The next wave of scientific innovation

Innovative Medicines & Early Development Biotech Unit
2015 – a year in review

Oncology combination therapies
AstraZeneca is investigating combinations of biologic and small-molecule therapies for the treatment of cancer. These combinations target the tumour directly and some help boost the body’s own immune system to induce tumour cell death.
Delivering the next wave of scientific innovation

Contents

Introduction
2
The next wave of scientific innovation
An introduction from Mene Pangalos
4
IMED 2015 in numbers
6
The story of osimertinib (or AZD9291)
Our 5R framework in action

Therapy area progress
10
Oncology IMed
18
Case study: The technology supporting our science – Confocal Microscope
20
Respiratory, Inflammation & Autoimmunity IMed
30
Case study: PT010 triple combination speeds into Phase III
32
Cardiovascular & Metabolic Diseases IMed
40
Neuroscience IMed

IMED functions
46
Discovery Sciences
52
Case study: The technology supporting our science – Acoustic mass spectrometer
54
Drug Safety & Metabolism
62
Personalised Healthcare & Biomarkers
72
Early Clinical Development
80
Shaping drug development in Asia

Collaborating for science innovation
82
Case study: Partnering to develop new medicines for neurodegenerative diseases
84
Three science units with one shared goal
86
Partnering to redefine the future of drug discovery
90
Case study: Partnering to develop the next generation of antisense-based therapeutics

An environment where science thrives
92
People: Inspiring great scientists
96
Our strategic science centres
98
Building our future in Cambridge
100
Case study: The next wave of innovation in DNA damage response
104
Our reputation for scientific leadership
108
Preparing for the future with our ‘IMED Futures’ teams

Biologics in the treatment of asthma

CGI image of AstraZeneca’s new Global R&D Centre and Corporate Headquarters, Cambridge, UK
The next wave of scientific innovation
An introduction from Mene Pangalos

2015 has been a remarkable year for our company, and for the IMED Biotech Unit.

In the last 12 months, we have continued to demonstrate the strength of our science, setting new records to deliver life-changing medicines to patients around the world. All of this has been made possible through the dedication and commitment of our amazing people, and their relentless passion for science and innovation.

During the year, our teams progressed a number of important projects within our main therapy areas, helping to further strengthen the AstraZeneca pipeline. While it is difficult to pick out highlights, I will call out three key progressions:

Firstly, in oncology, where we saw the approval of osimertinib (AZD9291) and the accompanying companion diagnostic in the US in lung cancer. This is one of the fastest, if not the fastest, drug approvals from first-time-in-human to launch in less than three years. Adding a positive CHMP opinion towards the end of the year rounded off an incredible achievement by our teams, of which I am incredibly proud.

Secondly, our Respiratory, Inflammation and Autoimmune team achieved a Phase II investment decision for PT010, our triple combination inhaler for the treatment of patients with COPD. The combination builds on the previously successful Phase III outcome of our dual-LAMA/LABA combination (PT063), and will also include the anti-inflammatory inhaled corticosteroid budesonide. Our proprietary porous particle co-suspension technology in the pMDI, developed by our colleagues at Pear Therapeutics, allows aerodynamically efficient drug delivery.

Finally, in CVMD, it was great to see the anti-microRNA from our Regulus partnership, AZD4076 (anti-mir103/107) for non-alcoholic steatohepatitis, reach the clinic. Oligonucleotides play an increasingly important role in our research portfolio, seeking to target novel proteins at the desired tissue more effectively, so these were important achievements for our teams.

The quality of our science was also demonstrated with our teams setting new records for scientific publications. Our transformation in the last five years is nothing short of exceptional, moving from a single high-impact publication in 2010 to a record of 29 high-impact publications in 2015. This not only reflects the quality of the research conducted in our laboratories, but also demonstrates how our science-driven culture is helping to build the scientific reputation of AstraZeneca.

Another personal highlight is our progress in personalised healthcare (PHC), developing targeted treatments matched using diagnostics to the patients most likely to benefit, which has been rapid by industry standards. In 2015, we launched seven diagnostic tests and signed 13 diagnostic partnerships. These achievements position AstraZeneca as a leading company in personalised healthcare amongst our peers – a tremendous accomplishment since the formation of our Personalised Healthcare & Biomarkers group in 2011. We also announced a collaboration with the Montreal Heart Institute (MHI) to search the genomes of up to 80,000 patients for genes associated with cardiovascular diseases and diabetes to support the discovery of new targeted treatments for these serious conditions.

The AstraZeneca Senior Executive Team further demonstrated the company’s commitment in this area at the end of 2015 by agreeing a broader genomics strategy across the spectrum of our discovery and development activities, something we look forward to sharing more about in 2016.

2015 also saw further progress in our pioneering approach to open innovation. Thanks to the outstanding work of a small team of people from our Strategic Partnering & Alliances group, working alongside colleagues from our iMeds and Functions, we have built a virtual pipeline supporting more than 20 clinical and 80 pre-clinical studies. Since the launch of our IMED Open Innovation portal in October 2014, we have seen >10,000 visits and reviewed >350 proposals for new drug projects. It’s a great example of how our scientists are being entrepreneurial, creating an environment that is open for collaboration and challenging conventional thinking.

Throughout the year, our teams continued to look to the future – exploring and investing in the next wave of scientific innovation. We supported recommendations for investment for our IMED Future teams to explore emerging technologies and innovations that have the potential to redefine the future of healthcare. We invested in organs-on-a-chip technology that could one day become an entire human body on a chip, bringing us closer to our goal of reducing, refining and replacing the use of animals in research. We also made significant investment in the use of CRISPR precision DNA-editing technologies across our discovery platforms, and we are looking forward to further understanding its application as a therapeutic option in our main therapy areas.

In the last quarter, our organisation entered into an exclusive agreement with the Wallenberg Centre for Protein Research to identify new targets for disease research in the groundbreaking area of the Secretome – research into all proteins that are secreted by a cell or that are exposed to the outside of the cell from within the cell membrane. The momentum continued right up to the end of the year. In December, our IMED scientists played a pivotal role, delivering the agreement to acquire a majority equity stake in Acerta Pharma, which gives us access to acalabrutinib (ACP-196), a potential best-in-class, small-molecule oral BTK inhibitor.

Although not possible to capture all of the details of the incredible contributions of our people across the IMED Biotech Unit in 2015, I hope this report gives you a flavour of the work we have done and the role we have played in helping to ensure AstraZeneca continues to push the boundaries of science.
IMED Biotech Unit by numbers in 2015

- **29 clinical projects**
- **60 clinical project combinations in oncology**
- **12 Phase I and Phase II starts**
- **120 post-docs**
- **Over $1bn investment in scientific research**
- **Over 60 major collaborations**
- **Almost 450 peer-reviewed publications**
- **2500 people with a passion for science**
- **Nearly $50m generated through Open Innovation**
- **2 positive Phase III investment decisions**
- **29 high-impact publications**
- **7 companion diagnostics launched**
- **90% projects with Personalised Healthcare approach**
- **Over 90% projects with Personalised Healthcare approach**
- **Over 60 major collaborations**
The story of osimertinib (or AZD9291)
Our 5R framework in action

The story of osimertinib or AZD9291 is a story of the fastest ever drug to make it from discovery to market. And it all began right here with our IMED Biotech team, living our values to follow the science, and challenge everything.

AZD9291 – or osimertinib as it is now known – received Food and Drug Administration (FDA) approval in November. 1.59 million people die of lung cancer every year, one of the biggest cancer killers in the world. Around 80-85% of lung cancers are non-small cell (NSCLC) and its five-year survival rate is less than 10%. Osimertinib was approved in the US for the treatment of patients with metastatic EGFRm T790M non-small cell lung cancer who have received prior EGFR-TKI therapy.

The T790M ‘gatekeeper’ mutation is prevalent in approximately two-thirds of cases of EGFRm advanced NSCLC. This was our biological target, and data from our clinical trials gave us confidence that osimertinib would have a clinically meaningful benefit and address an area of high unmet medical need.

“I arrived at AstraZeneca in September 2010, and one of the first jobs that I had to do was go through and review the portfolio to rank and prioritise projects. AZD9291 was in discovery at the time and I think it’s helpful to go back to the origins of thinking ‘why would we want a drug like this?’ because at the time it wasn’t as obvious as it is now that you have the data. I think you have to recognise that the scientists that came forward with this idea had to struggle against some prevailing wisdom that this might not be a useful thing to do.”

Susan Galbraith, Head of Oncology iMed

AZD9291 – or osimertinib as it is now known – received Food and Drug Administration (FDA) approval in November.

“The science in our labs that generated AZD9291 has been absolutely fantastic. I still remember the first time our scientists showed me our molecules binding to the T790M mutated receptor in 2010. The understanding of that science, the quality of the chemistry that we were doing, the biology, to enable us to progress the molecule so quickly through the research phase and ultimately get the candidate out in March 2013 was very, very impressive. This is something that I think all our scientists can be extremely proud of.”

Mene Pangalos, Executive Vice President, IMED Biotech Unit

Our 5R framework in action

Quality – not quantity

Osimertinib was one of the first examples where we applied the 5R approach, when it was identified as a ‘must-win’ project.

“Right target”
designed to overcome a common resistance mechanism, ‘gatekeeper’ mutation T790M

“Right tissue”
good bioavailability and widely distributed in tissues, potential objective response rate of 66%

“Right safety”
good tolerability profile, minimised hyperglycaemia risk and unwanted activity on the receptor which causes rash and diarrhoea

“Right patient”
companion diagnostic – cobas® EGFR Mutation Test v2 for the detection of T790M mutations in both tumour tissue and blood – developed in partnership with Roche Molecular Systems

“Right commercial opportunity”
defining the value, understand more quickly and deeply the patient subgroups and future viability

“Plus… Right culture”
team speed and flexibility to capitalise on the opportunity, and drive innovation in every aspect of how we discover and develop new therapies

The stats

Positive data on osimertinib in first-line EGFR mutated lung cancer at the American Society of Clinical Oncology (ASCO) meeting 2015:

– 81% patients on a once-daily dose of osimertinib were progression free at nine months
– Overall response rate 73%
– Longest duration of response was ongoing at 13.8 months at the time of data cut-off

The science in our labs that generated AZD9291 has been absolutely fantastic. I still remember the first time our scientists showed me our molecules binding to the T790M mutated receptor in 2010. The understanding of that science, the quality of the chemistry that we were doing, the biology, to enable us to progress the molecule so quickly through the research phase and ultimately get the candidate out in March 2013 was very, very impressive. This is something that I think all our scientists can be extremely proud of.”

Mene Pangalos, Executive Vice President, IMED Biotech Unit

The next wave of scientific innovation 7

Collaborating for

The next wave of scientific innovation

6 ©AstraZeneca 2016
A clear vision

“The early project team were a fantastic group of people to work with. I think what really helped was we had a really clear vision of what we wanted to do. We’d done a lot of discussion and a lot of consultation about what the profile of the molecule needed to be and we’d expanded it from its original vision and then we were really clear. The molecule needed to look like this. It needed to have these properties and this kind of potency, not this kind of toxicity. I think what really helps and the team really gelled. Initially we weren’t under the spotlight that AZD9291 is today. It was a bit of a slow burner if you like, but we delivered it very, very quickly.”

Teresa Klinowska, Early Project Leader Oncology iMed, IMED Biotech Unit

“In a project, you keep on making compounds, testing compounds, really until you’re absolutely sure you have a high-quality compound, clinical candidate. We had some early compounds that looked interesting. Unfortunately, when we looked at them in more detail we thought some of them had an issue with hyperglycaemia, which we believe is caused by off-target inhibition of the insulin receptor. As a chemistry team we were able to design out that activity with AZD6738, so AZD9291 came through and didn’t have that liability – this is something that we’re really proud of as a chemistry team.”

Richard Ward, Principal Scientist Chemistry, IMED Biotech Unit

Innovation in the clinic

Our increasing ability to identify the molecular or genetic mechanisms that drive cancer, such as non-small cell lung cancer (NSCLC), has allowed us to recognise and select defined patient subgroups where an individual’s cancer (disease segmentation) is identified by the molecular or genetic driver. However, this brings new challenges in drug development as patient subpopulations consequently become smaller.

Traditional clinical trials use a single drug for a given patient population. If that population is small (for example, genetically defined as 1% of the population), we would need to screen 100 patients to find the one patient that will benefit from the targeted drug.

Needless to say, screening hundreds of lung cancer patients to find the few with the correct genetic driver is slow and expensive, challenging for physicians, and frustrating for the patients – who have a lower probability of having the correct genetic driver for the single targeted drug being tested.

An emerging solution to these challenges, which leverages our broad portfolio in lung cancer, are ‘basket’ trials. These are trials that don’t test a single drug, but a ‘basket’ of drugs, each targeting a specific molecular or genetic driver of disease. Rather than screening for a single genetic driver in a patient population, we can then screen patients for drivers of their disease and match the right patient to the right drug in the ‘basket’.

This approach puts the patient at the centre of the trial, offering more drug options for the patient through a single trial process and a better chance of getting on the trial, while allowing us to test the drugs more quickly and effectively.

Basket trials speed up the discovery of new medicines making it possible to offer better medicines to more patients, more quickly.

“From the first time this molecule went into patients we were seeing a clinical response and that was just fantastic news for patients, for the team who worked on the molecule and for the organisation as a whole.”

Mark Anderton, Discovery Toxicologist Drug Safety & Metabolism, IMED Biotech Unit

“It was just amazing to sit in a room and actually see a slide of a patient before and a patient after six weeks of treatment and the tumour’s shrunk by 60%. It just doesn’t get any better in terms of the science that we do here. For me it was incredibly rewarding. Susan Galtinath came into the office and I’ve never seen her so excited, she was practically dancing. It was amazing!”

Ray Finlay, Medicinal Chemistry, IMED Biotech Unit

“To move so fast, you have to start from a very solid foundation. In this case the solid foundation was really, really excellent science. There was scientific purpose, there was excellence by design if you will. The drug was designed to do a job, and it did it.”

Flavia Borellini, Global Medicine Leader AZD9291, Global Medicines Development

What next for osimertinib?

Our teams continue to keep driving and keep looking for novel and next-generation strategies to benefit patients – from exploring potential benefits in other settings, combination therapies and first-line therapy. We are also starting to see that the same type of science and the same type of approach can be used in other patients with other diseases beyond oncology.

“The future is very exciting and osimertinib highlights a type of approach can be used in other patients with other diseases beyond oncology. What next for osimertinib?

Our teams continue to keep driving and keep looking for novel and next-generation strategies to benefit patients – from exploring potential benefits in other settings, combination therapies and first-line therapy. We are also starting to see that the same type of science and the same type of approach can be used in other patients with other diseases beyond oncology.
Oncology iMed

Our vision is clear. To help patients by redefining the cancer-treatment paradigm, with the aim of bringing six new cancer medicines to patients between 2013 and 2020. A broad pipeline of next-generation medicines is focused principally on four disease areas – breast, ovarian, lung and haematological cancers.
Susan Galbraith, VP Oncology iMed

“We have made a huge amount of progress in a short time while moving to our new location in Cambridge this year, including supporting Phase III investment decisions for osimertinib in the adjuvant setting, and expansion in leptomeningeal disease, and olaparib in prostate cancer. We also achieved three candidate drug investment decisions and two compounds entering first time in human trials. There was great progress in the Discovery phase, setting us up for exciting candidate drug progressions in 2016 and 2017. We now have over half our system entering first time in human trials. The approval of osimertinib towards the end of the year was a key highlight, just 32 months after first-dosing in patients. At the American Society of Clinical Oncology (ASCO) meeting 2015, AstraZeneca presented positive data on osimertinib in first-line EGFR mutated lung cancer. Data showed that 81% of patients on a once-daily dose of osimertinib were progression-free at nine months, with an overall response rate of 73%. The longest duration of response was ongoing at 13.8 months at the time of data cut-off. Beyond these exciting data, there were a total of 11 oral and 19 poster presentations with iMed authors at ASCO 2015. The iMed saw significant progress in its early discovery phase and clinical phase portfolio. In addition to nominating three new candidate drugs, we started clinical development of an ATM inhibitor (AZD0156) and an aurora kinase inhibitor (AZD3211). We moved three projects into Phase II clinical trials and made significant progress with our existing Phase II assets. Oncology also provided extensive support for the late-stage and Phase III pipeline: Osimertinib: Provided data supporting the potential for osimertinib in early-stage disease, supported circulating tumour DNA testing and generated exciting efficacy data in leptomeningeal disease. Olaparib: Provided scientific foundation for expanding the use of olaparib beyond germline BRCA for Solo 2 (ovarian cancer) trial and gastric trials as well as to support the Phase III investment decision in prostate cancer. Faslodex: Delivered data showing activity of Faslodex in tumours with ESFR1 mutations.

Highlights

**We set out to**

- Close two licensing deals.
- Demonstrate progress in at least two scientific areas based on external collaboration.
- Deliver new portfolio opportunities in an Emerging or Asian Oncology Market.
- Build a credible small-molecule drug discovery effort around immuno-oncology targets.
- Refresh our early-stage discovery strategy.
- To deliver a comprehensive solution for patients with EGFR-driven non-small cell lung cancer.

**We delivered**

- Opportunities with Starpharma and Heptares Therapeutics. For Starpharma, this was for the use of their dendrimer drug delivery technology, in the development and commercialisation of one of our oncology compounds with the potential to add additional compounds later. Heptares Therapeutics – we have gained exclusive global rights to develop, manufacture and commercialise HTL-1071 (now AZD4635), an adenosine A2A receptor antagonist.
- 22 papers derived from collaborations published/accepted in 2015. This included several publications in impactful journals, including on PI3K inhibition in Cancer Cell and on blockade of AKT and MEK in Ras-driven tumours in Clinical Cancer Research.
- Collaboration with China team on osimertinib; three Korean master agreements; launch of Taiwan translation fellowship programmes; Koc University (Turkey) studentship for target validation.
- A strategic push to explore possibilities for small-molecule drugs and relevant targets in the exciting immuno-oncology arena with the idea of integrating with and complementing the checkpoint antibodies and other biologics coming from our MedImmune colleagues. We developed key capabilities and hired staff with strong backgrounds in immunology. We focused on factors that promote the immunosuppressive microenvironment that exists in many tumours. We now have two ongoing clinical trials with antagonists of STAT3 signalling and CXCR2, both combined with durvalumab and we recently licensed a clinical phase I candidate Adenosine A2A antagonist (AZD4635).
- Focused effort into three main areas – oncogenic drivers and resistance mechanisms, DNA damage response biology and finally immuno-oncology.
- A drug combination strategy to drive deeper and more durable responses and have ongoing clinical studies combining our EGFR inhibitors with inhibitors of both MEK and mTOR, as well as a collaboration with Hycamite to explore JAKO, all pathways that have been shown pre-clinically and/or clinically to contribute to drug resistance. Finally, while osimertinib represents an important solution for patients with T790M resistant disease we are committed to exploring resistance mechanisms that arise in patients and initiating efforts to address those events.
New hormonal agents (abiraterone and enzalutamide) and to advance standard of care (SOC) with personalised (mCRPC). There is a high unmet need and an opportunity olaparib in metastatic castrate resistant prostate cancer.

In 2015, the Phase III investment decision was made for symposium with MedImmune.

Create the Cambridge Cancer Science pipeline.

Support the late stage and Phase III programmes.

Perform Next Generation Sequencing

Enhance AstraZeneca’s capability to perform Next Generation Sequencing programmes.

We set out to

We delivered

– Full recruitment of the Phase II trial for savolitinib (AZD6094; a cMet inhibitor) in papillary renal cell carcinoma and preliminary data from the TATTON trial was presented at the ASCO meeting, which supports combination therapy in patients with a cMet amplification who lack the T790M secondary mutation

– Data sets that showed AZD1775 (Wayl inhibitor) has activity in combination with platinum-based chemotherapy in ovarian cancer. Data from a single-centre study in platinum-resistant and refractory disease demonstrated a 41% response rate and was presented at the ASCO meeting. Importantly, combination dosing of AZD1775 with both durvalumab and olaparib was initiated in 2015

– Encouraging response rate data with AZD5363 (AKT) monotherapy in AKT1 mutant breast cancer; to drive increased durability of response the first patients have been dosed with a combination of AZD5363 and Faslodex

– Three compounds into Phase II clinical trials, AZD9150 is a STAT3 antisense oligonucleotide, which started a Phase II trial dosing in combination with anti-PD-L1 durvalumab. The trial also allows us to evaluate the combination of durvalumab with AZD9059, a small-molecule inhibitor of the chemokine CXCR2. The third compound was AZD3759, an EGFR inhibitor designed to have increased brain penetration. AZD3759 met the predefined PoM criteria

– An approved companion diagnostic for olaparib, and worked to identify and characterise mechanisms of clinical resistance. In addition, the team led work to support potential for olaparib beyond germline BRCA in ovarian, gastric and prostate cancers.

– Supporting the late stage and Phase III pipeline.

Style out to

– Support the Cambridge Cancer Science Symposium with MedImmune.

– A successful event with 286 attendees, 12 topics, 75 talks, 136 posters, 17 academic institutes that has encouraged early project openness and identified many immuno-oncology and combination approaches.

Osimertinib

The case was also successfully made to expand the osimertinib cohort in a CNS disease study, to characterise and explore label inclusion for leptomeningeal disease. Leptomeningeal Metastasis (LM) is a devastating complication of NSCLC and has been reported in 4-15% of NSCLC patients, resulting in a very poor prognosis. An increased risk of CNS involvement has been reported among patients with EGFRm NSCLC, in particular those treated with a first-generation EGFR-TKI. There is no established effective treatment for LM disease. Different treatment approaches are used such as radiation, systemic or intrathecal chemotherapy with limited success. The overall survival is 7-14 months with LM from EGFRm NSCLC previously treated with an EGFR tyrosine kinase inhibitor (EGFR-TKI). However, through collaboration with our Innovation Center in China, we have established a preclinical rationale for osimertinib activity in CNS disease and low incidence of progression in the brain among patients without brain metastases suggests potential for CNS control. Addressing an important unmet need, the opportunity for differentiation was highlighted at Portfolio Review in June 2015 to support the case for an expansion study in Q4.

The primary objective was to assess the safety and tolerability of osimertinib in patients with LM. All 13 patients were Asian with adenocarcinoma. Three of eight patients had improved neurological exam per investigator; of five patients with normal neurological exam at baseline, four had no change. Eight patients are continuing treatment with osimertinib beyond four months. One patient with neurological improvement was a 62-year-old Korean male, diagnosed with advanced non-small cell lung cancer (Ex19del, T790M) in March 2012 with the T790M secondary mutation.

Dan Stetson was a major contributor to the introduction of Next Generation Sequencing and has continued to drive the development of methodology for projects and novel technologies. Dan led the validation of the Illumina platform for NGS.

As a member of the KRAS team, Sarah Ross provided a significant contribution to the strategy for candidate nomination. Sarah saved significant investment on an HTS through detailed biochemistry. This was achieved in a year when Sarah moved to Cambridge, has taken on some line accountability and still delivers from the bench.

Olaparib

In 2015, the Phase III investment decision was made for olaparib in metastatic castrate resistant prostate cancer (mCRPC). There is a high unmet need and an opportunity to advance standard of care (SOC) with personalised medicine.

Prostate is the most common cancer in men and the sixth leading cause of cancer death among men. New hormonal agents (abiraterone and enzalutamide) and taxanes (docetaxel and cabazitaxel) are SOC. Although the heterogeneity of mCRPC is well recognised, treatment to date has not been driven by companion diagnostics (CDx). In 2015, we have generated limited but very encouraging data from TOPARP-A (biomarker +ve N=16) with an 88% response rate and mean progression-free survival of 9.8 months. Studies are ongoing with the new data expected towards the end of 2016. FDA provided useful insights, which will support our development plan and innovative trial design given the rarity of the patient population.

In addition, the translational science team have provided support for broadening the opportunity for olaparib beyond germline BRCA by developing the SOLITAIRE (combinatory Phase II trial in second-line ovarian cancer) for somatic tumour-based BRCA testing platform, and by running a successful concordance study for other mutations-in-genes involved in Homologous Recombination Repair (HRR) with Myriad and Foundation Medicine.
Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress

Feedback suppression of PI3Ka signalling in PTEN-mutated tumours is relieved by selective inhibition of PI3Kβ

An analysis of the attrition of drug candidates from four major pharmaceutical companies

Patient-centric trials for therapeutic development in precision oncology

Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harbouring EGFR T790M

Randomized, double-blind Phase II trial with prospective classification by ATM protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer

MEK1 and MEK2 inhibitors and cancer therapy: the long and winding road

Targeting the DNA damage response in cancer

Leptin, BMI and metabolic gene expression signature are associated with clinical outcome to VEGF inhibition in colorectal cancer

Oncology iMed small-molecule pipeline end of 2015

Key Oncology iMed collaborations in 2015

Key Oncology iMed publications in 2015
Automated confocal microscope
Our technique of choice for high resolution microscopy

The Automated confocal microscope (CV7000) is an automated confocal fluorescence microscope that can acquire images from live or fixed cells and tissue samples. Confocal microscopy is an imaging technique widely used for increasing cellular spatial resolution by eliminating out-of-focus light through the use of pinholes placed at the confocal plane of the lens. Confocal microscopy has become an essential tool for the life sciences and is the technique of choice for high resolution microscopy.

The scientist perspective

“The use of more physiological, cellular and tissue models including primary cells, stem cells and multicellular systems in preclinical drug discovery is now commonplace. Such models are often 3D in nature and therefore cannot be effectively imaged by traditional wide-field systems. In addition, AstraZeneca has invested heavily in phenotypic screening initiatives and precise genome editing. Having access to powerful detection microscopes that can detect subtle cellular phenotypic changes is critical to realising the full potential of such investments.

We evaluated current and future project demand and it was clear that there were many projects spanning our R&D functions that could benefit from the purchase of the CV7000. This instrument promises new capability with improved assay quality at fast acquisition rates and will enable Discovery Sciences to expand their assay portfolio to support all of the IMED Biotech Unit. The ability to image and extract data from more complex cellular models with improved physiological relevance early in drug discovery will speed up the discovery process and reduce attrition.

The microscope was installed at the latter end of 2015 and we have already started to use the system to impact projects where cellular spatial resolution is a requirement and for use with thicker tissue specimens. We are open to collaboration and would encourage interested parties to get in touch if they are interested in getting access to our microscopes.”

Samantha Peel, Senior Research Scientist, Discovery Sciences
AstraZeneca holds a unique position in respiratory disease, including asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), with a range of differentiated, potential medicines in development by leveraging novel combinations, biologics and devices. The pipeline also has a number of promising assets in inflammatory and autoimmune diseases within areas such as psoriasis, psoriatic arthritis, gout, systemic lupus and rheumatoid arthritis.
Respiratory, Inflammation & Autoimmunity iMed

“2015 has been a transformative year where we have become fully staffed with the optimal scientific profile. The right mix of scientists is now breathing science and working on the RIA iMed portfolio, which aims to transform the lives of patients with respiratory, inflammatory and autoimmune diseases.”

Maarten Kraan, VP RIA iMed

Transforming clinical practice and patient outcomes in chronic respiratory diseases

Our ambition is to drive the scientific excellence agenda and lead the development of game-changing, inhaled, immuno-modulatory treatments for asthma and COPD patients. All core functions work together to provide the necessary scientific innovation, patient insight and technology to achieve that goal. Some significant, industry-leading breakthroughs in 2015 included: characterisation of gene signatures for subsets of alveolar macrophages towards modulation of innate immunity in COPD; first ever measurement of in vivo lung receptor occupancy and early exploration of crystallisation conditions to fundamentally change inhaled drug dose estimation.

By polarising human alveolar macrophages ex-vivo, we have been able to identify unique COPD-specific gene signatures. The identification of novel gene signatures for polarisation status has led to new understanding of potential disease-relevant functions of alveolar macrophages in COPD. In addition, the experiments uncovered a remarkable cell plasticity independent of disease severity, opening up the potential for new therapeutic strategies targeting alveolar macrophages polarisation in COPD.

We have created a new paradigm in inhalation drug discovery. Without the means to assess the relationship between local tissue exposure and unbound pharmacologically active drug after inhalation, it has been notoriously difficult to establish solid PK/PD understanding for inhaled drugs. Our Drug Metabolism and Pharmacokinetics group has developed a new methodology to determine receptor occupancy in the lung, thus providing an elegant solution for describing PK/PD relationships. This was accompanied by a novel and sophisticated mathematical model, which gave input into drug design strategies and a way to better predict clinical outcome.

Our third breakthrough was discovering a vastly improved approach to access crystalline material in the early phase of inhaled delivery projects. This allows crystallisation conditions to be identified in a reproducible and controlled way, and consume only small amounts of compound. Multiple studies can be automated and processed in parallel, effectively removing one of the major bottlenecks in inhaled drug discovery projects.

"2015 has been a transformative year where we have become fully staffed with the optimal scientific profile. The right mix of scientists is now breathing science and working on the RIA iMed portfolio, which aims to transform the lives of patients with respiratory, inflammatory and autoimmune diseases.”

Maarten Kraan, VP RIA iMed
Transforming clinical practice and patient outcomes in chronic respiratory diseases

Progress the portfolio
Focused on the enhancement of inhaled therapeutics, stage one of RIA’s research strategy saw a number of successful developments in 2015. In June, the advancement of PT010 (a MDI-inhaled, combination of budesonide, glycopyrronium and formoterol) into Phase III clinical trials for chronic obstructive pulmonary diseases (COPD) marked a major step forward for the portfolio. This was made possible through our unique technology that creates stable co-suspensions of drug crystals in HFA propellants using lipid-based porous particles.

August saw the progression of an inhaled, dry powder formulation of AZD1084 into Phase II in asthma patients. The inhaled non-steroidal glucocorticoid receptor modulator (iSGRM) potentially provides a once-daily platform for novel anti-inflammatory combinations that may induce disease modification in obstructive airway diseases. A co-formulation of iSGRM with abediterol (beta2 agonist bronchodilators) potentially provides a glucocorticoid receptor modulator agonist/2 agonist bronchodilators combination treatments that will enable future inhaled combination treatments.

AZD9412 is being developed as an inhaled, on-demand therapy for asthmatics. In-licensed from Synairgen, AZD9412 is progressed into Phase II (from target selection to end of Phase II) to two projects with positive Phase II data out of which one was chosen for internal progression into Phase III (PT010 Tripla COPD). Two progressions into Phase II (inhaled SGRM and Inhaled IFNβ) the first of which will enable future inhaled combination treatments.

AZD1419 was safe and able to stimulate the local production of Type I interferons in the lung, the first step in the modulation of the immune response. AZD1419 generates an interferon signal in human lung at doses lower than those causing influenza-like symptoms.

2015 also saw pre-clinical development of RIA’s first small-molecule in development in a niche indication with AZD5634 – an inhaled epithelium sodium channel blocker (iENAC).

Transform disease management
A key project in 2015 focused on modifying the underlying pathology of disease is the inhaled toll-like receptor 9 (TLR9) agonist project in asthma. AZD1419 is an immune-stimulatory oligonucleotide analogue identified through collaboration with Dynavax Technologies in California. Pre-clinical studies have shown that stimulation of TLR9 in mice induces a long-standing protection against allergic inflammation in the lung. In healthy volunteers, inhaled AZD1419 was safe and able to stimulate the local production of Type I interferons in the lung, the first step in the modulation of the immune response. AZD1419 generates an interferon signal in human lung at doses lower than those causing influenza-like symptoms.

This paves the way for clinical evaluation focused on restoring airway hydration, mucociliary clearance (MCC) and improving lung function in cystic fibrosis (CF), an ultimately lethal respiratory condition resulting from the genetic dysfunction of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). In pre-clinical evaluation, AZD6364 increases airway surface liquid (ASL) in vitro, improves MCC in vivo, and thus, has the potential to rehydrate the airways, restore primary innate immune and impact upon disease progression in CF patients.

2016 will see RIA’s continued scientific innovation to address significant disease severity and unmet medical need in chronic respiratory diseases. This includes asthma and COPD.

Focused on the enhancement of inhaled therapeutics, stage one of RIA’s research strategy saw a number of successful developments in 2015.

**People spotlight – a new generation of RIA iMed scientists**

Our first rising star is Madelene Lindqvist, who joins us after four years as a postdoctoral fellow at Harvard Medical School, bringing with her profound expertise in adaptive immune mechanisms.

Madeleine has worked on T follicular helper cells and their role in context of HIV infection, which resulted in several publications in high-impact journals including Science Translational Medicine, Journal of Clinical Investigation, Nature Medicine and Nature Communications.

The recruitment of Kumar Krishnaswamy from Yale University School of Medicine even further strengthens the immunomodulation research in RIA. At Yale, Kumar’s postdoctoral research over the last four years was on innate-adaptive immune crosstalk with a particular focus on the role of dendritic cell subsets driving respiratory diseases like asthma. This generated key papers published in journals such as Proceedings of the National Academy of Science of the United States of America.

A major aspect of drug discovery and development is to impact on clinical outcome through predictive science. In RIA iMed DMPK, key approaches to prediction are mathematical modelling and Quantitative Systems Biology. In this context, Hoda Shariatian joined us from ETH Zurich (Swiss Federal Institute of Technology in Zurich) and brings a unique skill set to mathematically describe key biological processes against an overlay of relevant drug pharmacokinetic data. Her PhD at ETH modelled feedback regulations in the HOG MAPK pathway based on single cell measurements, resulting in high-quality publications in Molecular Systems Biology and Integrative Biology.

**The next wave of scientific innovation** ©AstraZeneca 2016
The Axl receptor tyrosine kinase is a highly conserved inhibitor of macrophage function and immune cell plasticity. The RIA iMed's collaboration with University of Helsinki, Finland has already yielded 15 joint projects. Functional for the last 18 months, and the collaborative enterprise has been fully breaking new ground in this area. This collaboration with Glasgow University's Institute of Infection, Immunity and Inflammation is fundamental knowledge and leadership in infection, immunity and inflammation. The RIA iMed's collaboration with GLAZGo Discovery Centre, Glasgow, UK has also been wholly successful.

Access to a large number of clinically well-characterized patients to help map somatic mutations in COPD patients. Insights into how RORg inhibitors modulate the function and plasticity of Th17 cells isolated from both patients with autoimmune diseases and healthy individuals.

Pre-clinical Dev | Phase I | Phase IIa | Phase IIb | Phase III
---|---|---|---|---
AZD7954/Aboditerol SGRM/LABA | AZD1419 Inhaled TLR9 | AZD9412 Inhaled IFN-beta | Aboditerol LABA | PT010 Triple MDI (COPD)
AZD7954/Idb SGRM/MABA | AZD7986 DPP1 | AZD7594 Inhaled SGRM | PT010 Triple MDI (Asthma) | PT001 LAMA
AZD5634 iENaC (CF) | AZD6871 MABA | AZD6934 Inhaled P38 | RDEA3170 URAT1 (Gout) | PT003 LABA/LAMA
AZD0284 RORg (LN) | AZD8999 MABA | | Lesinurad URAT1 (Gout) |

Disease Area | Asthma | COPD | Other

**Key RIA iMed collaborations in 2015**

- **Introduced in 2015**
  - University of Southampton, UK
    - Uppsala University, Sweden
    - Catholic University of Leuven, Belgium

- **Ongoing with 2015 achieved milestones**
  - University of Helsinki, Finland
    - University of Southampton, UK
    - State Key Lab of Respiratory Disease, Guangzhou Medical College, China
    - GLAZGo Discovery Centre, Glasgow, UK

**Key RIA iMed publications in 2015**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Journal of Respiratory and Critical Care Medicine</td>
<td>Role of B cell activating factor (BAFF) in chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Clinical Pharmacology and Therapeutics</td>
<td>Physiologically based pharmacokinetic modelling in drug discovery and development. A pharmaceutical industry perspective</td>
</tr>
<tr>
<td>Journal of Controlled Release</td>
<td>Specific accumulation of orally administered redox nanotherapeutics in the inflamed colon reducing inflammation with dose-response efficacy</td>
</tr>
<tr>
<td>Journal of Chemoinformatics</td>
<td>Target prediction utilising negative bioactivity data covering large chemical space</td>
</tr>
<tr>
<td>Molecular Pharmaceutics</td>
<td>Fast and general method to predict the physicochemical properties of drug-like molecules using the integral equation theory of molecular liquids</td>
</tr>
<tr>
<td>Journal of Leukocyte Biology</td>
<td>Targeting neutrophilic inflammation in severe neutrophilic asthma: can we target the disease-relevant neutrophil phenotype</td>
</tr>
<tr>
<td>American Journal of Respiratory Cell and Molecular Biology</td>
<td>Temporal and spatial expression of transforming growth factor-beta following progressive exposure to tobacco smoke in spontaneously hypertensive rats</td>
</tr>
<tr>
<td>Journal of Pharmacology and Experimental Therapeutics</td>
<td>A novel in vivo receptor occupancy methodology for the glucocorticoid receptor: toward an improved understanding of lung pharmacokinetic/pharmacodynamic relationships</td>
</tr>
</tbody>
</table>

**Key RIA iMed small-molecule pipeline end of 2015**
### Key RIA iMed publications in 2015

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Metabolism and Disposition</td>
<td>Lipid peroxide mediated oxidative rearrangement of the pyrazinone-carboxamide core of neutrophil elastase inhibitor AZD9819 in blood plasma samples</td>
<td>Gu C, Lewis RJ, Wells AS, Svensson PH, Hosagugurana VP, Johnsson E, Halstrom G</td>
</tr>
<tr>
<td>Expert Review of Respiratory Medicine</td>
<td>Immunology, genetics and microbiota in the COPD pathophysiology: potential scope for patient stratification</td>
<td>Mahotra R, Olsson H</td>
</tr>
</tbody>
</table>
Case study

A major innovation for respiratory medicine research

PT010 speeds into Phase III

The secret behind the co-suspension technology

The idea behind the co-suspension technology used in PT010 employs tiny porous floating particles, to which the crystals associate. With the floating particles holding their stability, there is no interaction between the medicines, which remain in a uniform suspension long after the simple inversion of the inhaler, meaning a consistent and correct dosage is inhaled every time. With the co-suspension technology, all strengths and combinations of a drug deliver the same aerosol performance. This attribute is very important to regulatory agencies and is a requirement for interpreting whether a drug delivers the same aerosolization properties, such as particle size distribution of the active drug into the lung tissue, but persistent problems limit their therapeutic potential. To ensure consistency and interpretation of clinical outcomes, the products must have consistent in-vitro delivered dose and aerosolization properties, such as particle size distribution of the active drug. Historically, achieving this consistency has been particularly challenging for both dry powder inhalers (DPI) as well as with conventional formulations of pressurized metered-dose inhalers (pMDI) that combine multiple drugs. The co-suspension crystal technology for pMDIs was developed to address exactly this challenge.

The global burden, personal struggle

There is a major global and individual unmet medical need in COPD. The World Health Organisation predicts the fast-growing lung disease to become the third leading cause of death by 2030, and it can severely affect quality of life for those in its grip. When symptoms worsen, patients become so short of breath they’re unable to undertake day-to-day tasks; struggling to climb the stairs, do the laundry, or participate in family life. The fast disease progression and often late diagnosis means that many sufferers find current treatments inadequate – failing to open the airways sufficiently to relieve the distressing effects of COPD.

The Pearl within

In June 2013, AstraZeneca completed the acquisition of Pearl Therapeutics, which is focused on the development of inhaled small-molecule therapeutics for respiratory disease. Pearl brought to the AstraZeneca family the innovative co-suspension technology used in PT010. August 2015 brought a positive Phase III investment decision for PT010: AstraZeneca’s fixed dosed triple for the treatment of COPD using Pearl’s innovative co-suspension technology. If successful, this will offer an improvement for patients suffering from a debilitating disease where true advances have been few and far between. PT010 combines three well-established compounds – a LABA (formoterol), LAMA (glycopyrronium) and an inhaled corticosteroid (ICS) (budesonide) in a totally new way that aims to enhance patient adherence and improve clinical outcomes.

The inhaler challenge

In respiratory disease, inhalers are crucial to ensure delivery of the drug into the lung tissue, but persistent problems limit their therapeutic potential. To ensure consistency and interpretation of clinical outcomes, the products must have consistent in-vitro delivered dose and aerosolization properties, such as particle size distribution of the active drug. Historically, achieving this consistency has been particularly challenging for both dry powder inhalers (DPI) as well as with conventional formulations of pressurized metered-dose inhalers (pMDI) that combine multiple drugs. The co-suspension crystal technology for pMDIs was developed to address exactly this challenge.

From dual to triple in record time

Patients with moderate or severe COPD commonly need two or three different medicines to effectively relieve their breathlessness. Adherence is key, and Pearl's co-suspension technology seems to offer a solution to the delivery challenge for fixed-dose combinations. The first step was to test the technology for PT003, a dual-combination pMDI of the two bronchodilators LABA and LAMA. This successful clinical development programme led to an NDA in June 2015 and the results paved the way for taking the technology one step further – to develop a fixed dose triple for COPD patients containing a LABA, a LAMA and a corticosteroid.

PT010 combines – in a single inhaler – crystals of two long-acting bronchodilators, LABA and LAMA with the ICS budesonide for immediate relief of symptoms. Relying on the extensive evidence for the three mono-therapies coupled with the positive data on PT003, the clinical team were able to design a Phase III programme that was able to select and confirm the doses for the individual components, enhancing it with dose-ranging studies that included budesonide. The Phase II studies were executed quickly due to the flexible approach of the teams, and by relying on the porous particle technology that allowed for such speed.

“...As a physician it’s great to see how innovative technology can breathe new life into long-established medicines for the benefit of patients. As a scientist, I’m envisioning a future treatment paradigm where we marry this technology with novel pathways and compounds which tackles different aspects of the underlying cause of the disease. To me, that’s the essence of ‘What science can do’.”

Maarten Kraan, VP R&D Imed

“...The journey so far with Pearl and the cosuspension technology has been a tremendous experience. We have successfully combined the know-how and muscle of the big, with the speed, agility and courage of the small. I’m really excited to bring the results to patients and physicians”

Martin Olovsson, VP Inhaled Respiratory, GPPS
Cardiovascular & Metabolic Diseases iMed

AstraZeneca’s strategy in CVMD focuses on ways to reduce morbidity, mortality and organ damage by addressing multiple risk factors across cardiovascular (CV) disease, diabetes and chronic kidney disease indications. The patient-centric approach is reinforced by science-led lifecycle management programmes and technologies, including early research into regenerative methods.
Introduction

Therapy area progress

IMED functions

An environment where science thrives

Cardiovascular & Metabolic Diseases iMed

“2015 was a year of achievements for CVMD iMed. We delivered exciting progress in our pipeline, continued to strengthen our new modalities platform and enhanced our capabilities with new collaborations with world-leading academic institutions and biotech companies. Our work is beginning to show the therapeutic potential of regenerative approaches in cardiovascular and metabolic diseases.”

Marcus Schindler, VP CVMD iMed

Throughout 2015, CVMD iMed continued to advance and break new ground with new and established projects, creating the next wave of scientific innovation. By making use of our extensive knowledge and expertise in the discovery and development of small molecules we have further expanded into a ‘new modalities’ platform of modified mRNA, micro RNA, and antisense oligonucleotides. CVMD iMed is now pursuing drug targets using all of these modalities, small molecules and combinations thereof.

Amongst this year’s achievements is the continued improvement of the quality and breadth of our key collaborations that provides us with the opportunity to expand into novel scientific areas whilst maintaining a clear scientific focus. As an example; together with Regulus Therapeutics our CVMD scientists successfully progressed the novel anti-microRNA compound AZD4076 for the treatment of non-alcoholic steatohepatitis (NASH) into first-time-in-man (FTIM). At the same time, our strategic collaboration with Ionis Pharmaceuticals provided us with the complementary toolbox of antisense oligonucleotides to address targets unsuitable for small-molecule drug discovery in CVMD. Our continued collaboration with Moderna Therapeutics showed promising results of the effect of VEGF-A modRNA in cardiac regeneration.

Highlights

- We set out to expand our scientific leadership in CVMD by collaborating with the best science outside AstraZeneca.
- We established 13 new collaborations that gave us the opportunity to work with new techniques, and that enhanced our capabilities and expertise. Our collaborations make a significant impact on our R&D pipeline in CVMD and we are looking forward to sharing and advancing our findings in 2016.
- We set out to enhance our scientific reputation and demonstrate scientific leadership.
- We delivered 93 new publications in major peer-reviewed journals of which 50 in high-quality journals and three in the world’s leading journals with particularly high-impact factor. Two of our collaborations (with Shanghai Institutes for Biological Sciences and with University of Michigan) each resulted in high-impact publications strengthening our scientific reputation. Our impact on the scientific community could also be seen by the degree of citations of our publications as well as attention from social media. Significant results reflecting the impressive advancement of our discovery and clinical stage programmes were presented at key conferences in 2015 including European Society of Cardiology (ESC), European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA), American Chemical Society (ACS) and American Society of Nephrology (ASN).
- We set out to strengthen our diabetes research and pipeline.
- We initiated an exciting five-year collaboration with Harvard Stem Cell Institute to bring in their novel breakthrough technique which creates human insulin-producing β-cells from stem cells. In record time our CVMD scientists successfully set up and mastered this technique, which is an immense achievement. The cells will be used in screens of AstraZeneca’s compound library and in the search for new treatments for diabetes. The collaboration also aims to better understand how the function of β-cells declines in diabetes and research findings will be made available to the broader scientific community through peer-reviewed publications.
Taking the road less travelled by making a difference with regenerative medicine and RNA therapeutics

Heart failure

In the cardiovascular arena CVMD scientists are targeting the growing challenge of cardiac dysfunction and heart failure. In heart failure the heart’s capacity to pump blood deteriorates over time and there are currently no treatment options to reverse or even address its severe and progressive nature. A key feature of heart failure is damage due to the gradually increasing loss of cardiac tissue such as cardiomyocytes and blood vessels and the aim of the CVMD research in this area is to find a way to help the damaged heart to repair itself. It was recently shown that progenitor cells, which may play a role in cardiac repair, are present in the adult heart. Our focus is to identify targets and pathways involved in the activation and differentiation of these progenitor cells.

In collaboration with Moderna Therapeutics, our scientists have access to modified mRNA (modRNA), which is an attractive modality for the investigation of the local production of paracrine factors known to be important for stem cell activation and differentiation. If successful, this approach has the potential to stimulate the generation of new cardiac tissue and reverse disease in patients with heart failure. One of the lead modRNA projects, VEGF-A, has shown promising results in animal models. A single injection of VEGF-A modRNA significantly increased vascular density, reduced scar area and improved the cardiac function in mice. In addition, VEGF-A stimulated cardiac stem cells (EPCs) and induced a state switch in these cells towards endothelial cells and to some extent to cardiomyocytes. These data demonstrate the regenerative potential of VEGF-A modRNA in the heart. The VEGF-A project is now moving to first-time-in-man to assess safety and tolerability as well as pharmacokinetics and local blood flow response, a key biological mechanism of VEGF-A.

In parallel, the team is using cardiac stem cells for screening of drug candidates; the aim is to identify targets and pathways involved in inducing and augmenting the human body’s ability to regenerate and repair damaged cardiac tissues. From these screens small-molecule programmes were identified and are now being validated using human cells and animal models of heart failure. The broad range of modalities including small and large molecules, antisense technology, CRISPR and modified mRNA available to our scientists enables investigation and targeting new potential and previously undruggable targets.

Diabetes/NASH

Non-alcoholic steatohepatitis (NASH) is inflammation and damage to the liver caused by a build up of fat in the liver. It is part of a group of diseases known as non-alcoholic fatty liver diseases. Some people with NASH have no symptoms while in others, the fat build-up causes inflammation, cell damage and in some cases cirrhosis, to a point where the liver cannot work properly. It is not known exactly what causes NASH, but it is thought to be caused by any number of factors, including environmental, lifestyle and genetics. NASH risk factors include obesity, insulin resistance (type 2 diabetes) high cholesterol, high triglycerides, and metabolic syndrome. Currently, there are no approved drugs for NASH despite the imminent progress to liver failure of these patients if left untreated. Our scientists are aiming to bridge this unmet medical need with the new modalities drug AZD4076.

AZD4076 is a GalNAc-conjugated anti-miR-103/107 oligonucleotide which was originally discovered in an alliance with Regulus Therapeutics. MicroRNAs (miR) are small RNA molecules, typically 20 to 25 nucleotides in length that do not encode proteins but rather regulate gene expression. More than 800 miRs have been identified in the human genome, and over two-thirds of all human genes are believed to be regulated by miRs. MiR expression, or function, has been shown to be significantly altered or dysregulated in many disease states, including oncology, fibrosis, metabolic diseases, and immune-inflammatory diseases. Targeting microRNAs with anti-miRs – chemically modified single-stranded oligonucleotides such as AZD4076 – offers a unique approach to treating disease by modulating entire biological pathways and may become a new and major class of drugs with broad therapeutic application.

Our pre-clinical studies have shown that inhibition of miR-103/107 by AZD4076 in mouse models, dramatically decreases liver triglyceride content and improves insulin sensitivity in both liver and peripheral tissues. AZD4076 has, therefore, the potential to act as an efficacious insulin sensitising therapy for NASH in patients with type 2 diabetes. With the collaborative effort of CVMD scientists and our partner Regulus Therapeutics Inc, we have just initiated dosing in a first-time-in-man Phase I clinical study. If successful, our compound would be a first-in-class treatment for NASH.

To further explore the possibilities of identifying new treatments for diabetes a collaboration with the Harvard Stem Cell Institute was initiated. In diabetes, pancreatic β-cells are destroyed by an autoimmune response (type 1) or the β-cells either fail to function properly or their numbers decrease (type 2). In the search for diabetes treatments, human β-cells are a great asset; however, these cells are extremely limited in number and availability. With this collaboration led by HSCI co-chairman and Howard Hughes Medical Institute Investigator, Professor Doug Melton, our CVMD scientists have access to a technique which allows potentially limitless quantities of β-cells to be produced from human-induced pluripotent stem cells generated directly from adult cells. These cells would be similar in all important aspects to those found in healthy individuals and can be utilised for a multitude of research purposes.

2015 was an exciting year and we are looking forward to further developing our science in 2016. Every member of CVMD iMed can be proud of our leaps forward.

Top Dividing pancreatic beta cells

Dr Magnone’s expertise is a crucial part of the research for CVMD iMed. With the ongoing paradigm shift from ‘blockbuster’ therapies towards a more personalised form of medicine, based on sophisticated patient stratification where prescribed drugs are based on specific biological phenotypes rather than clinical characteristics, her expertise is right on target. Chiara has led several programmes aimed at identifying patients’ molecular phenotypes predictive of disease progression and in response to investigational treatments as well as pre-clinical programmes for the development of novel personalised healthcare drugs. In addition, her experience from the fields of insulin resistance, obesity, type 2 diabetes, NASH and chronic kidney disease truly underlines the value she brings to CVMD iMed.
Key CVMD iMed collaborations in 2015

**Harvard University, Boston, US**
A strategic collaboration to discover and develop antisense oligonucleotide (ASO) therapies for cardiovascular, metabolic and renal diseases. AstraZeneca and Harvard have also developed a new ASO conjugate to further enhance delivery of oligonucleotides to mouse and rat tissues.

**Insmed Therapeutics, Cambridge, US**
A collaboration with Professor Matthias Kretzler in the area of chronic kidney disease. The collaboration will focus on the role of novel therapeutic targets for the treatment of CKD, focusing on the use of patient tissue and validation of pre-clinical models. We will also seek translatable animal models and predictive biomarkers for patient segmentation in-clinic, through a world-leading source (covering over 3,000 patients and seven animal models). Deliveries: human target validation data package for all portfolio projects and pre-TISD project, supporting decision-making on project progression and animal models selection.

**Regulus Therapeutics, San Diego, US**
The Alliance established in 2012 to discover and develop microRNA therapeutics in CVMD and Oncology has delivered a candidate drug, AZD4076. AZD4076 is a GalNAc conjugated anti-miR 103/107 oligonucleotide being developed for treatment of NASH in diabetic patients.

**INSMR, Paris, France**
The goal of this collaboration is to advance understanding of type 2 diabetes and chronic kidney disease (CKD) and to develop new treatments based on this. The first collaboration with Professor Dominique Langin will explore pharmacological ways to prevent adipose tissue release of lipid into the circulation, to normalize fat deposition and increase insulin sensitivity in peripheral tissues. And thirdly, we will collaborate with Dr Raphael Schachmann to develop models of human β-cells which have lost their ability to produce and release insulin to better understand the biology of this effect and how it can be corrected through treatment.

**University of Michigan, US**
A strategic collaboration to discover and develop ASO therapies for cardiovascular, metabolic and renal diseases. The collaboration will focus on identifying novel therapeutic targets for the treatment of CKD, focusing on the use of patient tissue and validation of pre-clinical models. We will also seek translatable animal models and predictive biomarkers for patient segmentation in-clinic, through a world-leading source (covering over 3,000 patients and seven animal models). Deliveries: human target validation data package for all portfolio projects and pre-TISD project, supporting decision-making on project progression and animal models selection.

**Key CVMD iMed publications in 2015**

**Pre-clinical**

**Phase I**

- AZD4831 (MPO) HIF6
  - Cardiovascular

- AZD5718 * Cardiovascular

- AZD4076 (mR103/107) * NASH
  - Cardiovascular

**Phase II**

- MEDIS111 (R1 Factor II) Trauma/Blending

- AZD4901 (hormone modulator) Polycystic Ovarian Syndrome

* Project progressed to current Phase in 2015

**Development**

- How to make a cardiomyocyte
  - Spalter D, Hansson EM, Zang L, Chien KR

**Stem Cells Translational Medicine**

- Human PSC-derived cardiac progenitor cells in phenotypic screening: a transforming growth factor-β type 1 receptor kinase inhibitor induces efficient cardiac differentiation

**Nature Medicine**

- c-kit+ cells adopt vascular endothelial but not epithelial cell fates during lung maintenance and repair

**Cell Metabolism**

- Sarpip1B1 promotes pancreatic B cell proliferation

**Science Translational Medicine**

- Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker

**Angewandte Chemie**

- Scalable synthesis of piperazines enabled by visible-light irradiation and aluminium organometallics
  - Sulez-Pantiga S, Colas K, Johansson MJ, Mendoza A

**Kidney International**

- Inhibition of the purinergic P2X7 receptor improves renal perfusion in angiotensin-II-infused rats

**Structure**

- Ligand binding mechanism in steroid receptors: from conserved plasticity to differential evolutionary constraints

**Journal of Medicinal Chemistry**

- Discovery of AZD6642, an inhibitor of 5-lipoxygenase activating protein (FLAP) for the treatment of inflammatory diseases

**Diabetes Care**

- Contemporary risk estimates of three Hba1c variables for myocardial infarction in 101,799 patients following diagnosis of type 2 diabetes
  - Ofsson M, Schnack V, Cabrera C, Skirf S, Lind M

**Drug Discovery Today**

- Targeting the podocyte to treat kidney disease
  - Lai M, Young K, Andarg U

**Atherosclerosis, Thrombosis, and Vascular Biology**

- Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction
  - Ye Y, Birnbaum GD, Perez-Polo JR, Nanthaw M, Nylander S, Birnbaum Y
The Neuroscience IMed model is unique in that it is dynamic and fully externalised, forming partnerships with leading-edge academic researchers, foundations and companies to create a portfolio of discovery and early development projects in neurological disease.
Neuroscience iMed

“In 2015, we continued to embrace our entrepreneurial and externalised approach with a number of new partnerships. These are particularly in the early portfolio and use our unique model to build for sustained delivery.”

John Dunlop, VP Neuroscience iMed

2015 has been a year where we have really seen the benefit and impact of the AstraZeneca Tufts Laboratory for Basic and Translational Neuroscience. This unique collaboration, established just two years ago, exemplifies our model of collaboration and externalisation. In this case, it is with a local group based in Boston, just a short distance from our Cambridge (MA) office. We now see tangible impact on both our portfolio and our science. This is best illustrated by the target validation and screening hit characterisation for the KCC2 modulator programme, performed in close collaboration with our IMED Discovery Sciences colleagues. KCC2 is a critical determinant of neuronal excitability in the brain and implicated in epilepsies and Amyotrophic Lateral Sclerosis (ALS). In addition to project support, the lab has delivered high-quality publications in the Journal of Neuroscience and the Proceedings of the National Academy of Sciences characterising the basic biology of this target.

Making headway in tackling Alzheimer’s disease

AstraZeneca has a unique, externalised approach to neuroscience drug discovery and development, partnering to advance the most exciting scientific opportunities in areas of high unmet medical need. In November, the team presented new data on MED1814, a humanised monoclonal antibody (mAb) selectively targeted to Aβ42, at the Clinical Trials on Alzheimer’s Disease (CTAD) 2015 conference in Barcelona. This event brought together world leaders in Alzheimer’s disease to discuss new results, candidate therapeutics, and methodological issues important to the development of the next generation of therapies.

Deposition of beta amyloid (Aβ) in the brain is a pathological hallmark of Alzheimer’s disease. There are two major Aβ isoforms: the 42-residue Aβ42 and the 40-residue Aβ40. Several studies have demonstrated that the Aβ42 species is both more toxic to neurons and more aggregate prone, despite the Aβ40 species being more predominant. AstraZeneca has been developing our selective monoclonal antibody against Aβ42, MED1814, and our most recent data demonstrate a selective and dose-dependent suppression of CSF Abeta1-42 but not Aβ40 in Phase 1 studies in Alzheimer’s disease patients. This is a compelling demonstration of mechanism of action and potential for therapeutic differentiation.

The team presented at CTAD the findings of tolerability and preliminary pharmacodynamics studies after single doses of MED1814 in mild-moderate Alzheimer’s disease. MED1814 shows:

- Dose-dependent increase in total plasma Aβ42 following single IV doses
- Selective target engagement following single IV doses
- Dose-dependent decrease in free Aβ42 in CSF following single IV doses

To date, MED1814 has a good safety profile and is well tolerated. No serious adverse events have been reported and there is dose-proportional serum Pk, as predicted for IgG1. Most importantly, it is the demonstration of selectivity for Aβ42 versus Aβ40 in CSF. The study continues into 2016 with single and multiple dose cohorts by intravenous and subcutaneous route of administration.

In parallel, clinical trials of AZD3293, an oral potent small-molecule inhibitor of β-secretase cleaving enzyme (BACE), have continued to progress. A co-development effort between AstraZeneca and Eli Lilly and Company (Lilly), AMARANTH is Phase II/III study of a BACE inhibitor currently in development as a potential treatment for Alzheimer’s disease. AZD3293 has been shown in Phase I studies to reduce levels of amyloid-beta in the CSF of Alzheimer’s patients. Inhibiting BACE is predicted to prevent the formation of amyloid plaque and eventually slow the progression of the disease. The studies are examining the safety and efficacy of AZD3293 compared with placebo in the treatment of early Alzheimer’s disease. The study is progressing toward a Phase III ID in 2016.
Neuroscience iMed clinical pipeline end of 2015

**Pre-clinical**

- MEDI7352: Analgesia
- MEDI1341: Parkinson’s disease

**Phase I**

- AZD6108: NMDA antagonist for suicidal ideation
- MEDI1814: amyloid β mAb for Alzheimer’s disease

**Phase II**

- AZD3241: myeloperoxidase inhibitor for Multiple System Atrophy
- AZD3293*: beta-secretase inhibitor for Alzheimer’s disease

*Partnered project

**Key Neuroscience iMed collaborations in 2015**

- **University of Pennsylvania and Stanford University, US**: Partnership funded by Target-ALS to discover new targets modifying the toxicity of ALS causative and risk genes.
- **Imperial College London, UK**: Preclinical data characterizing novel bifunctional mAb in analgesia.
- **University of Sussex, UK**: Working with the university’s Translational Drug Discovery Group to explore novel GABA receptor modulators in Huntington’s disease and anxiety disorders, funded by the MRC and Wellcome Trust.
- **Trinity College Dublin, Ireland**: Three-way partnership with biotech company Eolas and the NIH to advance orexin1 receptor antagonists in the area of addiction disorders, funded by the NIH Blueprint Neurotherapeutics network.
- **Eli Lilly, Indianapolis, US**: Generation of new mechanistic data on human Aβ and physiological measures of cognition.

**Key Neuroscience iMed publications in 2015**

<table>
<thead>
<tr>
<th>Journal/publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Psychiatry</td>
<td>Misassembly of non-mutant disrupted-in-schizophrenia 1 (DISC1) protein is linked to altered dopamine homeostasis and behavioral deficits</td>
<td>Brandon N</td>
</tr>
<tr>
<td>Nature Neuroscience</td>
<td>The cellular targets of antidepressants</td>
<td>Brandon N, McKay R</td>
</tr>
<tr>
<td>Cellular Signalling</td>
<td>Uncovering the function of disrupted in schizophrenia 1 through interactions with the cAMP phosphodiesterase PDE4: contributions of the Houslay lab to molecular psychiatry</td>
<td>Novothova Z, Pankko L, Sacci M, Redig G, Schindler C, Cross A, Mrzljak L, Medd A, Shaham Y, Goberg S</td>
</tr>
</tbody>
</table>
Discovery Sciences
Applying world-leading expertise to drive the identification of quality targets, hits, leads and drug candidates that will be safe and efficacious in the clinic.
“Discovery Sciences goes from strength to strength with another year of exceptional delivery and innovation. The Hit Identification platforms we developed in 2014 continue to provide world-class support for IMED small-molecule discovery, and we augmented this capability with the development of one of the most advanced genome editing-based target validation platforms in the industry. An incredible year indeed!”

Mike Snowden, VP Discovery Sciences

2015 has been an incredible year for Discovery Sciences. We continued with the development of our small-molecule Hit identification capabilities and employed plate-based high-throughput screening (HTS), DNA encoded libraries and fragment-based screening to more of our internal projects than ever before. We made our HTS compound collection available to a record number of academic collaborators, and initiated exciting projects with Brooks, Labcyte and HiRes to bring state-of-the-art robotic compound management and screening platforms to AstraZeneca as we prepare for the move of our state-of-the-art robotic compound management and screening platforms to Cambridge Biomedical Campus. To complement our Hit Identification platforms, and to ensure that we reserve them for the most validated drug discovery projects, we pushed ahead at pace with our ambitious plans to revolutionise our pre-clinical target validation capabilities through the widespread use of precise genome editing in both cellular and in pre-clinical animal model systems. Through collaboration with the very best external scientists in the world, and through significant internal investment we delivered an unprecedented number of both cellular and animal models to AstraZeneca projects and, importantly, developed the technological platform to optimise gene knockout generation, resulting in two patent filings and the potential for a number of high-impact publications in 2016. 2015 was a bumper year for publication for Discovery Sciences, with over 120 peer-reviewed papers, including over 50 high-impact and seven high-impact publications.

Highlights

We set out to

We delivered

Investigate the use of precise genome editing (CRISPR/Cas9) to deliver genetically engineered cell lines to IMED and external collaborators.

A phenotypic screen that used 120,000 compounds that is about ten-fold more than typically used. We executed this technically challenging screen using a seven-day proliferation assay that involved more than 50 steps using a novel beta cell, EndoC-βH1 and a high-throughput flow cytometry readout. The output from this screen will provide chemical equity for the Metlon collaboration, which is seeking modulators of beta cell growth.

Conduct a phenotypic screen using a larger collection of compounds than typically used for such assays.

A first-in-world exchange of 210,000 compounds between AstraZeneca and Sanofi, and a further 25,000 compounds exchanged with a leading agrochemical company.

Enhance the compound collection at AstraZeneca by the exchange of chemical equity with peer companies.

A first-class strategy aligned with several exciting collaborations. The first stage is the relocation of our solid store from Alderley Park to a world-renown expert, located in Europe. The temperature-controlled stores that house our liquid compound collection are being developed in collaboration with Brooks. With another partner, LabCyte, AstraZeneca is working on groundbreaking technology that will deliver compounds from tubes to plates using acoustic technology.

Establish a world-class HTS capability at Cambridge Biomedical Campus.

A strategic collaboration with HiRes of Boston to deliver a modular automation solution for HTS. Such systems provide a high degree of flexibility as the units are mounted on carts that can be moved around; to be easily reconfigured to fit the screening modality required.

Provide computational biology and mathematical modelling work packages to support IMED projects.

A tailor-made image analysis software package for a novel hepatotoxicity model that used cells grown in 3D, as spheroids. The package calculated the size/volume of these cell clusters, which was a critical measurement parameter that relied completely on the experts in-house, as there was no an off-the-shelf solution. In addition, we continue to explore statistical methods that reduce the number of animals used in experiments. The use of micro-sampling that takes ‘snapshots’ of the experimental design is reducing the number of animals required.

To deliver more predictive liver toxicity assays.

A novel hepatotoxicity model that cultures HepG2 cells grown in 3D rather than the conventional 2D/flat dish system. Cells grown under 3D conditions form spheroids rather than a monolayer, this 3D phenotype is more liver-like with cells expressing drug-metabolising enzymes (cytochrome p450s) unlike those grown in 2D conditions. The assay has been validated with known liver toxins and compares very favourably against the gold standard assay primary human liver cells. The new assay is about three times faster than the outsourced human liver assay and ten-fold cheaper.

Lafl

Mike Snowden, VP Discovery Sciences

To our partners in the Centre for Lead Discovery, Cancer HTS capability to the Cambridge Biomedical Campus, and platforms to AstraZeneca as we prepare for the move of our state-of-the-art robotic compound management and screening exciting projects with Brooks, Labcyte and HiRes to bring a record number of academic collaborators, and initiated ever before. We made our HTS compound collection available for use in evaluating which one of three isoenzymes was the drug target and secondly, provided a mutant form of EGFPR (C797L) to support that project.

To deliver the strategy for compound management in Cambridge Biomedical Campus.

The temperature-controlled stores that house our liquid compound collection are being relocated of our solid store from Alderley Park to a world-renown expert, located in Europe. The temperature-controlled stores that house our liquid compound collection are being developed in collaboration with Brooks. With another partner, LabCyte, AstraZeneca is working on groundbreaking technology that will deliver compounds from tubes to plates using acoustic technology.

Provide computational biology and mathematical modelling work packages to support IMED projects.

A tailor-made image analysis software package for a novel hepatotoxicity model that used cells grown in 3D, as spheroids. The package calculated the size/volume of these cell clusters, which was a critical measurement parameter that relied completely on the experts in-house, as there was no an off-the-shelf solution. In addition, we continue to explore statistical methods that reduce the number of animals used in experiments. The use of micro-sampling that takes ‘snapshots’ of the experimental design is reducing the number of animals required.

To deliver more predictive liver toxicity assays.

A novel hepatotoxicity model that cultures HepG2 cells grown in 3D rather than the conventional 2D/flat dish system. Cells grown under 3D conditions form spheroids rather than a monolayer, this 3D phenotype is more liver-like with cells expressing drug-metabolising enzymes (cytochrome p450s) unlike those grown in 2D conditions. The assay has been validated with known liver toxins and compares very favourably against the gold standard assay primary human liver cells. The new assay is about three times faster than the outsourced human liver assay and ten-fold cheaper.

©AstraZeneca 2016
Ian Sinclair joined AstraZeneca from Waters in 1999 to manage and develop the growth of Open Access LCMS across Alderley Park. Since 2007, he has examined the use of charged aerosol detection (CAD) for use in compound management and quality assurance. More recently, he has studied strategies to measure and improve quality within large compound collections. Ian brings an invaluable technical depth of knowledge while managing the project and liaison with our technical counterparts at Labcyte and Waters.

Martin Bachman is a postdoc within Discovery Sciences, joining AstraZeneca in April 2015 after completing his DPhil at Cambridge University. Martin’s main area of research, prior to AstraZeneca, was in the role of DNA modifications in epigenetics. He already has published in Nature Chemistry and Proceedings of the National Academy of Sciences, showing the use of mass spectrometry as a tool to test biological hypotheses. Martin supports the delivery of data for potential scientific applications and is currently building assays to demonstrate the system’s potential as a high-throughput screening platform.

Jon Wingfield joined AstraZeneca in 2000 as part of the oncology function, tasked with the delivery of automation to support secondary screening activities. After building delivery-focused screening teams, he moved into Discovery Sciences upon its formation in 2010. As a Principal Scientist, he is responsible for the strategic delivery of objectives and ensuring the projects have high visibility with both internal and external scientific communities. Jon uses his experience of drug discovery to showcase the potential value of this revolutionary technology platform with collaborative partners.

Key Discovery Sciences collaborations in 2015

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>

Key Discovery Sciences publications in 2015

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature Reviews</td>
<td>An analysis of the attrition of drug candidates from four major pharmaceutical companies</td>
<td>Michael J. Waring, John Arrowsmith, Andrew R. Leach, Paul D. Leeson, Sam Mandrell, Robert M. Owen, Garry Painaud, William D. Pickett, Jibo Wang, Owen Wallace, Alex Weir</td>
</tr>
</tbody>
</table>
Acoustic mass spectrometer

Our technique of choice for high-resolution microscopy

Mass spectrometry (or mass spec) is an analytical chemistry technique that helps identify the amount and type of chemicals present in a sample by measuring the mass-to-charge ratio and abundance of gas-phase ions. As standard, mass specs have three components – a component to convert sample from liquid to gaseous form. Then a component to ionise the sample (hit with high energy to turn to +ve or –ve ions), then the component to detect quantities of each ion (peaks of each ion seen). Instead of using a needle to aspirate and spray the samples as with standard mass specs, the acoustic mass spectrometer sends a sonic pulse through liquid creating a ‘mountain of liquid on the surface’. For compound handling, a 2.5 nanoLitre droplet is generated and fired from the liquid surface. For acoustic mass spectrometer we send a second pulse through the mountain of liquid and this explodes the 2.5nL droplet into hundreds of femtoLitre droplets. In effect, sending a tornado of droplets through a charged field to generate a stream of ionised particles into the acoustic mass spectrometer.

The scientist perspective

“When you see the droplets flying and you see the science behind it – it's astonishingly cool. It’s revolutionary. It allows us to work at very high throughput and with very small sample volumes – we only need 2µl of sample. Using this screening system we can screen more compounds or more targets for the same cost. For some assays we could reduce the cost of high-throughput screening by 80%.

AstraZeneca has brought together a world leading supplier of mass spec technology (Waters) and the global leader in acoustic droplet ejection technology (Labcyte) to deliver this revolutionary platform. It required the vision of AstraZeneca’s scientific leaders to recognise the potential of this system. We took the idea to the partners, suggesting that it is possible to use acoustics in a different way in mass spec. Being open about the work we are doing has shown the wider scientific community that AstraZeneca is prepared to invest in groundbreaking science, we are not just making a small change in mass spec, but we are leading a potential revolution in mass spec screening. As with any novel area of research this project carries an element of risk. Again, our openness shows that AstraZeneca is prepared to take scientific risks. We’re engaging the broader scientific community early in the process, and delivering real benefit to the community overall.

The acoustic mass spectrometer platform won the 2015 Innovation Award from the Society for Laboratory Automation and Screening. This is awarded to the podium presentation at the annual conference that shows the most innovation and impact in screening. AstraZeneca is the first non-US-based company to receive this award. The webcast of the podium presentation was made available to members after the meeting, and the society received so many requests to access this presentation that they made it free to non-members for a period, which is unprecedented. Subsequently, the society has decided to make the presentation available for free to the science community for two years. We have also had a paper about the platform accepted in a peer-reviewed journal (Journal of Laboratory Automation).”

Jonathan Wingfield, Principal Scientist, Discovery Sciences

The facts

- High throughput: 10,000 data points generated per hour, with three samples per second going into the acoustic mass spectrometer platform
- Small sample volumes required: only 2µl samples needed, meaning it is possible to get multiple samples more easily
- No cross-contamination: Using acoustics to move samples means no cross-contamination risk as nothing touches any surfaces

The stats

- Allows us to generate data points at 10,000 data points per hour
- The acoustics fire at 500Hz frequency (500 times per second) – that means we fire in 500 bursts of droplets every second
- For some analytes, we only need ~160 droplet bursts from a sample to generate enough ions – this means we can deliver samples to the acoustic mass spectrometer at a rate of three per second. Currently, the best high-throughput screening platform only sends one sample every ten seconds to the acoustic mass spectrometer.
Drug Safety & Metabolism
Driving our science to bring better, safer medicines to patients sooner.
Drug Safety & Metabolism

“2015 was an exceptional year for DSM. On top of delivering against all project timelines in the IMED and Global Medicines Development portfolio, I’ve been amazed with the progress of our teams, who have made particularly great progress with oligonucleotide-based therapies this year where we are already seeing really encouraging results.”

Stefan Platz, VP Global Drug Safety & Metabolism

Drug Safety and Metabolism (DSM) is an IMED function contributing to the entire value chain. Structured into six functions and with a purpose to drive science to bring better, safer medicines to patients sooner, we support and enable pipeline progression in AstraZeneca’s core therapeutic areas. With our vast range of expertise we deliver in silico, in vitro and in vivo data to deliver target and chemical risk assessments as well as metabolic quantitative translational safety models, including imaging for functional and pathological safety signals. We design and deliver tailored safety pharmacology and toxicology packages to support project decision-making and enable safe progression through clinical development.

Collaborative working was a focus for DSM in 2015. Within the ‘New Modalities’ space, a key strategic area for DSM, we worked with external partners to establish deeper understanding of oligonucleotide and modRNA therapeutics. We also initiated several key academic collaborations to strengthen our scientific reputation in the area of safety science, including one with the MRC Toxicology Unit (“Investigations into the interference of nucleotide modalities and their delivery systems on the translational machinery, nucleotide stress and immune signalling pathways”), and another with Uppsala University on expanding molecular imaging technologies to improve drug safety and efficacy understanding.

In Cambridge, our Laboratory Animal Sciences team, who provide invaluable support across IMED, became part of the new Research Support Facility (RSF), a combined IMED and MedImmune team, which is setting the direction for future collaborative working between the two groups. Our team also helped transition the Medical Research Council Laboratory of Molecular Biology to their new base in Cambridge.

The global DSM team also worked to define, build and lead the Patient Centric Risk Assessment (PCRA) strategy. 35 DSM colleagues, approximately 10% of the department, in four PCRA workstreams aimed to bring to life a common purpose, the patient, across DSM.

We continue to build our network within the local Cambridge community, and as well as hosting and sponsoring a number of local seminars and conferences, in 2015 we formed a pre-competitive alliance with Cambridge University and GlaxoSmithKline on medicines safety.

In addition to supporting the complete IMED pipeline, and through a time of significant footprint change, 2015 was an exceptional year for DSM; here are some of our key highlights:

- **Enabling Technologies** Next Generation Sequencing and health patch pilots initiated, a human tissue lead appointed and increased bioinformatics support
- **People and Organisation** Introduction of a PCRA engagement programme for DSM employees to help embed our PCRA strategy
- **CKD Pilot** – CKD is the newest core disease area within CVMD and the pilot offers the opportunity to build a patient-centric safety foundation to identify key areas of concern and map the potential need of new capabilities
- **COPD Pilot** – The COPD pilot offers an exciting opportunity to develop a more proactive approach to assessing risk pre-clinically
- **Internal and External Influence** The launch and implementation of pilot studies in two key disease areas in collaboration with the wider IMED organisation
- **Data Information and Integration** The agreement to recruit a Lead Information Officer, as well as extensive analysis of data capture and flow of information
Progressing with AZD8601 to candidate drug stage in October of 2015, and with the drug entering GLP toxicity studies in Q1 2016, we will enable first-in-human trials later in 2016.

A strong translational M&S team with a demonstrated track record of project impact, particularly in oncology. In addition, we have begun to construct novel safety modelling platforms in-house and through collaborations. Finally, we have increased our level of visibility and leadership among industry peers by, for example, chairing the platform session at the American Conference of Pharmacometrics (premier society meeting) on systems modelling for drug safety.

Create rat and dog liver-on-a-chip models as part of our ongoing organs-on-a-chip development. Scientists have presented both nationally and internationally on the safety concerns associated with CRISPR and we have set up a cross-company workgroup with key leaders to consider CRISPR safety.

We deliver

Collaborations with world-leading scientists for animal model builds, off-target analysis, DNA repair and targeted delivery. Our scientists have presented both nationally and internationally on the safety concerns associated with CRISPR and we have set up a cross-company workgroup with key leaders to consider CRISPR safety.

A strong translational M&S team with a demonstrated track record of project impact, particularly in oncology. In addition, we have begun to construct novel safety modelling platforms in-house and through collaborations. Finally, we have increased our level of visibility and leadership among industry peers by, for example, chairing the platform session at the American Conference of Pharmacometrics (premier society meeting) on systems modelling for drug safety.

Successful development and delivery of these models as well as securing a key collaboration with a German biotech company, TissUse, to explore the next wave of scientific innovation, which will connect individual organ units together.

Progression with AZD8601 to candidate drug stage in October of 2015, and with the drug entering GLP toxicity studies in Q1 2016, we will enable first-in-human trials later in 2016.

Safety data and documentation that enabled the first human dose to be administered in Phase I less than nine months from candidate drug identification.

We set out to

Consider the safety implications of CRISPR as a therapeutic modality and the use of CRISPR technologies for safety model build.

Become the industry leaders in the application of modelling and simulation (M&S) to address drug safety.

Create rat and dog liver-on-a-chip models as part of our ongoing organs-on-a-chip development.

Support the progression of the first AstraZeneca mRNA therapeutics therapeutic candidate drug stage.

Progress the first anti-microRNA oligonucleotide drug into man.

Highlights

Phase I less than nine months from candidate drug identification.

Entering GLP toxicology studies in Q1 2016, we will enable first-in-human trials later in 2016.

A strong translational M&S team with a demonstrated track record of project impact, particularly in oncology. In addition, we have begun to construct novel safety modelling platforms in-house and through collaborations. Finally, we have increased our level of visibility and leadership among industry peers by, for example, chairing the platform session at the American Conference of Pharmacometrics (premier society meeting) on systems modelling for drug safety.

Successful development and delivery of these models as well as securing a key collaboration with a German biotech company, TissUse, to explore the next wave of scientific innovation, which will connect individual organ units together.

Progression with AZD8601 to candidate drug stage in October of 2015, and with the drug entering GLP toxicity studies in Q1 2016, we will enable first-in-human trials later in 2016.

Safety data and documentation that enabled the first human dose to be administered in Phase I less than nine months from candidate drug identification.

Another line of investigation that has begun in 2015 is the use of exosome delivery systems to explore potential safety concerns. Exosomes are endogenous nanocarriers of RNA and proteins that mediate communication between cells. As many cancers are characterised by exosome-associated alterations, exosomes are considered to be relevant drug delivery vehicles for cancer treatment.

CRISPR (clustered regularly interspaced short palindromic repeats) is a genome-editing tool that allows fast and precise changes to be made in specific genes. The technology has two components – a homing device to a specific section of DNA (guide-RNA) and enzymatic ‘scissors’ that cut DNA (Cas9 nuclease). In the cell nucleus, the guide-RNA sequence directs the Cas9 nuclease to cause double-stranded breaks in the target DNA sequence. By harnessing the cell’s own DNA-repair apparatus, the gene being targeted can be altered either by deleting it, adding nucleotides to it or by turning its activity on or off.

As the potential delivery method of choice for oligo therapies, exosomes are critical for the successful development of CRISPR, enabling efficient transfer of Cas9 and guide-RNA. However, endogenous exosomal protein and RNA contamination raises safety concerns. Led by Mick Fellows, the DSM Discovery Safety department has set up a new collaboration in 2015 with leaders in the field to research and develop technologies that enable clean exosome preparation and to assess the risk from contamination whilst maintaining delivery efficiency. This is expected to significantly contribute to the translation of exosomes from the lab to the clinic and will place AstraZeneca in a unique position to lead in new modality delivery systems for the next generation of therapeutics.

AstraZeneca has been partnering with Moderna Therapeutics since 2013 to discover, develop and commercialise pioneering mRNA Therapeutics™. This unique approach uses proprietary mRNA containing nucleotide analogues, which are designed to stimulate the body’s natural ability to produce intracellular and secreted therapeutic proteins without triggering an innate immune response. Modified mRNA may dramatically reduce the time and expense associated with creating therapeutic proteins using current recombinant technologies. Moreover, as a therapeutic device, modified mRNA are:

- Flexible – can be encoded to produce any protein
- Adaptable – proteins can act intracellularly or be secreted
- Functional – diverse and potent therapeutic potential

DSM have been investigating the physiologically-based pharmacokinetic (PBPK) modelling approach for predicting biodistribution of mRNA-loaded lipid nanoparticles (LNPs) from a safety testing perspective. PBPK models are particularly well-suited for supporting model-translation from one species to another, e.g. species, exposure route, dose. This is because LNP kinetics differ from that of small molecules and are typically very non-linear and impacted distinctly through interactions with different tissues and cells.

The new modelling approach that has been developed generates accurate predictions for both intravenous and subcutaneous dosing and the biodistribution of LNPs. Unlike classical pharmacokinetic models, these mechanistic PBPK models are capable of describing the biodistribution of LNPs. Their ability to predict tissue/target-specific concentration profiles provides a model-based framework that can be used to maximise therapeutic index. Of particular significance is the fact that their physiological basis allows for more sophisticated approaches for model translation from one species to another.

Thinking differently about safety using CRISPR and mRNA modelling

AstraZeneca

Modern Therapeutics

Since his return to Sweden, Patrik Andersson, a Swedish national and biotech leader, has moved his Gothenburg family of five to the biotech cluster in San Diego for a 12-month secondment to learn more about oligonucleotide therapeutics. This drug platform has different properties to small molecules and they target RNA rather than proteins, leading to different challenges, approaches and screening cascades. Patrik’s objectives were to support ongoing projects in CVMD and Oncology and identify new collaboration opportunities for DSM.

From his experience in this US biotech environment, Patrik learnt the importance of sharing challenges through continuous and open debate. Acknowledging team efforts, working together, celebrating achievements and daring to try new things were prevalent traits in this professional environment. Equally applicable to scientific research and the Californian surf culture, Patrik realised that you need to lose your preconceptions and engage with the experts – what may at first appear simple may in fact have a more complex reality.

Since his return to Sweden, Patrik has contributed to the strategic and organisational work of DSM and on identifying new ideas for the Moderna platform.
Key Drug Safety & Metabolism collaborations in 2015

**TissUse, Berlin, Germany**
- Strengthening the IMED futures workstream, the TissUse collaboration has been established to explore the value of human bone marrow-on-a-chip model to predict drug-induced hematotoxicity and genotoxicity.

**University of Cambridge, UK**
- Experimental Medicine Ph.D. student. This project will explore bioinformatics algorithms for predicting drug-drug interactions based on clinical adverse event database mining.

**University of Cambridge, UK**
- Andreas Bender in Chemistry. The project will explore bioinformatics algorithms for predicting drug-drug interactions based on clinical adverse event database mining.

**Karolinska Institute, Stockholm, Sweden**
- This collaboration aims to develop and validate a new fast-responding and non-invasive CYP3A biomarker in urine, 1B hydroxydeoxycholic acid, for CYP3A inhibition DDI studies.

**Ludwig Maximilians University, Munich, Germany**
- This collaboration will look to generate pig models with inducible expression of Cas9 and with transgenic expression of humanised PCSK9.

**Uppsala University, Sweden**
- This collaboration is expanding molecular imaging technologies to improve drug safety and efficacy understanding and to discover and develop pathology biomarkers.

**Andreas Bender in Chemistry.**
- The project will explore bioinformatics algorithms for predicting drug-drug interactions based on clinical adverse event database mining.

**University of Cambridge, UK**
- This collaboration will study genetic variability in myocyte calcium handling and the consequences for drug-induced toxicity.

Key Drug Safety & Metabolism publications in 2015

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>British Journal of Pharmacology</strong></td>
<td>Effects of acute and chronic sunitinib treatment on cardiac function and calcium/calmodulin dependent protein kinase II</td>
<td>Mooney L, Skinner M, Coker SJ, Currie S</td>
</tr>
<tr>
<td><strong>Molecular Pharmaceutics</strong></td>
<td>Flagging drugs that inhibit the bile salt export pump</td>
<td>Montanari F, Pinto M, Khunweeraphong N, Wlcek K, Schall MJ, Noeske T, Boyer S, Chlieb P, Stieger B, Kuchler K, Ecker GF</td>
</tr>
<tr>
<td><strong>Archives of Toxicology</strong></td>
<td>Hepatic effects of repeated oral administration of diclofenac to hepatic cytochrome P-450 reductase null (HRN-) and wild type mice</td>
<td>Akingbasote J, Foster A, Wilson I, Sarda S, Jones H, Gerry Kanna J</td>
</tr>
<tr>
<td><strong>Analytical Chemistry</strong></td>
<td>Mapping drug distribution in brain tissue using liquid extraction surface analysis mass spectrometry imaging</td>
<td>Swales J, Tucker J, Spreadborough M, Iverson S, Clink M, Webborn P, Goodwin R</td>
</tr>
<tr>
<td><strong>Toxicological Sciences</strong></td>
<td>Re-evaluation of the mutagenic response to phosphorothioate nucleotides in human lymphoblastoid TK6 cells</td>
<td>Saleh A, Priestley C, Goodeham N, Fellows M</td>
</tr>
<tr>
<td><strong>Toxicological Sciences</strong></td>
<td>Correlation of in vivo versus in vitro benchmark doses (BMDs) derived from micronucleus test data: a proof of concept study</td>
<td>Soeteman-Hernández L, Fellows M, Johnson G, Slob W</td>
</tr>
<tr>
<td><strong>Chemical Research in Toxicology</strong></td>
<td>Aortic binding of AZD65248, mechanistic insight and reactivity assays to support lead optimization</td>
<td>Bragg R, Brocklehurst S, Gustafsson F, Goodman J, Hickling K, MacFaul P, Swallow S, Tugwood J</td>
</tr>
</tbody>
</table>
Personalised Healthcare and Biomarkers

Personalised Healthcare is an integral part of our approach to discovering and developing new medicines; we use diagnostics and biomarkers to target our treatments to patients most likely to benefit.
Personalised Healthcare and Biomarkers

“We see Personalised Healthcare as the future of medicine – it shows us what science can do.”

Ruth March, VP PHB

Personalised Healthcare is an integral part of our approach to discovering and developing new medicines; we use diagnostics and biomarkers to target our treatments to patients most likely to benefit. More than 80% of A2’s clinical pipeline, and 95% of our small-molecule IMED pipeline, is following a Personalised Healthcare approach, with over 50 planned drug launches in the next eight years requiring a linked diagnostic test.

In 2015, we have launched seven diagnostic tests linked to our products (see highlights) and led companion diagnostic development for AstraZeneca’s three FDA-approved PHC drugs.

To stay at the forefront of Personalised Healthcare science, we are constantly looking for novel diagnostic technologies that can help us deliver better solutions to patients. For example, the EGFR mutation test launched in the EU for osimertinib (AZD9291) is the world’s first diagnostic test intended for both circulating tumour DNA (ctDNA) derived from plasma and tumour DNA derived from solid tissue. Indeed, we are now able to include diagnostic testing based on plasma for many drug projects, achieving a label update in China for gefitinib in 2015. Such use of plasma for testing enables up to 25% more patients without evaluable solid tumour samples to access the right treatment. In addition, we are continuing to explore diagnostic technologies based on next-generation sequencing in several of our drug programmes, through partnerships with Illumina and Foundation Medicine. This year we have started to explore the potential of Droplet Digital PCR (ddPCR) in partnership with Sysmex-Inostics, a highly sensitive diagnostic technology.

We set out to

- Exploration of novel diagnostic technologies, such as ctDNA, NGS and ddPCR, in nine drug projects for biomarkers, including FGFR, AKT, MET, TP53, KRAS and EGFR as well as gene panels
- Shaping of the diagnostic landscape through industry-wide collaborative initiatives, such as the Stratified Medicines Innovation Working Group, ICH E18 Genomics Working Group and European Biopharmaceutical Enterprises
- Advancing new diagnostics and treatments arising from the 100,000 Genomes project through the Genomics England public-private GENE consortium
- Over 30 new staff hired to enhance our diagnostic and biomarker expertise

We delivered

- Seven diagnostics launched with our diagnostic partners linked to four AstraZeneca products:
  - Myriad’s tumour BRCA analysis (EU) for olaparib
  - Qiagen’s EGFR companion diagnostic test (US), and circulating tumour DNA EGFR plasma test (EU) for gefitinib
  - Roche Molecular System’s EGFR tissue and plasma test (EU) – the world’s first diagnostic test for both circulating tumour DNA and tumour tissue, and EGFR companion diagnostic test (US) for osimertinib
  - Ventana’s PD-L1 diagnostic test (Class I in vitro diagnostic test) in US and in EU for durvalumab – first FDA regulated PD-L1 diagnostic

Achieve leadership in PHC science.

Bring the benefits of PHC to all core therapy areas.

- In inflammatory disease, we are developing a handheld uric acid diagnostic test for patients with inflammatory disease
- In cardiovascular and metabolic disease, we are collaborating with the Montreal Heart Institute to search the genomes of up to 80,000 patients for genes associated with cardiovascular and diabetes disease, their complications and treatment outcomes

Invest in strategic collaborations.

- 14 new collaboration agreements signed with diagnostic companies, increasing our investment to €813m
- Partnerships with leading academic centres, including the Karolinska Institute, Cambridge University, Montreal Heart Institute, and The Wellcome Trust Sanger Institute

“Personalised Healthcare is an integral part of our approach to discovering and developing new medicines; we use diagnostics and biomarkers to target our treatments to patients most likely to benefit.”

Ruth March, VP PHB

©AstraZeneca 2016

The next wave of scientific innovation
Developing a companion diagnostic test for a breakthrough therapy

Non-small-cell lung cancer (NSCLC) is the most common form of cancer worldwide. Patients that have activating mutations of the Epidermal Growth Factor Receptor (EGFR) gene are more likely to benefit from EGFR Tyrosine Kinase Inhibitors (TKIs) such as gefitinib, and diagnostic tests for these mutations are used to select patients for first-line treatment. Although EGFR-TKIs are effective in these patients, the majority develop resistance after 10-12 months, and in around 60% of these cases, resistance is associated with the emergence of another EGFR mutation, known as T790M. Knowledge of the biological role of these mutations helped AstraZeneca to design osimertinib (AZD9291), an irreversible EGFR-TKI that targets both the sensitising mutations of EGFR and the T790M mutation that confers resistance.

Osimertinib achieved one of the fastest clinical development programmes on record, taking less than three years from first-time-in-man to first launch. One of the contributing factors of AZD9291’s success was its ability to use a companion diagnostic test to select the right patients for treatment from the earliest stages of clinical development. AstraZeneca’s PHB function partnered with Roche Molecular Systems (RMS) to develop the cobas® EGFR Mutation Test as a companion diagnostic test to identify the right patients for treatment, often accelerating delivery of essential diagnostic modules to enable fast-tracking of drug development timelines. In November 2015, osimertinib was approved by the US FDA for the treatment of patients with metastatic epithelial growth factor receptor (EGFR) T790M mutation positive non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy, with the companion diagnostic being approved on the same day. Just five weeks later, the Committee for Medicinal Products for Human Use of the European Medicines Agency announced a positive opinion for the same drug.

People spotlight

Joachim Reischl brings expertise in global biomarker strategy and development from Bayer, combined with scientific leadership in pharmacology and genomics. As PHB site head in Gothenburg and member of PHB’s leadership team since July 2015, Joachim heads up the new, global Policy, Portfolio and Externalisation (PPE) group that drives organisational efficiency within PHB and provides diagnostic project management across a growing portfolio. The PPE group is also responsible for providing content for AstraZeneca’s policy initiatives on Personalised Healthcare.

Carolina Haefliger is the new Head of Companion Diagnostics for Cardiovascular and Metabolic Diseases (CVMD), and is also responsible for Opportunistic therapy areas such as Neuroscience. An MD in clinical genetics with expertise in both CVMD and oncology translational science and the leadership of observational biomarker studies, Carolina joined PHB from Novartis in July 2015, and focuses on providing diagnostic options to our CVMD portfolio as well as championing strategic collaborations such as our genomics initiative with Montreal Heart Institute on behalf of the CVMD Therapy Area Leadership team. A member of PHB’s leadership team based in Gothenburg, Carolina also serves as PHB’s Medical Adviser.

Craig Barker brings expertise to PHB from Leica in Tissue Diagnostics, including regulatory interactions and commercial markets. As the new Head of Tissue Diagnostics and member of PHB Labs leadership team based in Cambridge, he has built a team of dedicated diagnostic scientists who deliver companion diagnostic assays that select patients most likely to benefit from linked AstraZeneca drugs. Since joining PHB in January 2015, Craig has rapidly established his group’s ability to manage global deployment of the diagnostic assays and work with diagnostic partners to submit regulatory packages against tight timelines.

Osimertinib achieved one of the fastest clinical development programmes on record, taking less than three years from first-time-in-man to first launch.
## PHC adoption across AstraZeneca pipeline end of 2015

### Phase I
- **30 New Molecular Entities**
  - **Small molecule**
    - AZD1419# TLR9 asthma
    - AZD7966 DP1 COPD
    - AZD9999 MABA asthma/COPD
    - AZD9977 MCR diabetic kidney disease
    - AZD7959 or AZD9321 BLOOD EGF R NSCLC brain mets
    - AZD3512# androgen receptor prostate
    - AZD7638 ATR solid tumours
    - AZD8186 PKa solid tumours
    - AZD8635 PKa solid tumours
    - AZD9150# STAT3 haens & solids
    - AZD9480 SERD ER+ breast
    - ATM AV# BL/BLI EBI
    - AZD6108 MM4A suicidal ideation
  - **Large molecule**
    - MEDI4920 CD40L-133+ JS6
    - MEDI5872# B7RP1 SLE
    - MEDI7836 IL-13 asthma
    - MEDI0382 GLP-1/glaucon diabetes/obesity
    - MEDI0102 LCAT ACS
    - MEDI0562# hOX40 solid tumours
    - MEDI0680 PD-1 solid tumours
    - MEDI1361 ANG-2 solid tumours
    - MEDI1565# CEA BITE tumours
    - MEDI2638# Ox40 FF solid tumours
    - MEDI4447 CD73 solid tumours
    - MEDI1814 amyloid Alzheimer’s
    - MEDI3902 PaP aPV pneumonias
    - MEDI550 pandemic influenza virus vaccine
    - MEDI8852 Influenza A treatment

### Phase II
- **25 New Molecular Entities**
  - **Small molecule**
    - AZD7594 Inhaled SGRM asthma
    - abediterol (AZD0548) Inhaled p38 inhibitor COPD
    - AZD7624 Inhaled p38 inhibitor COPD
    - RDEA3170 URT-1 hyperuricemia/gout
    - AZD4001 PCOS
    - AZD1775# Wnt-1 ovarian
    - AZD2014 mTOR 1/2 solid tumours
    - AZD4547 FGFR solid tumours
    - AZD5365# AKT breast cancer
    - savolitinib# MET pRCC
    - AZD5241# MPO Multiple System Atrophy
    - MEDI9929# CD19 DLBCL
    - MEDI8997# RSV passive prophylaxis
  - **Large molecule**
    - MEDI0112 LCAT ACS
    - MEDI0207I IL-23 Crohn’s
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI0207# IL-23 Crohn’s
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis

### Phase III
- **10 New Molecular Entities**
  - **Small molecule**
    - PT010 LAB/LAMA/ICS COPD
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
  - **Large molecule**
    - mavelimumab# GM-CSFR rheumatoid arthritis
    - brodalumab# IL-17R pioralsis
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - tralokinumab IL-13 severe asthma
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - mavelimumab# GM-CSFR rheumatoid arthritis
    - brodalumab# IL-17R pioralsis
    - selumetinib# SELECT-1 MEK 2L KRAS+ NSCLC
    - mavelimumab# GM-CSFR rheumatoid arthritis
    - brodalumab# IL-17R pioralsis
    - mavelimumab# GM-CSFR rheumatoid arthritis
    - mavelimumab# GM-CSFR rheumatoid arthritis

### Applications under review
- **5 New Molecular Entities**
  - **Small molecule**
    - PT003 PINNACLE LAB/LAMA COPD
    - MEDI7986 DPP1 COPD
    - MEDI5872# B7RP1 SLE
    - MEDI0382 GLP-1/glaucon diabetes/obesity
    - MEDI0102 LCAT ACS
  - **Large molecule**
    - MEDI6012 LCAT ACS
    - MEDI0207I IL-23 Crohn’s
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI5514 CD19 neumorellis optica
    - abilumab# o4p7 Crohn’s/ulcerative colitis
    - MEDI9928# TSLP asthma/atopic dermatitis
    - MEDI5514 CD19 neumorellis optica

### Key PHB collaborations in 2015
- **Qiagen, Hilden, Germany**
  - Master Collaboration Agreement focused on BRCA testing in pancreatic, lung, breast and ovarian cancers.
- **Myriad, Salt Lake City, US**
  - Partnership focused on the development of an Oncogene Panel and Therapy Selection System, and the implementation of next-generation sequencing as an FDA-approved companion diagnostic.
- **Roche Molecular Systems, Basel, Switzerland**
- **Ventana, Tucson, US**
  - Agreement focused on prostate cancer: PTEN biomarker test, gastric cancer: ATM-IHC diagnostic tissue test, and PD-L1 expression Class I device and companion diagnostic test.
  - Agreement focused on prostate cancer: PTEN biomarker test, gastric cancer: ATM-IHC diagnostic tissue test, and PD-L1 expression Class I device and companion diagnostic test.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature: Insight</td>
<td>Precision medicine, AstraZeneca’s approach</td>
<td>March R</td>
</tr>
</tbody>
</table>
Early Clinical Development

Where science meets the patient, skilled transitional clinical scientists who evaluate whether our research can change lives.
**Early Clinical Development**

“In 2015, the second year of Early Clinical Development (ECD), we created significant positive change in our strategy, people, operations and culture. ECD has attracted world-class talent globally and established a Clinical Discovery Unit (CDU). Operational simplification was reflected in substantial improvements in clinical trial cycle times, underpinned by an increasingly entrepreneurial and accountable culture.”

Tony Johnson, VP Early Clinical Development

---

**Highlights**

<table>
<thead>
<tr>
<th>We set out to</th>
<th>We delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progress the pipeline across the core therapeutic areas.</td>
<td>Enrolment of Phase I studies for oncology (e.g. c-met inhibitor, AZD6094 and AKT inhibitor, AZD5363) were completed with encouraging data thus far; multiple Phase I and Phase II starts; RIA P38 Phase II trial achieved its interim analysis; CVMD – dosed the MCR antagonist in humans and completed the MAD study.</td>
</tr>
<tr>
<td>Implement innovative study designs.</td>
<td>Over 20 clinical trials incorporated an adaptive design, increasing our ability to be responsive to the evolving knowledge of our product candidates. Certain respiratory studies have been initiated with novel early phase endpoints which, in some cases, halved the required number of patients and reduced the study durations, e.g. P38 MAPK inhibitor. Scientifically innovative model-based evaluation of biomarker data has also been incorporated within our adaptive study designs to achieve earlier PDM, e.g. DPP1.</td>
</tr>
<tr>
<td>Increase patient-centricity.</td>
<td>Real-time data capture from patients (e.g. PROACT) and real-time visualisation of clinical trial data (e.g. REACT) have guided clinical trial adaptation and more efficiently determined the right dose/regimen and patient population for our novel medicines. In 2015, REACT was further improved to become web-based and incorporate safety, efficacy, PK and biomarker data, a significant industry-leading achievement.</td>
</tr>
<tr>
<td>Foster excellence in scientific leadership.</td>
<td>ECD produced 124 publications – 32 of which were high quality and five were high impact, a 118% improvement from 57 publications in 2014. These demonstrated world-class early clinical development science in oncology, RIA, CVMD, Quantitative Clinical Pharmacology (QCP) and Biometrics.</td>
</tr>
<tr>
<td>Systematically integrate data from multiple sources.</td>
<td>QCP developed renal disease models incorporating pharmacokinetics and pharmacodynamics for lesinurad and the two xanthine oxidase inhibitors, allopurinol and febuxostat, which included the key documented influence of renal filtration on clearance of uric acid key components in gout. Using model-based simulations, it was demonstrated that lesinurad exhibits a positive benefit-risk in key clinical scenarios identified by the FDA.</td>
</tr>
<tr>
<td>Be the partner of choice to external partners.</td>
<td>ECD scored a rating within the top three for our managed relationships with external partners.</td>
</tr>
</tbody>
</table>

---

A strategy with three principles

ECD’s new strategy reflecting our focus on ‘where science meets the patient’ was communicated in October 2015. Skilled translational clinical scientists evaluate whether our research can change lives, dependent on three fundamental principles:

- Design and deliver innovative clinical studies to progress the pipeline
- Integrate data from multiple sources systematically to inform research and development
- Accelerate human target validation (HTV) across AstraZeneca core therapeutic areas

In addition, we have built strategic alliances with some of the best teaching hospitals, including Cambridge, Harvard and Manchester.

We have also recruited six exceptional physician scientists from top universities to push the translational science agenda in ECD. Process improvement has been another key area of focus, with the implementation of eight new initiatives to ensure simplification and improved operational efficiencies. Compared to 2014, we have reduce our cycle times in Phase I by 28% and in Phase II by 41%. These improvements have generated significant cost reduction and 36% increased efficiency.

In order to achieve such improvements, ECD has progressively evolved its culture to foster agility and accountability in decision-making coupled with an entrepreneurial ‘can do’ attitude.

---

**Opposite**

Immune response to cancer

Top

Tony Johnson, VP Early Clinical Development
Development (GMD). phase under the supervision of Global Medicines completed, while the trial is entering the expansion The dose-finding phase of Tatton has now been parallel recruitment so that patients could always Within the Tatton study, a rolling-arm allocation was administered in combination with targeted agents. using immunotherapy agents, which are often are added to the protocol from the outset, to create the flexibility to test combinations dependent on evolution in each patient’s cancer. Placeholders are added to the protocol from the outset, to create the feasibility to test combinations dependent on the specific molecular cancer drivers detected. Within the Tatton study, a rolling-arm allocation was used as a specific design feature to ensure ongoing parallel recruitment so that patients could always join an appropriate trial arm in an efficient manner. The dose-finding phase of Tatton has now been completed, while the trial is entering the expansion phase under the supervision of Global Medicines Development (GMD).

We integrate data and inform research and development. In the context of improving data integration to knowledge, the second ECD strategic pillar, significant enhancements have been delivered at the patient interface using REACT. ECD’s partnership with Tessa Technology is to develop innovative new technologies that allow data-driven, scientific decisions during, rather than on completion, of a clinical trial. This augments R&D efficiency by earlier discontinuation of those drugs with a low probability of meeting their predefined safety and/or efficacy goals. REACT was developed to enable AstraZeneca researchers to view patient information from ongoing clinical trials within 24 hours of data reaching AstraZeneca. REACT tracks laboratory tests, adverse events, and can monitor biomarker and efficacy data on both population and subject-specific levels during the course of a clinical trial. In 2015, REACT has evolved to become much more user-friendly through conversion to a web-based format. In addition, the ability to incorporate safety, efficacy, biomarkers and PK in a single study, as was achieved with a key savolitinib study, allows many scientific questions to be evaluated. This enables a data-driven, appropriate adaptation of the study design during the course of a trial and is an exciting improvement of real-time data visualisation capabilities.

We accelerate human target validation. ECD is focusing increasing effort on accelerating Human Target Validation (HTV). All functions of ECD are involved and will increasingly be boosted by the development of the Clinical Discovery Unit. HTV will often be achieved in collaboration with academic partners. For example, in collaboration with Lars Lund at Karolinska, the CVMD TMU demonstrated that Myeloperoxidase (MPO)-related biomarkers outperformed NT-proBNP in predicting NYHA score. This significantly adds to previous work suggesting that MPO drives endothelial dysfunction and mortality in heart failure with preserved ejection fraction. Other CVMD TMU examples include FLAP in inflammatory disease and GPR44 in dysfunction of human pancreatic beta cells. CDU, working with key ECD partners, commenced work on a study to recruit a large cohort of patients with COPD who will be very thoroughly characterised. As well as providing greater understanding of the different disease phenotypes, this will enable segmentation of the COPD population and rapid recruitment of patients to multiple molecularly targeted Phase II studies using novel portfolio agents.

Operations. Due to ECD’s disciplined coordination between operational activity, efficiency and licence to operate, our clinical operations have improved their overall efficiency by 36% since being established in 2014. Clinical Pharmacology Unit (CPU) costs have been reduced by 12%, laboratory costs by 15% and CPU protocol deviations by 27%. Most significantly, we set out to deliver 20% improvement in our Phase I and Phase II cycle times. We achieved a reduction of 28% in Phase I (16m v industry 24m) and a reduction of 41% in Phase II (44m v Industry 31m), underscoring the enabling role of ECD across IMED’s delivery programme.

We deliver innovative clinical studies. Innovation in fit-for-purpose clinical trial design is a key strategic pillar for ECD. In 2015, ECD initiated its first basket trial design in the AZD9291 Tatton lung cancer study, collaborating with the oncology IMED. The creativity is reflected in multiple treatment options for patients within a single trial based on the molecular driver of each patient’s cancer. In addition, the design allowed for combinations of therapies to be tested using the extensive AstraZeneca portfolio of small and large molecules while also enabling more efficient progression through trials of each monotherapy or drug combination regimen. AstraZeneca has been an early adopter of this approach from an industry perspective. Use of the portfolio power and agility of AstraZeneca creates the opportunity to search for early scientific signals from potential therapies, alone or in combination, targeting niche patient populations. Taking a modular approach makes it possible for ECD to truly follow the science, as different combinations can be added in response to evolution in each patient’s cancer. Placeholders are added to the protocol from the outset, to create the feasibility to test combinations dependent on the specific molecular cancer drivers detected. Such an approach is especially effective for using immunotherapy agents, which are often administered in combination with targeted agents. Within the Tatton study, a rolling-arm allocation was used as a specific design feature to ensure ongoing parallel recruitment so that patients could always join an appropriate trial arm in an efficient manner. The dose-finding phase of Tatton has now been completed, while the trial is entering the expansion phase under the supervision of Global Medicines Development (GMD).

The Clinical Discovery Unit was set up in 2015 by Professor Tim Eisen. Its primary purpose is to expand the capacity for translational clinical science and accelerate HTV as a key contribution for ECD. People are at the heart of CDU’s function – through collaboration with leading academic institutions and by recruiting and developing talented physician scientists across therapeutic areas. Professor Stephen Reid is Chief Clinical Scientist and a respiratory physician whose key area of interest is to recruit a large cohort of chronic obstructive pulmonary disease (COPD) patients and to characterise them fully. This will identify COPD clinical subsets and allow us to target the right drugs to the right patient. The CDU is actively looking to recruit PhD clinical scientists to further expand the AstraZeneca talent pool. Two academic clinical lecturers have been seconded from the University of Cambridge to build collaborative links in CVMD and oncology respectively. Further secondments both from within and from outside AstraZeneca are being explored. The Experimental Medicines Initiative at the University of Cambridge is another key collaboration for the CDU. AstraZeneca funds one PhD and two academic lecturer positions for clinicians per year. The first PhD scientist has been appointed and will start work with the Drug Safety and Metabolism (DSM) team in early 2016. The aim is to expand this model to other key academic partners. Importantly, recruitment has been a major focus for ECD in 2015. We have attracted world-class talent globally across all departments and disciplines to consolidate our geographical footprint in Cambridge (UK), Boston and Gaithersburg (US) and Gothenburg (Sweden). Recruiting and retaining world-class talent is fundamental to the innovation, creativity, dedication and execution-focus that will enable ECD to become industry leaders. During 2015, we have recruited 66 positions in ECD, 70% in Cambridge (UK), 20% in Gothenburg (Sweden), 9% in Boston (US) and 1% in Gaithersburg (US). By the end of 2015, the permanent ECD headcount was 237, an increase of 12% compared to 212 at the end of 2014.
Key Early Clinical Development collaborations in 2015

**National Jewish Health, Denver, US**
Investigator: Associate Professor Elena Goleva, PhD, Division of Pediatric Allergy and Immunology
This project examines the role of p38 MAP kinase in steroid resistant asthma, and explores the effect of AZD7624 (inhaled p38 inhibitor) in severe steroid-resistant asthma.

**Boston University School of Medicine, US**
Investigator: Professor Avrum Spira, MD, MSc, Division of Computational Biomedicine, Department of Medicine
This project seeks to find key gene expression and protein biomarkers that identify, COPD patients with high levels of p38 MAP kinase and MEK activity in order to correlate protein kinase activity with clinical outcomes in COPD and lung cancer and to identify patients who might best respond to specific p38 and MEK inhibitors.

**University of Georgia, US**
Investigator: Assistant Professor K. Melissa Hallow, PhD, Joint appointment in College of Engineering and College of Public Health, Department of Epidemiology and Biostatistics
The project involves diabetes disease modeling in collaboration with DMPK CVMD and DSM and provides support to late stage and early diabetes assets including chronic kidney disease.

**Institute of Cancer Research and The Royal Marsden Hospital, London, UK**
Investigator: Professor Johann De Bono, MD, MSc, PhD, FRCP, FMedSci, Professor of Experimental Cancer Medicine, Honorary Consultant Medical Oncologist at the Royal Marsden Hospital and Institute of Cancer Research
Expert at developing molecular targeted therapies for prostate cancer patients and the projects have involved evaluating AstraZeneca novel therapeutics in prostate cancer.

**Sarah Cannon Research Institute, London, UK**
Investigator: Dr Howard A. Skip Burris, III, MD, FACP, President, Clinical Operations and Chief Medical Officer, Sarah Cannon
Providing AstraZeneca with clinical development expertise, access to molecular profiling data and timely, cost-efficient CRO trial management for early phase novel oncology clinical trials with potential for personalised medicine approaches.

**Karolinska Institute, Stockholm, Sweden**
Investigator: Professor Peter Stenvinkel, MD, PhD Renal Medicine and Kerstin Brismar, MD, PhD Growth and Metabolism
Collaboration set up to provide access to clinical samples and data from several large cohorts of CKD patients as well as healthy controls, which were and will continue to be used to assess HTV in multiple targets for the management of CKD, as well as some pre-TSID CKD projects.

---

**Key Early Clinical Development publications in 2015**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nature Reviews Cancer</strong></td>
<td>VHL, the story of a tumour suppressor gene</td>
<td>Gossage L, Eisen T, Maher ER</td>
</tr>
</tbody>
</table>
Shaping drug development in Asia

A key growth area for AstraZeneca

Our drug discovery programmes in the chronic kidney disease area are progressing as planned. We prioritise kidney disease targets with a strong human genetic link, followed by animal models to establish causal relationship between the genetic change and disease phenotype. Realising the huge and increasing unmet medical needs, especially in China, we started our investment in the respiratory disease area, with a focus on chronic obstructive pulmonary disease (COPD).

One of our strategic objectives is to realise the benefit of our new drugs for Chinese and Asian patients as quickly as possible. Asia iMed worked closely with global teams during 2015, and actively explored new potential drugs for the treatment of diseases that are most prevalent in China and Asia. Building on our pre-clinical findings, the olaparib team has initiated AstraZeneca’s first Phase III study in gastric cancer. To ensure clinical studies in China are efficiently executed, the biomarker team also delivered essential biomarker studies for osimertinib, olaparib, volitinib, and MEDI4736 in 2015.

We enhanced our external scientific reputation through high-impact publications, presentations at major international scientific conferences, and collaborations with leading research institutions. The positive results of olaparib Phase II study in gastric cancer was published in the Journal of Clinical Oncology in 2015. Our poster on AZD3759 Phase I study was selected for oral discussion at ASCO 2015. Several of our senior scientists have been invited to join leading academic institutions such as Beijing University as faculty members.

AZD3759 is the first investigational drug discovered by Asia iMed and targets EGFR mutation positive advanced stage non-small cell lung cancer.

– Clinical activities have been demonstrated in patients with CNS metastasis. Patients who have failed multiple lines of therapies showed benefit from AZD3759 treatment

– The dose and schedule for further clinical studies has been identified through Phase II clinical studies initiated in 2015

– China IND filing was accepted by China FDA in April 2015. This is the first category 1.1 (China Innovation) filing by AstraZeneca

Scientific leadership in action to accelerate delivery of our innovative medicines to patients in China

In December 2015, AstraZeneca, along with MedImmune, its global biologics research and development arm, announced a range of strategic initiatives to accelerate the delivery of medicines to patients in China, the company’s second largest market globally and a key growth platform. These plans aim to help us accelerate development of our medicines in this important market by expanding our clinical development activities, including all clinical development phases, and further developing local capabilities in drug substance synthesis and drug product development.

These investments and dedicated R&D capabilities are aimed at accelerating Chinese patient access to innovative medicines to address significant unmet need in AstraZeneca’s main therapy areas – respiratory; cardiovascular and metabolic diseases; and oncology. AstraZeneca’s commitment to bring cutting-edge biopharmaceutical science to China and to partner with the local science community is aligned with the Chinese Government’s focus on increasing innovation to support economic development and access to healthcare.

The initiatives and investments include:

– An investment of $50 million to build an additional development and launch facility alongside our existing manufacturing site in Wuxi City to support the development and manufacture of innovative small molecules discovered in China and our global R&D sites

– Additional investments include the creation of a new global hub for Pharmaceutical Development – alongside those in the UK and Sweden – with up to 50 scientists based in Shanghai and Wuxi City, to support both China and global needs. AstraZeneca is also establishing an integrated China medicines development organisation, bringing together early- and late-stage medicines development across small molecules and biologics

– A strategic alliance with WuXi AppTec, a leading Chinese biologics manufacturer and contract research organisation, to produce innovative biologics locally in China

– A strategic discovery partnership with Pharmaron, a leading R&D service provider based in China. Pharmaron works closely with our teams to deliver discovery services in chemistry, as well as in drug metabolism and pharmacokinetics (DMPK)
In 2013, AstraZeneca IMED entered into a collaboration with the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD). Together, we hope to enable breakthrough discoveries and bring new medicines to patients who are suffering from neurodegenerative diseases.

The focus of our collaboration with the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) is to discover and develop novel positive allosteric modulators of the muscarinic M4 receptor for the treatment of psychiatric complications associated with Alzheimer’s disease and Parkinson’s disease.

Our collaboration is breaking new ground, with a new way of targeting this class of receptors where other efforts have been unsuccessful.

Professor Jeffrey Conn, Director, Vanderbilt Center for Neuroscience Drug Discovery:

“This new model for advancing neuroscience drug discovery pioneered by AstraZeneca fits perfectly with the mission of the VCNDD and makes it an ideal partnership for having an impact on these devastating disorders.

This is a really special collaboration on multiple levels. First of all the science is innovative, and a fundamentally new approach to treatment of Alzheimer’s disease or other related neurodegenerative disorders.

In diseases like Alzheimer’s and Parkinson’s, we still have a huge unmet medical need. There are very, very poor treatments available for patients and especially for the psychiatric complications, which can become very burdensome not only to the patients but also to the caregivers.

In interacting with AstraZeneca as a scientist, it’s clear that they are there for a purpose, that they want to have an impact on patient care. They can see the possibilities of really having a positive impact.

The thing I enjoy most about working with AstraZeneca is the shared passion.

When we have meetings, when we talk on the phone, we can sense that passion and it creates an atmosphere where we’re very strategic, very focused. We get to the issues that are most important for the programme rather than thinking about process or other issues that could be distracting.

I’m really excited to be a part of something as innovative as the Neuroscience iMed, discovering new treatments for neuroscience-related disorders.

Together we are aiming to get a new compound into clinical testing. Working together, we can explore new possibilities for treating patients who suffer from these devastating diseases.”
Collaborating to exploit combination therapeutic strategies

**PD-L1 (MEDI4736)/AZD5069 and AZD9150**
On 10 August 2015, the first patients were dosed on the durvalumab (MEDI4736) oncology combination trial with the oligonucleotide STAT3 inhibitor, AZD9150 or the small molecule CXCR2 inhibitor, AZD5069.

This important study milestone was successfully achieved due to the collaborative approach, led by the AZD9150 team together with colleagues from the IMED, Global Medicines Development (GMD) and MedImmune organisations. Durvalumab, our Phase III PD-L1 checkpoint inhibitor, is currently demonstrating strong potential to combine with both immunotherapy and small molecules. We have an extensive development programme under way across our science units and across multiple tumour types and stages of disease, assessing the potential for immunotherapy to either replace or combine with traditional chemotherapy.

Following the science, it became evident to the IMED team that both AZD9150 and AZD5069 inhibit signalling that tumours use to evade the host immune system. Paul Lyne, Senior Director and Global Project Lead for AZD9150 and AZD5069, believes that the combination of a Tumour Microenvironment (TME) modulator with immune checkpoint blockade offers a potential to improve patient outcomes as seen with immune checkpoint inhibition alone.

*Immune checkpoint blockade therapies are transforming the therapeutic landscape for oncology patients, and have validated the clinical strategy of supporting the patient’s immune system to treat cancer. The next generation of immune-oncology approaches will include therapies that combine complementary immune targeting mechanisms to increase the proportion of patients that can benefit. These studies represent a key component of our organisation’s strategy for immuno-oncology and will hopefully bring increased benefit to patients*.— Carl Cook, Senior Director, Oncology TMU, IMED

By following the science, we are confident that together we can transform the lives of patients around the world.

<table>
<thead>
<tr>
<th>Discovery and Early Development</th>
<th>Late-stage Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecules</td>
<td></td>
</tr>
<tr>
<td>Innovative Medicines and Early Development (IMED) Biotech Unit</td>
<td></td>
</tr>
<tr>
<td>Collaborations and Combinations</td>
<td>Global Medicines Development</td>
</tr>
<tr>
<td>Biologics</td>
<td>Market</td>
</tr>
<tr>
<td>MedImmune Biotech Unit</td>
<td></td>
</tr>
<tr>
<td>For further information please click here</td>
<td></td>
</tr>
</tbody>
</table>
| Focused on using state-of-the-art discovery platforms and translational science in small molecules, oligonucleotides and other emerging technologies.
| MedImmune                       |                        |
| For further information please click here |
| Focused on biologics across our core areas and pioneers innovative research using unparalleled expertise in protein engineering, translational sciences and immunology. |

The next wave of scientific innovation
Collaborating and sharing data to redefine the future of drug discovery

“…We’ve worked hard to enrich our compound library in recent years and this exchange, which is by far the largest we’ve achieved, enables us to significantly increase its diversity. Most importantly, it will accelerate our ability to identify unique starting points that could become new medicines for patients.”

Mene Pangalos, Executive Vice President, IMED Biotech Unit, on exchange of 210,000 compounds with Sanofi.

Our teams are leading the way in creating open research environments that go beyond the usual collaboration models. We are always on the lookout for novel ways of working with others to advance medical science and speed up delivery of new medicines to patients. In 2015, we continued to build our network of collaborations with academic institutions, biotech and pharmaceutical companies in our key therapy areas as well as in rapidly evolving technologies such as CRISPR and antisense oligonucleotides. We are also pioneering new approaches to open innovation, creating a permeable research environment where scientists both inside and outside AstraZeneca can more freely share their ideas and collaborate on projects.

Partnering: a way of life

In 2015, our teams established around 60 major collaborations covering key therapy areas and exciting new technologies that are set to drive progress in medical science innovation for years to come.

We signed four research collaborations aimed at harnessing the power of CRISPR, a pioneering genome-editing technique, across our entire discovery platform. Partnerships with the Wellcome Trust Sanger Institute, the Innovative Genomics Initiative, Thermo Fisher Scientific and Broad Institute/Whitehead Institute complement our in-house CRISPR programme.

We engaged in a number of collaborations designed to advance treatment in areas of diabetes and chronic kidney disease, with key partners such as the University of Michigan, the French National Institute of Health and Medical Research (Inserm) and Harvard Stem Cell Institute. We also kicked off a partnership with the Montreal Heart Institute, which is now genotyping up to 80,000 DNA samples from our biobank, looking for genes associated with cardiovascular diseases and diabetes, their complications and treatment outcomes.

We joined a public-private consortium with Genomics England to accelerate the development of new diagnostics and treatments arising from the 100,000 Genomes Project. The GENE Consortium is a unique partnership between industry, academia and the National Health Service (NHS) Genomic Medicine Centres, which aims to transform treatment for patients with cancer and rare diseases, providing faster access to the right therapy and personalised healthcare.

Several innovative compound-sharing agreements underlined our commitment to open innovation and information sharing. One of these involved a direct exchange of 210,000 compounds with Sanofi from our respective compound libraries.

“We’ve worked hard to enrich our compound library in recent years and this exchange, which is by far the largest we’ve achieved, enables us to significantly increase its diversity. Most importantly, it will accelerate our ability to identify unique starting points that could become new medicines for patients,” said Mene Pangalos.
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.

Advancing the science through Open Innovation

Our Open Innovation initiative continued to gain momentum in 2015. Our Open Innovation portfolio now has around 24 clinical, 180 preclinical and 30 target innovation projects. We also added 30,000 new compounds to our high-throughput screening library and funded 12 R&D challenges during the year.

We also joined forces with the Wellcome Trust Sanger Institute, the European Bioinformatic Institute, Sage Bionetworks and the DREAM community on the AstraZeneca-Sanger Drug Combination Prediction DREAM Challenge, an established crowd-sourcing effort in the oncology area. Our unprecedented release of preclinical data from over 50 of our medicines reinforced our commitment to open innovation and our belief that therapeutic combinations have the potential to transform the way cancer is treated.

Out-licensing is another area of focus to ensure progression of indications that fall outside our core focus areas. In 2015, we signed deals with Millendo Therapeutics for AZD4901, an NK3 antagonist, for Polycystic Ovary Syndrome and Hot Flushes and with Corvidia for MEDI5117 (anti-IL-6 mAb), a precision medicine approach for Cardio-Renal Syndrome type 4.

A global science network
Our open innovation partnerships with academic translational drug discovery centres and government-linked funding agencies includes leading scientific institutions globally, who help facilitate our interactions with leading scientists. Our partners include:

- United Kingdom: Medical Research Council
- Germany: Lead Discovery Center
- United States: National Institutes of Health/National Center for Advancing Translational Sciences; Academic Drug Discovery Network
- Canada: NeoMed
- Taiwan: National Research Program for Biopharmaceuticals
- Singapore: A*Star; National Health Innovation Centre-Duke

An invitation to innovate
For further information please click here
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.

- Compound bank of ‘patient-ready’ active and discontinued compounds
- Pharmacology toolbox of compounds with strong pharmacological properties
- Collaborative effort to validate new targets, which may include high-throughput screening
- Advanced chemoinformatic capabilities to explore therapeutic potential of new molecules
- R&D challenges open to anyone willing to offer innovative solutions

Open Innovation initiative
24 clinical projects
180 preclinical projects
30 target innovation projects
30,000 new compounds added to our high-throughput screening library
12 R&D challenges funded during the year
Our most recent collaboration with US-based Ionis Pharmaceuticals, signed in August 2015, aims to discover and develop antisense therapies for cardiovascular, metabolic and renal diseases. This builds on a broad existing relationship and supports our strategic approach in these therapeutic areas using novel RNA-targeted treatments.

Antisense drugs are short, chemically-modified, single-stranded nucleic acids (antisense oligonucleotides) that have the ability to target any gene product of interest. They offer new opportunities for therapeutic intervention because they act inside the cell to influence protein production by targeting RNA to either prevent the production of disease-causing proteins, increase the production of proteins deficient in disease, or target toxic RNAs that are unable to generate proteins.

Since our first collaboration with Ionis in 2012, we’ve continued to expand our partnership every year and are now working together in the key therapy areas of oncology, cardiovascular, metabolic and renal diseases.

“We greatly value our collaboration with AstraZeneca. One aspect of the collaboration that we particularly value is the vision that AstraZeneca has for RNA therapeutics in general. They have placed a major investment in new platforms for drug discovery such as antisense, that go beyond the traditional drug platforms like small molecules and antibodies.

We have been very pleased partnering with AstraZeneca over multiple collaborations. AstraZeneca has a strong vision for applying RNA therapeutic approaches to go after diseases that have significant unmet needs with current therapeutics on the market.”

Brett Monia, SVP Drug Discovery, Ionis Pharmaceuticals

“This expansion of our collaboration with AstraZeneca establishes our second strategic relationship. This new collaboration will help broaden the application of our antisense technology to targets in cardiovascular and metabolic disease. AstraZeneca is committed to finding novel best-in-class therapies for some of the largest, most complex and fastest-growing disease segments in the developed world. Combining our antisense technology with AstraZeneca’s strong knowledge, leadership and commitment in these areas should be very valuable in fully exploiting these opportunities and moving new therapies effectively and efficiently toward the market.”

B. Lynne Parshall, Chief Operating Officer at Ionis Pharmaceuticals

“Antisense-based therapies are rapidly gaining momentum in the clinic and becoming an important component of our early-stage pipeline. Our collaborations with Ionis combine the world-class antisense drug research capabilities of Ionis with our expertise in oncology, cardiovascular and metabolic diseases drug discovery and development. By working together, we aim to uncover targets and pathways that can be manipulated using antisense drug therapy.”

Mene Pangalos, Executive Vice President, IMED Biotech Unit

“AstraZeneca is committed to finding novel best-in-class therapies for some of the largest, most complex and fastest-growing disease segments in the developed world.”

B. Lynne Parshall, Chief Operating Officer at Ionis Pharmaceuticals
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.

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

In 2015, 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 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.

In IMED, we’re committed to continually seeking ways to work across industry and academia to advance great science and address unmet patient needs. Some of our IMED colleagues come to us with long and distinguished academic careers – many of whom retain their academic links during their time with us – while others complement their AstraZeneca career by taking up teaching or research positions in the academic world. Our post-doc programme offers motivated, talented post-doctoral scientists the opportunity to make a difference with an academic-style position in a global pharmaceutical environment, and our graduate programme gives high-performing graduates the opportunity to gain experience across the research spectrum.

We also put continuous development of our people across IMED high on our agenda. From dedicated People Development Weeks to cross-team secondments and shadowing, our programmes ensure we continue developing the skills and capabilities to equip our scientists to be the best they can be. In quarter four of 2015 alone, we saw over ten IMED colleagues take up assignments outside their core role to broaden their learning and experience.

Prof. Dr Maarten Kraan MD PhD
VP R&D Adjunct Professor of Rheumatology at Gothenburg University

“Throughout AstraZeneca, there is true intent to follow the science. Combining my academic and clinical work with my AstraZeneca role puts me at the hard face of drug development. I see my primary job as being part of the IMED and driving our portfolio, but I have a live interface with patients and academia which keeps me awake and sharp, and which gives me many ideas. At AstraZeneca you can do world-class science but you can explore your scientific talents as well as your leadership talents. It’s a friendly, collaborative company and there is such a wide spread of people, skills and experiences. AstraZeneca offers an opportunity for curious people to explore.”

Stephen Rennard
Chief Clinical Scientist, Clinical Discovery Unit, Early Clinical Development, AstraZeneca

“My main interest as a respiratory physician is chronic obstructive pulmonary disease (COPD), which despite being a major cause of death worldwide is poorly understood and researched. The attraction for me in joining AstraZeneca was that the company is making a major commitment to respiratory disease and to driving the science. Novel treatments require novel approaches and AstraZeneca’s willingness to pursue these approaches offers the potential to impact drug development and clinical care. This role was an opportunity to participate in that. AstraZeneca has a lot of committed, hard-working scientists and there is every reason to believe that the drive to science in the company will lead to major advances.”

Tim Eisen, PhD FRCP
VP Head of Clinical Discovery Unit, Early Clinical Development & VP Interim Head of Oncology Translational Medicine Unit, Early Clinical Development, AstraZeneca
Professor of Medical Oncology, University of Cambridge

“At AstraZeneca I am working with a much broader range of people than I would do in academia. The IMED is an exciting place to work, where you can combine very good science with an ability to drive things forward. Things move much more quickly in AstraZeneca than I could as a purely clinical academic. I am hoping to create a more productive relationship between pharma and academia and having experience of drug development gives me a better feel for the way industry works and where there are opportunities for collaboration. We in AstraZeneca spend an enormous amount of time developing talent. I think we offer young scientists a very active and accelerated career, with the training and opportunities to develop in industry and academia. It is an experience and an opportunity which I think is unique.”
Robert Unwin
Chief Scientist, CVMD iMed
Professor of Nephrology and Physiology
(St Peter’s Chair) at University College London

“Having never had any experience of industry before, I’ve been very impressed and excited to meet the breadth of scientists in AstraZeneca. My academic and clinical colleagues are very interested, surprised and even envious of the opportunity I have had to be able to combine industry and academia and bring the two worlds together. I think the scientific ethos at AstraZeneca is very strong and the company has a reputation for being very science-driven. I think it’s an attractive option to consider for young scientists and for clinical scientists in particular. It is very hands-on, educational and stimulating. I still see patients in my clinic once a week and I get ideas from them that I can bring back into drug development programmes. I also continue to collaborate with colleagues in my clinical and academic roles but I can now bring added insight into the conversations.”

Björn Over
Postdoc, CVMD iMed, Medicinal Chemistry

“The culture is really collaborative here. You have experts in so many fields, everybody is very supportive and they help each other out. People are curious about science; they love what they do and are really engaged. Without the guidance of the AstraZeneca experts, my project would not have been so successful. What we do as postdocs is really appreciated. We interact with academia and are able to publish our results, which is really important to our careers.”

Marta Wylot
IMED Graduate Scientist

“I like the diversity at AstraZeneca and the flexibility I have to develop my skills. It’s such a pleasure to work with so many people who are willing to share expertise and ideas. What has impressed me most is the way the scientists work together. They try to find solutions and combine their expertise to get a better outcome. I’m very grateful for the experience to work in AstraZeneca. It’s been a great journey and I’ve learned a lot. I am not worried about my future now as I have gained so much experience on this programme.”

Katerina Pardali
Successfully completed the 2015 women in leadership programme

Women as Leaders

In the AstraZeneca IMED we are committed to increasing the number of women in senior scientific roles. We firmly believe that the most innovative science is produced in diverse teams with different backgrounds, experiences and skills. That’s why we consistently seek to identify and develop the very best talent, wherever it exists. Our ‘Women as Leaders’ programme gives our female scientists a chance to come together to discuss issues such as career progression and personal development with a view to increasing their awareness of opportunities and the confidence to pursue them. We believe that by giving women the skills and support to make good career choices early, we will develop more role models and increase the number of women in senior roles... ultimately broadening diversity and driving innovation. In the 18 months the ‘Women as Leaders’ programme has been running, we have seen 30% of the participants take up expanded, larger roles.

“The IMED is an exciting place to work, where you can combine very good science with an ability to drive things forward.”

Tim Eisen, VP Head of Clinical Discovery Unit, Early Clinical Development & VP Interim Head of Oncology Translational Medicine Unit, Early Clinical Development
Our strategic science centres

UK – Cambridge
In 2013, AstraZeneca announced plans to move our UK research activities to a new $500m facility in the centre of Cambridge. Our new facility at the Cambridge Biomedical Campus will become the company’s largest centre for oncology research and a centre of excellence for pre-clinical research, medicinal chemistry and high-throughput screening.

During 2015, we laid the foundations for our new home on the Cambridge Biomedical Campus, and expanded our interim high-quality lab and office facilities to accommodate our growing presence in the city.

Our evolving science footprint in the North West means a small number of IMED colleagues remain at our Macclesfield campus, and at Alderley Park until our R&D exit of the site is completed. The growing Alderley Park BioHub is successfully creating an optimum environment for emerging businesses to thrive.

Sweden – Gothenburg
Our strategic R&D centre in Gothenburg is the centre of our research for two of our therapy areas: cardiovascular & metabolic diseases and respiratory & inflammation. It is also home to a large number of our scientists from our early phase Discovery Sciences unit and our Drug Safety and Metabolism team.

Our vibrant Gothenburg facility has seen the BioVentureHub go from strength to strength since its inception in 2014, with 14 companies and one academic group now working in this innovative ecosystem.

Below
AstraZeneca’s strategic R&D centre in Gothenburg

Opposite top left
AstraZeneca’s small-molecule research facility in Boston, North America

Opposite bottom left
AstraZeneca’s small-molecule research facility in Shanghai, China

Opposite bottom right
The Gothenburg ‘Coffee Lab’ is an AstraZeneca first – to inspire employees to world-class idea development

US – Boston
Boston is home to AstraZeneca’s small-molecule research in North America, with state-of-the-art laboratories in Waltham, just west of the city centre, and our Neuroscience team in the heart of the city’s Technology Square.

Our Boston-based scientists focus on the discovery and development of new medicines for the treatment of cancers and neurological disorders. The site also houses the Gatehouse Park BioHub, which is thriving with nine research companies already in place since launch in September.

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

Creating vibrant Biohubs
Stimulating ‘cross-fertilisation’, both between the hub companies and with AstraZeneca, is key to the success of the biohub approach in our evolving sites. A bold, new R&D initiative to foster life sciences discovery and the exchange of ideas between scientists, our Gatehouse Park BioHub, along with the BioVentureHub at the Gothenburg site in Sweden, and the BioHub at our Alderley Park site in the UK, all have vibrant but distinctive features offering an energising environment, all about sharing ideas and tapping into great science.

“AstraZeneca has been on a transformative journey over the past few years, placing great science at the heart of everything we do in the delivery of breakthrough medicines to patients. Our ambition is to improve the lives of 200 million people by 2025. Such an ambition would not be possible without establishing collaborations of all types with academia and industry. Our biohubs provide a fantastic opportunity to explore collaboration even further.”

Kumar Srinivasan, Head of AstraZeneca R&D Boston and VP Scientific Partnering and Alliances
Building our future

Our new Cambridge site

In 2013, AstraZeneca announced plans to build a global Research and Development Centre and its Corporate Headquarters on the Cambridge Biomedical Campus. This is one of our flagship initiatives and is part of redefining our future and aspiration to be one of the best scientific institutions in the UK and globally.

Our new R&D Centre will become the company’s largest centre for oncology research and a centre of excellence for pre-clinical research, medicinal chemistry and high-throughput screening. Beyond cancer research, our R&D will focus on cardiovascular and metabolic diseases, respiratory, inflammation and autoimmune diseases and conditions of the central nervous system.

It’s an exciting time for IMED as we continue to establish ourselves in the Cambridge science community, building on the long-standing presence of our colleagues from AstraZeneca’s global biologics research and development arm, MedImmune. We chose to be in Cambridge because we wanted to be at the heart of one of the best scientific centres in the world.

In 2015, we laid the foundations for our new home on the Cambridge Biomedical Campus. This proximity to leading research and academic institutions is key to our culture of open innovation and partnering. We also continue to develop scientific partnerships and outreach programmes. While these are supported by our local presence, they have UK-wide and global reach.

At the end of 2015, we welcomed our thousandth AstraZeneca employee into Cambridge. This strong and growing presence allows us to deepen our scientific relationships as part of the local life-sciences ecosystem, before we move into our new R&D Centre where IMED MedImmune and Global Medicines Development will sit side by side in an open, collaborative workplace. The site will bring together our small molecule and biologics R&D, as well as all our discovery science capabilities and late-stage development, opening up opportunities to work collaboratively across these areas to create the next generation of medicines that will positively impact the lives of millions of people.

Our new Cambridge site will house 2,300 colleagues, with world-class capabilities in target biology, medicinal chemistry, protein engineering, translational science, biopharmaceutical and clinical development. Our presence in Cambridge allows us to play an active role in enabling a permeable scientific hub, where the best ideas flow out, as well as in.

In addition, our PhD programmes with the University of Cambridge and ongoing commitment to STEM programmes in the local community underline our commitment to support, develop and inspire the next generation of Cambridge scientists. By moving to Cambridge, AstraZeneca is helping to build an attractive UK life sciences destination for investment, and deliver a magnet for top scientific talent – underpinned by a world-leading science base, a vibrant and entrepreneurial environment that drives innovation, as well as timely patient access to innovative medicines. Cambridge Biomedical Campus will be an open, welcoming and vibrant centre that will inspire our IMED team and our partners to push the boundaries of scientific innovation.

IMED continued integration into the Cambridge community during 2015

Science retreat

In October, we welcomed over 250 IMED scientists to our Science Retreat at Robinson College in Cambridge. Opened by Nobel Laureate Sir Venki Ramakrishnan, the meeting immersed delegates in inspiring science with topics ranging from immunology, to our progress in open innovation, the patient perspective plus a futuristic look into science and technology that may impact IMED research over the next decade.

Supporting the next generation of scientists

In 2015, we began funding academic clinical lectureships and PhD students at the University of Cambridge, with 80 agreed across AstraZeneca and MedImmune over the next five years. We also support the Cambridge Judge Business School’s “Accelerate” programme designed to identify, train and mentor start-up life science businesses. AstraZeneca’s volunteer mentors come from a range of roles, with expertise in areas like business development, intellectual property and innovation alliances.

Cambridge Cancer Science Symposium

As part of our open innovation strategy, IMED and MedImmune brought top scientists from academia and industry together to share the next generation of oncology science at the Cambridge Cancer Science Symposium, Churchill College.

Delegates were not only impressed by the quality of the science, but also the opportunity to get so many academic and industry organisations together, under one roof, sharing different perspectives in striving for the same goal – to accelerate new and improved treatment options for cancer patients.
Case study

The next wave of innovation in DNA Damage Response

Building a world-leading pipeline

The AstraZeneca portfolio targets distinct aspects of the DNA Damage Response (DDR). This relates both to their different roles in DNA repair and at what point in the cell cycle they exert their effect. AstraZeneca has a number of DDR-targeted compounds in clinical development.

There are three main aspects of the DDR that are different in cancer and therefore provide a rationale for drug targeting:

- DDR pathway loss results in greater dependency on remaining DDR pathways
- Increased replication stress leads to greater dependency on ATR-CHK1-Wee1
- Increased levels of endogenous damage and genomic instability results in greater sensitivity to exogenous DNA damage

Targeting DDR in cancer

An underlying hallmark of cancers is their genomic instability, which is associated with a greater propensity to accumulate DNA damage. Historical treatment of cancer by radiotherapy and DNA-damaging chemotherapy is based on this principle, yet it is accompanied by significant collateral damage to normal tissue and unwanted side effects. Targeted therapy based on inhibiting the DNA Damage Response (DDR) in cancers offers the potential for a greater therapeutic window by tailoring treatment to patients with tumours lacking specific DDR functions.

An invited review in Molecular Cell by Mark O’Connor (Oncology iMed) summarises the scientific data behind olaparib in the context of it being the first approved, targeted cancer medicine for patients with a tumour-specific deficiency in their DDR biology, and it discusses the future significance of DDR-based agents in cancer therapy.

Covering all DDR-targeted agents that either have been approved or are in clinical development, the article demonstrates that AstraZeneca has a world-leading pipeline of compounds that target DDR pathways in cancer.

AstraZeneca portfolio targets distinct aspects of DDR

Chosen for both their different roles in DNA repair and when in the cell cycle they play their primary role

<table>
<thead>
<tr>
<th>Target</th>
<th>Effect</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III, approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Inhibits repair of Double Strand Breaks</td>
<td>AZD0156</td>
<td>AZD2811</td>
<td>AZD6738</td>
</tr>
<tr>
<td>AURORA B</td>
<td>Deregulation of chromosome segregation and cytokinesis</td>
<td>Effect is manifest in M phase</td>
<td>Effect is manifest in M phase</td>
<td>Effect is manifest in M phase</td>
</tr>
<tr>
<td>ATR</td>
<td>Inhibits S phase replication stress response and repair of Double Strand Breaks</td>
<td>Effect is manifest in M phase</td>
<td>Effect is manifest in M phase</td>
<td></td>
</tr>
<tr>
<td>Wee1</td>
<td>Inhibits S phase replication stress response and G2/M cell cycle checkpoint</td>
<td>Effect is manifest in M phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARP</td>
<td>Inhibits repair of Single Strand Breaks</td>
<td>Effect is manifest in M phase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Selective targeting of tumours that harbour a DDR deficiency means that, unlike with radiotherapy or chemotherapy, tumour cells can be killed without causing significant side effects or damage to normal tissue. In 2015, clinical validation was provided by regulatory approval of the PARP inhibitor olaparib in ovarian cancer patients whose tumours have a mutation in BRCA1 or BRCA2, which encode proteins involved in the DDR. Olaparib activity is now being explored in the clinic in non-BRCA DDR deficient cancers (for example ATM-low gastric cancers in the Phase III Gold trial in Asian patients), and additionally in prostate cancer.

There are potential advantages of combining olaparib with other DDR-targeted compounds, or with agents such as the AstraZeneca VEGFR TKI cediranib that target other cancer pathways; these combinations could provide broader and more effective responses than a monotherapy approach.

Olaparib – the first medicine based on DDR

The recent approval of olaparib the poly (ADP-ribose) polymerase (PARP) inhibitor for treating tumours harbouring BRCA1 or BRCA2 mutations, represents the first medicine based on this principle, exploiting an underlying cause of tumour formation that also represents an Achilles' heel.

DNA replication stress – a promising target for DDR-based therapies

Another hallmark of cancer linked to the DDR is DNA replication stress, which occurs to a greater degree in cancer cells than normal cells and is therefore a potential target for DDR-based therapies such as AZD6738 and AZD1775, which inhibit the DDR regulators ATR and Wee1, respectively. DNA damage caused during the DNA replication phase of the cell cycle (S phase) can lead to cell death if it is not repaired before cell division (M phase): one therapeutic strategy to maximize the amount of DNA damage is to inhibit the checkpoints at which the cell cycle is halted until any DNA damage has been repaired; for example, AZD1775 inhibition of Wee1, which regulates the G2/M checkpoint, allows accumulated DNA damage to be carried into M phase, inducing cancer cell death.

Investigation of both the cell cycle and cell death effects resulting from treatment with the ATR and Wee1 inhibitors in DLBCL models highlighted differences consistent with the greater potency of the Wee1 inhibitor in these models; an assessment of in vivo activity further supported these findings. Results presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in November on AZD1775 treatment of a larger panel of in vivo patient-derived explant (PDOX) models of multiple tumour types demonstrated both the significant breadth and depth of the Wee1 inhibitor single-agent activity. There is also potential for this activity to be enhanced further through combination with olaparib, a PARP inhibitor that induces S-phase DNA damage. Together, these data have led to the recent initiation of AZD1775 monotherapy as well as AZD1775/olaparib combination clinical trials.

Strategy for the use of DDR inhibitors as anti-cancer agents

What’s next?

The phase III olaparib development programme also includes two additional studies; a prostate cancer study that received FDA breakthrough status. In addition, there is also a study of olaparib in combination with durvalumab (DUO study, D081CK00002). The ATM inhibitor AZD0156 is the latest DDR targeted agent to enter the clinic and will be used in combination with olaparib to investigate whether this novel DDR agent combination can extend the patient population that can benefit from olaparib. AZD0156 also has the potential to increase the effectiveness of chemotherapies that require ATM function. Pivotal to optimising the clinical use of these novel therapeutic category of anti-cancer agents will be the selection of the most appropriate treatment combinations for DDR-targeted therapies. Due to the strong mechanistic links between DDR and different aspects of the immune response, this includes the potential for combinations with immunotherapy agents. Another key aspect for success will be targeting of specific patient populations whose cancers carry definable DDR gene mutations. What is clear is that targeting DDR represents an exciting new advance in our ability to treat cancer.

The next wave of scientific innovation 103

Mark O’Connor, Senior Principal Scientist IMED Biotech Unit (Oncology)

O’Connor NL. Targeting the DNA-damage response in cancer. Molecular Cell 2015; 60(4)
Our reputation for scientific leadership

Our commitment to being a science-led company doesn’t end with our work in the lab. We believe that continued innovation relies on us fostering a culture of scientific excellence, empowering our scientists to not only keep abreast of the latest developments and breakthroughs, but to drive them.

Our continued drive to develop a thriving science environment has generated great progress during 2015, both inside IMED and within the broader scientific ecosystem.

Our publications

We strengthened our scientific reputation through an increased focus on high-quality scientific publications in 2015 with 455 papers published. We also saw outstanding progress in publishing our science in high-impact, peer-reviewed journals, moving from a single high-impact publication in 2010 to 29 in 2015.

Our continued drive to develop a thriving science environment has generated great progress during 2015, both inside IMED and within the broader scientific ecosystem.

Role of B Cell-Activating Factor in Chronic Obstructive Pulmonary Disease

American Journal of Respiratory and Critical Care Medicine

About the paper: Lymphoid follicles have been associated with COPD disease severity, with localised overexpression of B cell-activating factor (BAFF) demonstrated in patients with severe COPD. This paper, a collaboration between IMED, MedImmune and Ghent University Hospital has further described the role of BAFF in COPD, demonstrating BAFF overexpression in COPD patient lung tissue and in a mouse model of chronic cigarette smoke exposure. Furthermore, it was shown that antagonising BAFF can protect against alveolar destruction and pulmonary inflammation.

Impact: This research has demonstrated novel findings that will influence future strategies in the treatment of COPD.

Lead AstraZeneca authors: Anja Schinwald, Daren Cunososamy, Claudie Malanda, Alan Sabirah, Eileen McCall, Liz Flavell, Ronald Herbst

IMED Science Awards

Our continued progress towards scientific leadership is down to the collective effort of dedicated and talented individuals striving to make a difference. The prestigious annual IMED Science Awards aim to recognise and reward individual and team efforts, share great achievements and inspire even more great work from our scientists.

The 2015 IMED Science Awards celebrated some of the best breakthrough, high-impact science taking place at AstraZeneca. 150 global nominees were invited to join the IMED Leadership Team and members of the review panel at a black-tie celebratory dinner. The awards recognised outstanding scientific achievement; high impact work acknowledged as game-changing. Winning teams and individuals received trophies and certificates, and are also rewarded with tailored opportunities to support future research and enhance their careers.

Science Retreat

The 2015 IMED Science Retreat took place in October at Robinson College, Cambridge. The packed agenda of scientific innovation, patient insight and technology of today and tomorrow helped deliver a meeting of high-quality science and inspiration, opened by Nobel-winning structural biologist Sir Venki Ramakrishnan. The IMED Science Retreat is an important event in the AstraZeneca science calendar, enabling colleagues to get a view of the latest developments outside their areas, share ideas and look at how we can apply science in new and different ways to drive scientific leadership.

“This environment, buzzing with science and energy, is a great place for learning about the research going on across IMED, and to share our progress. I really enjoyed the patient insight sessions, they were truly powerful and reminds us of our goal.”

Sepideh Hagvall Heydarkhan, Associate Principal Scientist CVMD IMed

Structural and dynamic insights into the energetics of activation loop rearrangement in FGFR1 kinase

Nature Communications

About the paper: The FGFR family of kinases are key mediators of both developmental and disease associated blood vessel growth. Prior work had only ever shown FGFR1 with a key element to binding ATP (the energy source) being folded in ready to activate the protein. This paper, a collaboration between IMED and MedImmune scientists, for the first time details the interactions and stability associated with protein being ‘flipped’ into a non-active form.

Impact: This work has significance in the design of kinase inhibitors and the understanding of the stabilisation of the non-active form of the target protein.

Lead AstraZeneca authors: Gareth Davies, Geoff Holdgate and Chris Phillips

c-kit+ cells do not generate lung epithelium during maintenance and repair

Nature Medicine

About the paper: It has been reported that c-kit+ progenitor cells resident in the human lung regenerate epithelial cells upon transplantation into injured mouse lung. For the first time, our scientists demonstrated that during normal function and regeneration conditions after injury, c-kit+ cells adopt vascular endothelial cell fate and not any type of lung epithelial cells. In addition, c-kit+ cells proliferate after injury and contribute to new blood vessel formation within the lung.

Impact: This study unravelled the true fate of c-kit+ cells during lung homeostasis and lung repair, calling attention to the clinical application of c-kit+ progenitor cells as lung epithelial progenitors for the treatment of pulmonary disease.

Lead AstraZeneca author: Qing-Dong Wang

About the paper: Lymphoid follicles are key mediators of both developmental and disease associated blood vessel growth. Prior work had only ever shown FGFR1 with a key element to binding ATP (the energy source) being folded in ready to activate the protein. This paper, a collaboration between IMED and MedImmune scientists, for the first time details the interactions and stability associated with protein being ‘flipped’ into a non-active form.

Impact: This work has significance in the design of kinase inhibitors and the understanding of the stabilisation of the non-active form of the target protein.

Lead AstraZeneca authors: Anja Schinwald, Daren Cunososamy, Claudie Malanda, Alan Sabirah, Eileen McCall, Liz Flavell, Ronald Herbst

IMED Science Awards

Our continued progress towards scientific leadership is down to the collective effort of dedicated and talented individuals striving to make a difference. The prestigious annual IMED Science Awards aim to recognise and reward individual and team efforts, share great achievements and inspire even more great work from our scientists.

The 2015 IMED Science Awards celebrated some of the best breakthrough, high-impact science taking place at AstraZeneca. 150 global nominees were invited to join the IMED Leadership Team and members of the review panel at a black-tie celebratory dinner. The awards recognised outstanding scientific achievement; high impact work acknowledged as game-changing. Winning teams and individuals received trophies and certificates, and are also rewarded with tailored opportunities to support future research and enhance their careers.

Science Retreat

The 2015 IMED Science Retreat took place in October at Robinson College, Cambridge. The packed agenda of scientific innovation, patient insight and technology of today and tomorrow helped deliver a meeting of high-quality science and inspiration, opened by Nobel-winning structural biologist Sir Venki Ramakrishnan. The IMED Science Retreat is an important event in the AstraZeneca science calendar, enabling colleagues to get a view of the latest developments outside their areas, share ideas and look at how we can apply science in new and different ways to drive scientific leadership.

“This environment, buzzing with science and energy, is a great place for learning about the research going on across IMED, and to share our progress. I really enjoyed the patient insight sessions, they were truly powerful and reminds us of our goal.”

Sepideh Hagvall Heydarkhan, Associate Principal Scientist CVMD IMed
Preparing for the future with our ‘IMED Futures’ teams

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

During 2015, our teams interrogated emerging technologies, explored new approaches to drug discovery and challenged conventional thinking in the search for new opportunities to bring benefit to patients. Here we shine a spotlight on four of our programmes.

Digital health

The wealth of ‘big data’ in healthcare is revolutionising our approach to R&D. We are already seeing how the next generation of medicines are being shaped by our ability to capture, interpret and apply data. Combining insight from clinical health records with large-scale genomics data is enabling scientists to better predict disease outcomes in the clinic. However, our team have been investigating connecting multiple data stacks from anywhere and of any type, from proprietary data to real world evidence, even social media platforms. This data stack would truly allow us to map 360 degree views of patient journeys and gain understanding of the interplay between ‘nature’ (from genetic information) and ‘nurture’ (environmental data e.g. smartphone/sensor data) to make breakthroughs in science and ultimately patient care. In 2016, the team hopes to begin a collaboration to create such a complex data stacks in the oncology therapy area, aiming to get targeted medicines to genetically matched patients faster.

“Connecting data stacks of patient data is not new. What would be cutting-edge is if we could design them to handle ever increasing data types, ‘stacking’ multiple layers of patient data – making them flexible to connect with whichever data is current.”

Hitesh Sanganee, Digital Futures Lead

Targeted drug delivery

Improved understanding of the physiological barriers to efficient drug delivery has resulted in significant advances in delivery systems. This, coupled with novel analytical and imaging techniques allow for even more sophisticated delivery systems opening up new target space. Our team is looking to improve target efficacy by enhancing our targeting capabilities to allow delivery of both small molecules and oligonucleotide therapeutics – miRNA, mRNA and antisense. To do this our team has focused on three key areas: 1) cellular targeting, 2) improving cellular uptake and 3) enhancing drug delivery. In the latter case, we have already initiated collaborations with BIND Therapeutics for their ACCURINS® polymeric nanoparticle technology and with Starpharma exploring their dendrimer technology platform. Both these technologies improve therapeutic index and ability to formulate challenging molecules.

“A key to advancing drug delivery in the next decade for RNA therapeutics will be to enhance trafficking and cellular uptake, to and by the desired tissue and cell type.”

Malin Lemurell, Targeted Drug Delivery Futures Lead

Pre-clinical futures

To enhance the impact of current online data monitoring, our teams have been exploring the possibilities within the rich data source provided by sensor technology and wearable devices. Incorporating biosensor technology into our pre-clinical studies will allow us to change current practice, improve translation and safety read-outs, while reducing the number of animal studies.

Current technology allows measuring the body’s vital signs using health patches but our team recognises the true value for pre-clinical monitoring lies with invasive biosensor technology. In the future, developing pre-clinical sensors that monitor drug exposure and biomarkers of safety and efficacy will have the potential for clinical use – providing online biosensors for patients, and hence changing the status quo for patient care.

“Today we have already seen the approval of wearable devices to measure online glucose levels for diabetic patients. If we can discover reliable biomarkers and couple these with sensitive sensor technology this opens up a wealth of opportunities.”

Colina d’Cruz, Pre-clinical Futures Lead

Microphysiological systems

As we advance our understanding of biology and integrate our knowledge of cellular behaviour and tissue function, it is apparent that the current pre-clinical in vitro models have limitations when predicting organ functionality. Complex cellular microphysiological systems (mPSS), consisting of interacting organs-on-chips or tissue-engineered, 3D organ constructs, present an opportunity to bring new tools to biology, medicine, pharmacology, physiology, and toxicology. By placing human or animal cells in a more ‘natural’ environment, we can start to recapitulate the dynamics of drug-organ, drug-drug, and drug-organ-organ interactions to allow better predictivity of clinical translation. Our team is collaborating with some of the leading experts in the world at TissUse, Harvard and Vanderbilt Universities.

“With advances in cell culture and microfluidics it is now possible to emulate human biology on a microscale. Taking this one step further and connecting these organ units together, human-on-a-chip technology will allow us to advance our understanding of the safety and efficacy earlier in drug discovery.”

Lorna Ewart, Microphysiological Systems Futures Lead

“Connecting data stacks of patient data is not new. What would be cutting-edge is if we could design them to handle ever increasing data types.”

Hitesh Sanganee, Digital Futures Lead