therapies for respiratory diseases using Ethris’ SNIM™RNA technology. Delivery of mRNA can be targeted to the lungs where local production of target proteins may modulate respiratory disease processes and provide new opportunities to modify the course of respiratory disease or its symptoms.

Building on our expertise in respiratory disease and inhaled delivery technologies, we are aiming to develop new targets for investigation in asthma, chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. This is aligned with our aim to transform the treatment of respiratory disease through our growing portfolio of medicines across modalities and delivery techniques, and our focus on research into disease modification.

AstraZeneca and MedImmune will have the option to take exclusive worldwide licenses upon completion of the research plan for each target within the collaboration.

Case Study

Bicycle Therapeutics: Bicyclic peptide potential across respiratory, cardiovascular, renal and metabolic diseases

When our Scientific Partnering team was looking for promising collaborators to develop novel therapeutic modalities, the exciting work of scientists at Bicycle Therapeutics made the company an obvious partner. Like AstraZeneca, this pioneer of bicycle peptides is based in Cambridge. Indeed, the company is the brainchild of Sir Gregory Winter from the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) – a world leading research institute with which AstraZeneca has close ties.

The Bicycle technology has application across medicine and so we formed a partnership with AstraZeneca because of its expertise in respiratory, cardiovascular, renal and metabolic disease which will allow us both to explore this modality in these new areas. It feels like one team because of the way we engage at the scientific level.”

Michael Skynner, Vice President, Bicycle Therapeutics

Bicycles®, a novel class of small molecules, are designed to overcome many of the limitations of existing drug modalities. They exhibit the affinity and exquisite target specificity usually associated with antibodies but in a small molecule format enabling rapid tissue penetration and flexible routes of administration. Their peptide nature provides a ‘tunable’ pharmacokinetic half-life and a renal route of clearance has the potential to avoid liver and gastrointestinal tract toxicities sometimes seen with other drug modalities.

As we move ahead with our collaboration, the bicyclic peptide platform expands our drug discovery capabilities and enables us to broaden the range of targets we can pursue across a range of disease indications.
Collaborating for science innovation

Achieving scientific leadership through entrepreneurial partnerships

The IMED Biotech Unit achieves scientific leadership through a dynamic, agile and entrepreneurial culture that operates like a biotech and has the resources of a major global pharmaceutical company. We are innovative and flexible, and take the initiative to achieve results.

The IMED Biotech Unit fosters an environment where our scientists can freely share their ideas and collaborate with the best external scientists and partners. 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.

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. In 2017, we continued to partner with top scientists. Our IMED teams established close to 40 major collaborations covering our main therapy areas and exciting new technologies that are set to drive progress in medical science innovation. We are committed to ensuring that we contribute to scientific advances that will benefit patients outside our main therapy areas, which we achieve through open innovation and externalisation.

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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, Vice President, Scientific Partnering and Alliances

In 2017, we continued to partner with top scientists. Our IMED teams established close to 40 major collaborations covering our main therapy areas and exciting new technologies that are set to drive progress in medical science innovation. We are committed to ensuring that we contribute to scientific advances that will benefit patients outside our main therapy areas, which we achieve through open innovation and externalisation.

The Blue Sky Fund collaboration brings to life a transformational methodology that wouldn’t be possible without the joint effort and skills of the great minds at MRC-LMB and AstraZeneca. Since its launch in 2014, the programme has funded 22 research projects characterised by ground-breaking science. Not only is working together of value to both organisations, but it will eventually bring benefit to patients by accelerating our understanding of the biology of diseases. Our excellent relationship demonstrates the success that collaboration and knowledge sharing can bring to industry, academia and the wider community.”
Professor Sir John Savill, MRC Chief Executive Officer

Our new collaboration with AstraZeneca will add to the emerging culture of innovation and knowledge exchange between academia and industry, fostered in our Institute. It is a significant step in the Crick’s approach to unite applied scientists from industry and Blue Sky researchers in “close distance translation”, and a great way to make the most of the research and ideas Crick scientists explore every day.”
Veronique Birault, Head of Translation, Francis Crick Institute

The IMED scheme opens tremendous opportunities to tackle important health problems in a way that cannot be achieved by industry or academia alone. Being given the opportunity to repurpose a drug for a completely different disease area is mutually beneficial, by catalysing downstream grant funding and commercial exploitation.”
Dr. Channa Jayasena, Clinical Senior Lecturer in Endocrinology, Imperial College London

Academic collaborations

IMED scientists work side-by-side in dedicated universities and institutions to support scientific research. In 2017, AstraZeneca and Imperial College London jointly funded a unique research collaboration that brings together some of the brightest scientific minds to address some of the greatest challenges for drug discovery today, by fast-tracking promising research from the laboratory to the clinic. This included the announcement of a joint research laboratory focussing on drivers of respiratory disease. A new collaboration was also established with the Francis Crick Institute. The five-year initiative will see researchers from AstraZeneca and the Crick collaborate on early-stage research that could translate into new treatments and health innovations in the future. Similarly, our exciting initiatives with Medical Research Council Laboratory of Molecular Biology (MRC-LMB), the Karolinska Institutet’s Integrated Cardio Metabolic Centre, the GLAZgo Discovery Centre at the University of Glasgow, the Max Planck Institute of Molecular Physiology and the AstraZeneca-Tufts Laboratory, continue to generate productive, high impact science to support future advances in life changing therapies.
Collaborating for science innovation
Achieving scientific leadership through entrepreneurial partnerships

Industry collaborations
By actively sharing our expertise and technology we partner with the world’s leading scientists to advance drug discovery.

Some great examples of peer-to-peer industry collaborations in 2017 include: a global strategic oncology collaboration between AstraZeneca and Merck and an agreement with Takeda Pharmaceuticals to jointly develop a potential treatment for Parkinson’s disease.

Working with smaller biotechs our focus in 2017 has been to expand the breadth of our new modalities, allowing us to explore novel biology. We announced platform partnerships with, Piers, to develop novel inhaled Anticalin® proteins for asthma, Bicycle Therapeutics, to develop bicyclic peptides for our CVRM and RIA therapy areas, Ethris on mRNA based therapies and a licensing agreement with Regeneron to produce antibody-drug conjugates (ADCs) as potential cancer treatments. We also announced a research collaboration, option and asset agreement with AstraZeneca to support the further development of AZD3386 (APT100), a uniquely different human apryrase therapy aiming to treat thrombotic diseases.

The science behind AZD3386 provides an exciting possibility for a new era of cardio protection and cerebral protection during the critical acute phase after a heart attack or stroke, using a novel modality. Marking the advancement of our new modality portfolio saw the first programme from our collaboration with Moderna Therapeutics – an investigational modified mRNA that encodes for vascular endothelial growth factor (VEGF-A) – ready for Phase IIa clinical trials. This is a significant milestone for both the science of regenerative medicine in cardiovascular disease, and AstraZeneca.

We continue to invest in cutting-edge drug discovery technology both in-house and through partnerships. In oncology, we entered a technological collaboration with Genomic Vision, in the field of targeting DNA damage response for novel anti-cancer treatment strategy. Through the use of their DNA molecular combing platform, FiberVision®, we will evaluate the impact of WEE1 kinase inhibitor in pre-clinical models. We will investigate DNA replication progression in cancer cells, and how the induction of replication stress contributes to WEE1 anti-tumour efficacy in specific cancer genetic backgrounds. Then to advance the translational of organ-on-chip data we entered into a collaboration with CNBio Innovations, through funding from Innovate UK to develop computational modelling to facilitate the interpretation of organ-on-chip data and improve how we optimise drug scheduling and combinations.

““Our global strategic collaboration agreement with Merck, to co-develop olaparib, provides a great opportunity to evaluate the full potential for olaparib as a monotherapy and in several combinations across multiple tumour types. The Joint Development Committee and the working teams from IMED, Global Medicines Development and Global Portfolio and Product Strategy are working very collaboratively with the Merck team, resulting in new trial proposals, which will start over the next several months. The increased capacity to deliver these important studies rapidly demonstrates the added value of our combined resources.””

Susan Galbraith, Vice President, Head of IMED Oncology

“It’s been super exciting to partner with a team that completely shares your motivation, passion and sense of urgency and brings a competency set that’s so complementary to ours. When we get together, we have a really deep and common understanding of the potential for the discovery and development of mRNA medicines.”

Tal Zaks, Chief Medical Officer, Moderna Therapeutics

“Our partnership with AstraZeneca accelerates the transformation of Pieris into a fully-integrated drug development and commercial organisation, comprising two main pillars in immunology: respiratory disease and IO, each of which is now anchored by a major alliance. We recognise AstraZeneca’s unparalleled expertise in the development of inhaled drugs, which will maximise the potential of inhaled Anticalin® molecules to become valuable assets for both companies.”

Stephen Yoder, President and Chief Executive Officer of Pieris
Collaborating for science innovation

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.
Collaborating for science innovation

Open Innovation

Our Open Innovation programme is designed to create a permeable research environment where scientists both inside and outside AstraZeneca can freely share their ideas and collaborate on projects. Since it was launched in 2014, we have concluded 250 partnerships and we have now reviewed over 500 proposals from scientists in 23 countries across four continents. Our Open Innovation collaborators have been awarded $56.5 million in grant funding to enable their research projects utilising our drugs.

Momentum for our Open Innovation programme continued in 2017. Our Open Innovation portfolio has 26 ongoing or planned clinical trials and more than 100 pre-clinical trials. For example, AZD4901 (neurokinin 3 receptor antagonist) was evaluated in a clinical study in women with menopausal hot flush symptoms, and the initial results have been published in The Lancet. We also launched two target innovation strategic alliances in 2017 with the Eastern Canada drug discovery group, Institute for Research in Immunology and Cancer — Commercialization of Research (IRICoR) and our first Swedish alliance with Chemical Biology Consortium Sweden (CBCS), a drug discovery group based at Karolinska Institutet. At the heart of our Open Innovation programme is our collaborative environment. We recently added a new Data Library module to our Open Innovation portal, which offers access to pre-clinical data sets, including preclinical safety and oncology combinations data. Sharing pre-clinical data on this scale is an industry first and it means that our Open Innovation partners can access over 11,000 sets of previously undisclosed data.

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 at our new Headquarters and research facility in Cambridge UK.

Visit our website to find out more
openinnovation.astrazeneca.com/data-library.html

“At AstraZeneca, we have great scientists doing truly ground-breaking 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 applied science.”
Mene Pangalos, Vice President IMED Biotech Unit and Business Development

“By providing AstraZeneca’s annotated library to our network of academic collaborators, we will facilitate opportunities to unveil new discoveries and investigate uncharted biology.”
Anna-Lena Gustavsson, Platform Director, CBCS
Collaborating for science innovation
Open Innovation

An invitation to innovate

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 clinical compounds; a pre-clinical toolbox of compounds with strong pharmacological properties; a collaborative effort to validate new targets, which may include high-throughput screening; advanced cheminformatics capabilities to explore therapeutic potential of new molecules; and research and development challenges open to anyone willing to offer innovative solutions.

Clinical compound bank
We offer patient ready compounds for novel, clinical and translational research into diseases with significant unmet medical needs. These compounds, which have demonstrated evidence of target coverage and manageable tolerability in humans, provide opportunities for anyone to explore disease biology, advance medical science and potentially discover novel therapies for patients. We invite interested investigators to explore our clinical compound bank and submit a clinical research ‘concept proposal’ for consideration for full project plan development.

Pre-clinical toolbox
We offer compounds with optimised pharmacological properties for pre-clinical research that will advance scientific knowledge by exploring novel disease biology. We invite disease expert physicians and basic scientists to partner with us, with each other and with public or private funding bodies to brainstorm, design and execute pre-clinical translational research. The aim is to generate high quality, novel data to support the future discovery and development of new therapeutics through target validation, efficacy in models of disease and mechanistic insight into the pathophysiology of human disease.

New molecule profiling
We provide access to sophisticated cheminformatics and screening technologies, as well as physical chemistry profiling. At the same time, we aim to create partnerships with top global research talent to help advance the discovery of novel therapies that improve the lives of patients. All evaluations and data are free of charge with no obligations, and the applicant retains IP rights to the molecule.

Challenges
In order to expand our problem solving ecosystem, we are openly sharing key research and development challenges and looking for ways to collaborate with anyone willing to offer innovative solutions. Our challenges span many therapeutic areas and disciplines.

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

+500 Proposals received from scientists in 23 countries across four continents
250 New partnerships formed
250 Pre-clinical studies initiated or planned
30 Clinical studies initiated or planned

“Collaboration is essential to advancing our understanding of diseases and accelerating the discovery and development of ground-breaking oncology and immuno-oncology treatments that benefit patients”

Dr. Neil Maresky, Vice President of Scientific Affairs, AstraZeneca Canada
New joint venture promotes innovation in medical science: Dizal Pharmaceutical – a ground-breaking joint venture

In 2017, AstraZeneca launched a ground-breaking joint venture with the Chinese Future Industry Investment Fund (FIIF) to accelerate the development of innovative, high quality, affordable medicines to help address unmet medical needs in China and around the world. The new company, Dizal Pharmaceutical, strengthens our deep, long-term commitment to healthcare in China, which goes back more than 20 years.

The new joint venture will enable us to contribute to the promotion of public health for China’s population of approximately 1.4 billion, and to advances in domestic research and development in a country with rapidly emerging life sciences capabilities. It leverages both AstraZeneca’s industry experience and the local expertise offered by the FIIF and builds on the strong presence we already have in the important Chinese market.

Dizal Pharmaceutical has been established by AstraZeneca and FIIF as an equally-owned, stand-alone company that incorporates all the scientific and technical capabilities of AstraZeneca’s Innovation Center China (ICC). FIIF is managed by the SDIC Fund Management Company (SDIC Fund), a private equity fund management company with a strong track record of investing in innovation. SDIC is partially owned by the China State Development and Investment Corporation, which contributes funding and expertise to establish strategic partnerships in China.

AstraZeneca’s China story
Since entering the Chinese market in 1993, AstraZeneca has established itself as a long-term partner and has pursued a development strategy that has consistently been in line with China’s objectives for a healthier and more prosperous country. Our goal is to be in China for China.

In 2007, AstraZeneca opened the Innovation Center China (ICC) to build local research and development capabilities in China. Our scientists from the ICC, who will now be a part of Dizal Pharmaceutical, have developed a strong reputation in China for delivering cutting-edge translational science. The ICC’s work includes biomarker research into cancer therapies specifically relevant for Chinese and Asian patients. The ICC has also focused on innovative drug development, culminating in the progression of AZD3759 (tyrosine kinase inhibitor), a lung cancer drug, which is now in Phase II clinical trials with an external partner. AZD3759 was the first investigational drug discovered by the ICC and is a great example of an innovation made in China that could potentially bring benefits to patients across the globe.

Our strategy in China includes partnership in order to achieve common goals, and many of the expected benefits from this new joint venture will come from its unique form of private sector partnership. We see this type of collaborative effort as an effective way to bring resources together, and combine strengths for win-win outcomes.

Ultimately, this joint venture will enable us to continue toward our patient-centric goals of accelerating scientific innovation in order to deliver new medicines wherever patients need them.
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 2017 alone, the IMED Biotech Unit welcomed 433 new starters.

We want to attract the brightest minds, the best talent, the boldest innovators – people who share our passion for science. 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 are rewarded and where great science comes alive.

By promoting an engaged culture of inclusiveness, we unlock the full potential within ourselves. As a way of moving us towards this ideal culture, the UK Employee Resource Group (ERG) system was established to recognise peer-to-peer networks that support employees by driving improved work environments, by unlocking new opportunities throughout teams, functions and sites, and by expanding the network of connections with others across the business. Mene Pangalos and Karen Sutherland from the Leadership Team are the sponsors for our UK ERG groups – our Network for Women, our AstraZeneca Plus Network for LGBT+ (lesbian, gay, bisexual and transgender) colleagues and our AstraZeneca Inspire groups for our young professionals.

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.

As part of creating a diverse workforce, we are committed to increasing the number of women in senior scientific roles.

Our ‘Women as Leaders’ programme gives female colleagues 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. In 2017 120 women attended the programme. People that have attended the programme have seen a 30 per cent promotion rate, and gained sponsors, coaches and mentors. Our 2017 Annual Women’s Summits, held in Gothenburg, Cambridge and Ghent, brought together over 1,100 employees to actively participate in conversations on diversity and inclusion in the workplace.

We also ensure all our line managers receive unconscious bias training and have diversity plans in place. Since 2012 we have increased the number of women in senior roles from 31 to 42 per cent and our aim is to further increase this going forward. Our target is 45-55 per cent women in senior roles by 2020.

Development

Continuous development of our people is high on our agenda, the majority of which comes from on-the-job experience. From our Development Marketplace, a monthly bulletin which offers in-house development opportunities for colleagues, to cross team secondments and shadowing opportunities, our programmes ensure we continue developing the skills and capabilities of our scientists, to equip them to be the best they can be.

Throughout 2017, we saw more than 60 IMED colleagues take up assignments outside their core role to broaden their learning and experience. The Marketplace has been very successful with around 30-40 opportunities being experienced every year.

In 2017 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.

During 2017 we ran a programme called Quest, which invited 120 of our IMED employees to participate in a 12 month programme to learn about various aspects of our business from clinical trial design, to genomics, to investor relations and business development, it also gave them the chance to network with colleagues from different IMED areas.

We also launched Blue Ocean Brain – an online development resource for IMED employees.

Graduate programme

In 2017, our two year graduate programme went from strength to strength, hosting 40 graduates in a variety of placements, with a total of 20 people graduating from the programme. Graduates complete three placements across Innovative Medicines and Early Development, giving them a breadth of laboratory experience across drug discovery and development.

As well as developing technical skills by working with world-class scientists using state-of-the-art facilities, all graduates are enrolled onto the Global Graduate Development Programme where the focus is on the softer skills that are required to make the successful transition to industry and are mentored throughout the programme.

Postdoctoral programme

The postdoc programme brings together motivated and innovative postdoc scientists who have a passion for great ideas and a desire to make a difference through an academic style postdoc position in a global pharmaceutical setting. The three year programme funds postdoc projects originating from IMED scientists/clinicians across the research areas and scientific disciplines within AstraZeneca. By the end of 2017 approximately 130 postdocs were in place with 75 publications, many in high quality journals such as Nature Medicine, Science Immunology and PNAS.

During the course of the year we identified 50 new postdoc projects which will help push our understanding of biology (in areas such as DNA Damage Response, exosomes, diabetic nephropathy and protein misfolding), chemistry, new chemical modalities and analytical approaches like machine learning. We continue to raise awareness of the programs science using cross-site seminars and are enhancing posting frequency and adding modules in entrepreneurship.

I completed the Women as Leaders programme in 2015 and attended the UK Women’s Summit in 2016. I was so inspired through participation that I joined the AstraZeneca UK Network of Women (NoW). In 2018 we’ll continue to strive to have diversity and inclusion reflected across the business units and locations, and encourage new members to join. Our ‘Lunch with Senior Leaders’ series is a motivating component for professional development. My personal ambition is to welcome more men to participate in the conversation and to truly engage diverse perspectives in our workplace.”

Shetah Morgan, Clinical Project Director, Early Clinical development, UK Network of Women Cambridge hub lead

The secondment in the IMED Communications team was a fantastic opportunity to explore my longstanding interest in science communications and a chance to expand my skill set. I have developed a much better understanding of the breadth of our portfolio and made so many great new contacts.”

Elina Kansikas, Nonclinical Submission Manager, Drug Safety and Metabolism

I believe that the strongest innovation comes from ideas that are tested by the most diverse teams and a confident LGBT+ workforce is an integral part of this. A personal highlight from this year was representing AstraZeneca alongside straight and LGBT+ colleagues at Manchester Pride, which in itself says a lot about our culture.”

Neil Reavey, Assurance Manager and Cambridge Hub Lead for the AZenplus LGBT+ Employee Resource Group
Our thriving science centres and biohubs

UK – Cambridge
Our new facility at the Cambridge Biomedical Campus (CBC) will become AstraZeneca’s largest research and development centre in the UK with over 1,600 scientists working in the building across all our therapy areas and drug discovery platforms. Importantly, it will also bring scientists from IMED Biotech Unit and MedImmune under one roof, encouraging further collaboration. In 2017, we had more than 2,400 employees located in temporary Cambridge locations across eight sites. In 2018, we will be preparing the move to our new home on the CBC.

AstraZeneca’s registered address moved to the CBC, 1 Francis Crick Avenue, in 2016, which marked a key point in delivering our science-led strategy. The construction of the new research and development centre and corporate headquarters continues, and the growing campus will successfully create an optimum environment for emerging businesses to thrive.

To build vibrancy across our science centres in Europe, we also have a dedicated air shuttle service across Cambridge, Gothenburg and Manchester.

UK – Macclesfield/Alderley Park
Our Macclesfield site is an important hub for AstraZeneca and the second largest pharmaceutical manufacturing site in the world. A centre for science, technology and excellence for advanced manufacturing, it is home to our Pharmaceutical Sciences team, who work alongside colleagues in Pharmaceutical Technology and Development Operations to design innovative manufacturing processes and drug delivery technologies. The Pharmaceutical Sciences facilities include laboratories and a good manufacturing practice (GMP) facility, where we manufacture drug substances for clinical trials and evaluate novel manufacturing technologies.

In 2017, the BioHub at Alderley Park continued to support the creation and growth of successful life science companies, with an optimum environment for emerging businesses to thrive in the UK. The Biohub is currently undergoing a £160 million investment programme, housing 61 SMEs, plus another 150 companies in start-up or virtual mode. As a vibrant life science centre and the largest Biohub in the North West, it is now also the interim home for the Cancer Research UK Manchester Institute with laboratory and office space that will see over 300 scientists conducting research on site.

US – Boston
Boston is home to the IMED Biotech Unit 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 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 IMED Oncology, Discovery Sciences, Pharmaceutical Sciences, Drug Safety and Metabolism (DSM) and Early Clinical Development (ECD) delivering innovative ways to target a trio of new drug targets for the oncology cell death portfolio (AZD5861, inhibitor of myeloid cell leukemia 1 (MCL1), AZD4573, a cyclin dependant kinase (CDK9) inhibitor and AZD0466, a B-cell lymphoma 2/extra large (BCL2/XL) nanoparticle). The IMED Neuroscience partnership with Tufts University laboratory goes from strength to strength contributing to key project milestones and publications.

In addition, our collaborations with Moderna, EmulateBio Foundation Medicine, Dana-Farber Cancer Institute and Massachusetts General Hospital (MGH) drive innovative pre-clinical and clinical science for discovering and developing new cancer medicines, MGH also validating and screening targets for neurological disorders.

Launched in 2015, the BioHub houses the Boston-area’s fastest growing and most desirable Biotech location. On average there are 10 research companies in place sharing and exchanging ideas. This includes the AstraZeneca spinout Entasis, Alkaxis, Persomics and Morphic TX. Several collaborations have already been established with tenant companies and several are taking advantage of access to high end equipment like NMRs and MassSpec as well as the vivarium.

In 2017, we proudly showcased our innovative science to a group of VIP Swedish business leaders as part of the Swedish Royal Academy of Science and Engineering technology mission to the US.

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Therapy area progress

An environment where science thrives

Collaborating for science innovation

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Therapy area progress
An environment where science thrives

Our thriving science centres and biohubs

Sweden – Gothenburg

Our strategic research and development centre in Gothenburg is the centre of our research for two of our main therapy areas; IMED Cardiovascular, Renal and Metabolism and IMED Respiratory, Inflammation and Autoimmunity. It is also home to a large number of our scientists from our early phase Discovery Sciences function and our DSM team. In addition to this we have teams from Operations, Scientific Partnering and Alliances, ECD, Precision Medicine and Genomics (PMG) and Pharmaceutical Sciences.

In 2017, we also launched Lab4Life, creating an open and truly shared research environment that goes beyond the usual laboratory model. By breaking down the traditional lab walls, automating processes and driving state-of-the-art IT, we will create novel ways of working to speed up delivery of new medicines. This is done by designing technology centres for up to 800 scientists to share knowledge and collaborate across disciplines, side-by-side. The transformation will enable a highly dynamic and agile research environment tailored to portfolio needs, today and for tomorrow.

The Gothenburg BioVentureHub continues to grow and foster life science innovation. There are currently 21 companies and one academic group in the hub, as a result Labiotech.eu included our Gothenburg hub in its list of the top 15 biotech incubators in Europe. AstraZeneca is actively collaborating with seven of the companies and numerous collaborations have been started between the companies themselves. Highlights during 2017 include Althera Biotechnologies initiating a Phase IIa study on arterial inflammation, a Vicore Pharma extension study indicating positive effects on lipid metabolism and Cereno Scientific entering the clinic with its drug candidate for thrombosis prevention. Delivering on our ambition to combine life science value chains, innovative ideas and entrepreneurial mindsets, two digital health companies, one medtech company and one diagnostic company have joined the hub in 2017. The first new company, OnDosis, was formed and joined the hub as part of the Spin Out project, in which we are establishing a model to build new life science companies based on innovative ideas originating out of AstraZeneca. OnDosis has the mission to enable personalised administration of medicines by connecting medicines, devices and digital health to benefit patients.

Our Gothenburg ‘Coffee Lab’ is a place for employees and people in the BioVentureHub companies to meet and share ideas, and in 2017 we saw true evidence of our culture of collaboration pushing the boundaries of science, with breakthrough modalities now in development.

Amazing Journey

In 2017, as part of our 50 year celebration of the Gothenburg site, we launched the Amazing Journey. The new attraction is a visitor tour that showcases the labs and what happens within them, all brought to life by our scientists who guide visitors through a total of nine interactive modules. All colleagues in Gothenburg can guide the tour, which is a way for visitors to step into the labs to discover our processes and technologies, all the while getting a taste of our open and collaborative research environment.

The journey provides a glimpse of the entire lifecycle of a medicine and an opportunity to encounter the great people and amazing science that are at the heart of the discovery in Gothenburg.
Cambridge Connections

Our presence in Cambridge – as a hub for collaboration between science, medical and academic communities – is already enabling us to drive change. By accelerating our scientific productivity, we will bring new medicines to patients, transform our company and contribute to the ecosystem of Cambridge. As a cluster with an important role to play for the successful future of life sciences in the UK, Cambridge has a key role to play to reinforce the importance of this sector as a growth driver for the economy. In parallel to the progress made in the construction of our future home, we have seen our scientific collaborations in Cambridge grow and deliver outstanding scientific insights across the University of Cambridge. Our scientists in discovery sciences are already working side by side with the scientists from the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) and Cancer Research UK (CRUK). We are also collaborating with CRUK Cambridge Institute on the CBC and Cambridge-based biotech companies, to name a few. Seeing Richard Henderson from the MRC Laboratory of Molecular Biology win the 2017 Nobel Prize for Chemistry, together with Jacques Dubochet and Joachim Frank, was an opportunity for us to celebrate with Cambridge, now home to 19 Nobel Prizes since 2000. Collaborating to develop the cryo-electron microscopy (cryo-EM) technology was facilitated by our co-location in Cambridge.

The number of collaborative research projects between the University and AstraZeneca has grown year-on-year, from 34 in 2015 to over 130 at present with 74 PhD scholarships, 15 post-doctoral fellowships and four clinical lectureships, spanning translational, basic and clinical research. AstraZeneca has several capacity-building initiatives with the University, which largely fund next generation scientists. Among these is the Cambridge MedImmune Programme in Biomedical Research, designed to train scientists in early phase clinical trials involving novel therapeutics. AstraZeneca is also a partner in the Experimental Medicine Initiative for 2016–2022 and, between 2015 and 2024, will fund nine PhD studentships each year for ten years across the Departments of Chemistry, Pharmacology and Biochemistry. In support of how our growing community in Cambridge represents our global organisation, we hosted our first global life science networking event, AstraZeneca Exchange Cambridge and our third Cancer Symposium in Cambridge in 2017. These are examples of how both our global business functions and our scientific leadership convene strategic discussion around opportunities to address unmet patient needs and translate scientific research into real world application and context. This is an essential connection to make. These connections also rely on an infrastructure that allows people to come to work, come together and collaborate. The announcement in the 2017 Autumn Budget of Government funding to accelerate the delivery of a Cambridge South train station is a significant boost for Cambridge, the region, and the UK life sciences sector at large and the result of significant public-private collaboration over many years. We welcome this development as it will help realise the full potential of the research cluster in Cambridge. In addition, it will improve connections across the ‘Golden Triangle’ of Cambridge, Oxford and London, which in turn will help drive growth and investment in UK science and accelerate the rate at which scientific discoveries are translated into viable new medicines for patients.

As part of our relationship with Cambridge Judge Business School, we support a number of programmes run by the Business School’s Entrepreneurship Centre. This includes coaching and mentoring fledgling life sciences start-ups as part of the Accelerate Cambridge programme. We also contribute and provide mentors for the Pitch@Palace scheme, a platform launched by His Royal Highness the Duke of York to help entrepreneurs across the UK advance their business ideas.
An environment where science thrives

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 2017, both inside the IMED Biotech Unit and across 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 2017 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 high quality scientific publications. High impact publications increased from four per cent in 2005-2010 to 19 per cent in 2016. Phase III completion has improved by more rigorous and quantitative drug nomination, as well as the development of the right culture where ‘truth seeking’ is encouraged by more rigorous and quantitative decision-making. Overall, the success rate from pre-clinical development to Phase III completion has improved from four per cent in 2005-2010 to 19 per cent in 2013-2016.

Our IMED functions

Collaborating for science innovation

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Therapy area progress

Lancet Respiratory Medicine

Science Translational Medicine

Nature

Nature Reviews Drug Discovery

Key publications in 2017

A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-doc analysis of randomised controlled trials

Targeting KRAS – dependent tumours with AZD4785, a high-affinity, therapeutic antisense oligonucleotide inhibitor of KRAS

Structural insight into allosteric modulation of protease-activated receptor 2

Impact of five-dimensional framework on research and development productivity at AstraZeneca

Lancet Respiratory Medicine

Science Translational Medicine

Nature

Nature Reviews Drug Discovery

About the paper:

This paper is a shining example of our innovative approach to clinical science. It describes a novel tool for accelerating the evaluation of efficacy in clinical trials of new respiratory treatments. By modelling a combination of frequently occurring patient events rather than utilising traditional endpoints, ComEx has the potential to cut the time of Phase II trials in half.

Activating mutations in the KRAS gene underlie the pathogenesis of up to 20 per cent of human tumours, KRAS being one of the most frequently mutated genes in cancer. This paper describes the development and pre-clinical characterisation of our novel antisense oligonucleotide inhibitor of KRAS, AZD4785. The publication reveals the activity of AZD4785 in patient-derived xenograft models of non-small cell lung cancer and demonstrates the potential of this novel approach to targeting KRAS.

This paper describes the foundations for our early success in the development of compounds that inhibit protease-activated receptor 2 (PAR2), a highly desirable and previously undetectable target in pain. In a collaboration with Napp Therapeutics we resolved the world’s first ever crystal structure of PAR2 which showed us a number of novel and exploitable binding sites.

In response to the well documented decline in research and development productivity across the pharmaceutical industry, AstraZeneca carried out a major revision of its strategy with the aim to improve research and development productivity. A 5R framework (the right target, right tissue, right safety, right patient and right commercial potential) was established as the cornerstone of the new approach.

Impact:

ComEx is a composite outcome for the evaluation of new asthma therapies, which will allow the design of shorter clinical trials that require fewer patients than the traditional studies assessing severe asthma exacerbations, while preserving the ability to show a treatment effect compared with severe exacerbations. It has the potential to be used broadly in the design of new therapeutic interventions for asthma.

The data revealed AZD4785 as an attractive potential therapeutic for the treatment of KRAS-driven human cancer, due to its safety profile, robust target knockdown and activity, which was demonstrated in a broad set of tissues in both mice and monkey, without any adverse effects.

The definition of the crystal structure provides a basis for the development of selective PAR2 antagonists for a range of potential therapeutic uses. More specifically, the revelation of multiple allosteric sites can be used for structure-based drug design.

The 5R framework has improved the quality of candidate drug nomination, as well as the development of the right culture where ‘truth seeking’ is encouraged by more rigorous and quantitative decision-making. Overall, the success rate from pre-clinical development to Phase III completion has improved from four per cent in 2005-2010 to 19 per cent in 2013-2016.

Lead AstraZeneca authors:

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Karl Edman, Stefan Gescherwinth, Nils-Olov Hermansson, Patrik Johansson, Arjan Snijder, Linda Sundstrom Nik Delker
Bengt Hamrén, Anthony Johnson, Ruth E. March, James Matcham

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Jerome Mettetal, David J. Nicholls, Stefan Platz, Steven Rees, Michael A. Snowden, Mereana N. Pangalos
An environment where science thrives

Our reputation for scientific leadership

Science Awards

The 2017 IMED Science Awards celebrated and recognised scientists from across IMED who have delivered outstanding science and contributions over the last 12 months. 170 global nominees were invited to join the IMED Leadership Team at a black-tie celebratory dinner held in Cambridge. The awards recognise outstanding scientific achievement and high impact science in the IMED.

Science Retreat

In 2017, IMED colleagues from around the world gathered together in Cambridge for two days of exciting scientific discussion and collaboration for their annual global Science Retreat. The theme of the event was ‘Learn, Connect, Collaborate’.

Global Chemistry Symposium

The Global Chemistry Symposium was held in Cambridge, attended by chemists from across AstraZeneca’s business units. Delegates discussed key advancements in discovery chemistry, application of technology, new chemical motifs and development and scale-up.

Discovery Sciences DNA damage response (DDR) oncology symposium

The Discovery Sciences DDR oncology symposium held in Cambridge, provided scientists the opportunity to share recent progress within the area of DDR. Attended by approximately 100 scientists from Discovery Sciences and IMED Oncology, and with over 30 presentations, a number of cross-DDR collaborations were initiated as the result of the lively and informative day.

Ideas Incubator

2017 saw the return of the Ideas Incubator Initiative, where our IMED scientists had the chance to pitch for up to $50,000 of research funding to support their Blue Skies proposals. 82 IMED scientists submitted their ideas to be reviewed and shortlisted by three local panels. Of the 82 submissions, the ideas that were successful ranged from complex screens to novel approaches to stratifying patients with respiratory diseases.

"I felt so proud of my colleagues and to be working for AstraZeneca! I could really feel the cool and stellar science that we do – the Science Retreat was the best conference I have attended in many years. Good work!”

Ulrika Tehler, Associate Principal Scientist, Pharmaceutical Sciences

"A fantastic day of pitches from seven extremely talented and passionate scientists. The breadth and depth of expertise in IMED was illustrated by the science presented and excited all of the IMED Leadership Team in some really tough discussions to select the winners. Well done to all finalists, I look forward to hearing how your projects progress over the coming months.”

Mene Pangalos, Vice President IMED Biotech Unit and Business Development
An environment where science thrives

### High impact publications in 2017

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<tr>
<td><strong>British Medical Journal</strong></td>
<td>Obesity and gynaecological and obstetric conditions: umbrella review of the literature</td>
<td>Gabra H</td>
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<tr>
<td><strong>Cell</strong></td>
<td>Selective inhibition of FOXO1 activator/repressor balance modulates hepatic glucose handling</td>
<td>Linden DJ, Ericson E, Norris TE, Johannson, AM</td>
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<tr>
<td><strong>Cell</strong></td>
<td>Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis</td>
<td>Peng X</td>
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<td><strong>Cell Host Microbe</strong></td>
<td>SMYD2-mediated histone methylation contributes to HIV-1 latency</td>
<td>Godin R</td>
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<td><strong>Cell Research</strong></td>
<td>Fibroblasts in an endocardial fibroelastosis disease model mainly originate from mesenchymal derivatives of epicardium</td>
<td>Wang QD</td>
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<td><strong>Clinical Microbiology Reviews</strong></td>
<td>Susceptibility testing of medically important parasites</td>
<td>Sjo P</td>
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<td><strong>Gut</strong></td>
<td>Fibroblast drug scavenging increases intracellular gemcitabine accumulation in murine pancreas cancer</td>
<td>Bapine TE, Tashimo E</td>
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<td><strong>Immunity – cell</strong></td>
<td>Regulatory T cell migration is dependent on glucokinase-mediated glycolysis</td>
<td>Smith Dn</td>
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<td><strong>Journal of American Medical Association</strong></td>
<td>Effect of an intensive lifestyle intervention on glycemic control in patients with Type 2 diabetes: A randomized clinical trial</td>
<td>Vaaq A</td>
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<td><strong>Journal of American Medical Association</strong></td>
<td>Selumetinib plus docetaxel compared with docetaxel alone and progression-free survival in patients with KRAS-mutant advanced non-small cell lung cancer: The SELECT-1 randomized clinical trial</td>
<td>Kohlmann AG, Smith PD, Alexander G</td>
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<td>Biomarker-based Phase II trial of savolitinib in patients with advanced papillary renal cell cancer</td>
<td>Morgan SR, Frigault M, Clark E, Handzel A</td>
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<td><strong>Journal of Clinical Oncology</strong></td>
<td>Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to First-Line gefitinib (IMPRESS): overall survival and biomarker analyses</td>
<td>Thress K, Rukazenkov YE, Haddad VA</td>
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<td><strong>Molecular Cell</strong></td>
<td>PTEN regulates P(3,4,5)P2 signaling downstream of class I PI3K</td>
<td>Couzilich SC, Barmeda D</td>
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<td><strong>Nature</strong></td>
<td>Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer</td>
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<td><strong>Nature Biotechnology</strong></td>
<td>ETX2514 is a broad-spectrum β-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including Acinetobacter baumannii</td>
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<td><strong>Nature Chemical Biology</strong></td>
<td>MiR-antibiotic complex reveals details of tunicamycin mode of action</td>
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<td>Domain-dependent effects of insulin and IGF-1 receptors on signaling and gene expression</td>
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<td>Identification of a hybrid myocardial zone in the mammalian heart after birth</td>
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<td><strong>Nature Communications</strong></td>
<td>Mapping the sugar dependency for rational generation of a DNA-RNA hybrid-guided Cas9 endonuclease</td>
<td>Taylor BJ, Blata MJ, Cuomo EM, Gordon E, Read JA, Wrigley JD</td>
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<td>Nature Communications</td>
<td>Prevalence of sexual dimorphism in mammalian phenotypic traits</td>
<td>Karp N</td>
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<td>Nature Genetics</td>
<td>Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis</td>
<td>Remand S, Megan H</td>
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<td>Nature Medicine</td>
<td>Enhancing the precision of genetic lineage tracing using dual recombinases</td>
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<td>Nature Medicine</td>
<td>HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures</td>
<td>Ramakrishna M</td>
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<td>Nature Medicine</td>
<td>The small molecule CLP037 does not modify activity of the K+–Cl– co-transporter KCC2 but does potentiate GABAA receptor activity</td>
<td>Brandon N</td>
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<td>Nature Methods</td>
<td>CRISPR-UMI: single-cell lineage tracing of pooled CRISPR-Cas9 screens</td>
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<td>Drug development in the era of precision medicine</td>
<td>Platt AS</td>
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<td>Legacy data sharing to improve drug safety assessment: the eTOX project</td>
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<td>Nature Reviews Drug Discovery</td>
<td>Mechanistic enzymology in drug discovery: a fresh perspective</td>
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<td>Phillips C, Fisher D, Pollard HK, Truman CM</td>
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<td>Science Immunology</td>
<td>Migratory CD11b+ conventional dendritic cells induce T follicular helper cell–dependent antibody responses</td>
<td>Krishnaswamy K, Mattson J</td>
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<td>The Lancet</td>
<td>Neuropeptide 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial</td>
<td>Weibert L</td>
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<td>The Lancet</td>
<td>Long-term incidence of microvascular disease after bariatric surgery or usual care in patients with obesity, stratified by baseline glycaemic status: a post-hoc analysis of participants from the Swedish Obese Subjects study</td>
<td>Carlsson LMS, Carlsson C</td>
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<td>The Lancet Oncology</td>
<td>Olaparib in combination with pacitasin in patients with advanced gastric cancer who have progressed following first-line therapy (SOLID): a double-blind, randomised, placebo-controlled, Phase III trial</td>
<td>Hodgson D, Liu Y2</td>
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<td>The Lancet Respiratory Medicine</td>
<td>Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM-Phase I, open-label, dose-escalation and dose-expansion study</td>
<td>Yang P, Cohen-Rabbie S, Harrop BJ, Overend P</td>
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<td>Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort</td>
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Preparing for the future with our IMED Futures teams

The IMED Futures programme gives our scientists the space to look beyond the work of today and explore how we can best use emerging science technology to accelerate the drug development of tomorrow.

With our novel drug discovery platforms, we are moving towards novel drug classes that target the biology of disease in totally new ways. Artificial intelligence (AI) is helping us address our biggest challenges across research and development, and our informatics transformation will help convert ‘big data’ into knowledge.

We are rapidly identifying innovative delivery systems that improve tissue targeting and intracellular uptake of our novel therapeutics, such as oligonucleotides, to either enhance or inhibit a cell’s ability to make or inhibit proteins. As we expand our drug platforms, we are also improving our ability to accurately predict their effects in humans. We are collaborating with world-leading experts in ‘organ-on-a-chip’ design, technology and biology to develop microphysiological systems (MPS) for pre-clinical tests on our novel drug candidates. MPS model developments support several IMED projects and continue to increase in complexity as we start to join organ chips together and move towards disease modeling.

Making pre-clinical models more human

Although very exciting, MPS won’t replace conventional pre-clinical drug testing models just yet. It’s essential we adapt current models to test our molecules with their increasingly complex mechanisms of action. For example, new pre-clinical models are being developed for drug resistant tumours, which are adapted to incorporate the fully active human immune system, so we can explore how human immune cells respond to tumours. High fidelity models like these are showing us the future because they better represent the patients we are trying to treat, and enable us to evaluate both our targeted therapies and our new potential therapeutic agents.

At the forefront of the ‘big data’ revolution

From discovery to delivery of new medicines, a digital revolution is transforming the way we collect, interrogate and analyse the ‘big data’ that now underpins every stage of the drug discovery and development process.

A key part of this is the use of machine learning and other forms of AI to connect and interpret disparate information sources and leverage our data landscape to develop a better view of how biology leads to disease. One key component is privacy and data security, and with evolving regulations and cross-industry collaboration, patient data security and safety is kept at the heart of the digital future. Our team continues to explore how data will enable a digital future that fundamentally delivers improved outcomes for patients.

We have developed a new virtual screening platform for hit identification built on the breakthrough Fast VS technology. The technology makes it possible to perform Google-like probes of millions of molecules to create a vast database of accessible unsynthesised compounds. We are also implementing an AI controlled fully automated design-make-test-analyse (DMTA) cycle. We initiated a problem-solving ‘hack-week’ involving teams of cross functional experts from across AstraZeneca to build a prototype and test the concept of running fully automated DMTA cycles continuously, without interruption, in under two hours.

“Coupling automation with AI offers huge potential to revolutionise drug discovery and enable us to optimise hits and leads in a completely different way.”

Garry Pairaudeau, Head of Hit Discovery, Discovery Sciences.

Novel approaches to drug delivery

As our drug discovery platforms extend beyond traditional small molecules we are rapidly identifying innovative delivery systems that improve tissue targeting and intracellular uptake of our novel therapeutics.

We are finding ways to improve cell uptake with ‘homing’ technologies to broaden the scope of novel molecules across disease areas.

Improving translational models

While focussing on expanding our drug platforms, we are also improving our ability to accurately predict their effects in humans. We are collaborating with world-leading experts in ‘organ-on-a-chip’ design, technology and biology to develop microphysiological systems (MPS) for pre-clinical tests on our novel drug candidates. MPS model developments support several IMED projects and continue to increase in complexity as we start to join organ chips together and move towards disease modeling.

Introduction

Therapy area progress
An environment where science thrives

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