

AstraZeneca R&D: Turning science into medicine

January 2021



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Led by science. Driven by patients

Our R&D culture

We are driven by science, united by science, and every day, we push the boundaries of science to deliver life-changing medicines.

We have a unique R&D culture where people with curious minds are inspired to think creatively. Free from fear of failure, free to ask the right questions, make bold decisions, and dig deep into the biology of complex disease.

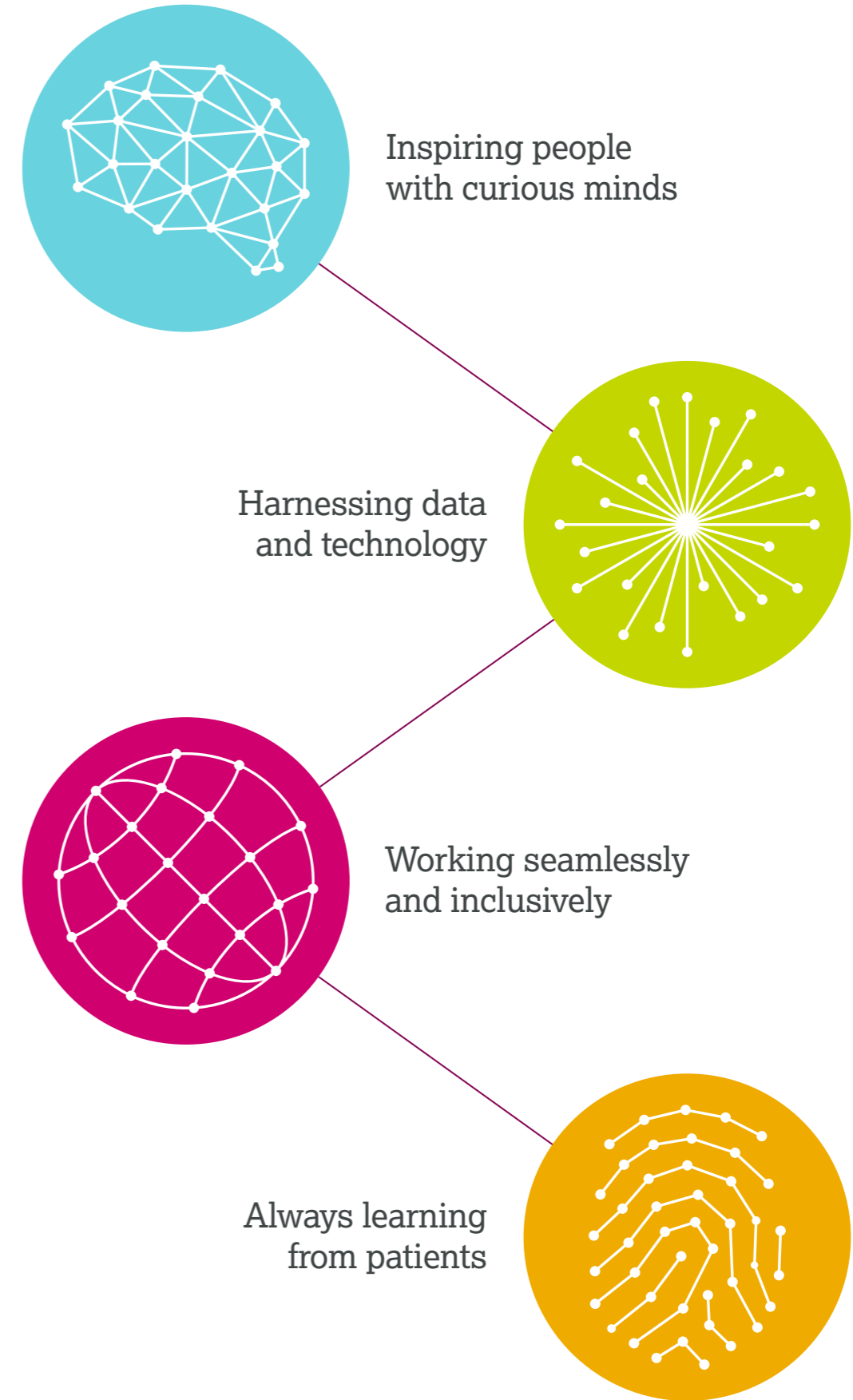
At the same time, we are harnessing data and technology to fast-forward the pace of our science. Helping us achieve the next wave of breakthroughs and do things that have never been done before.

It is a culture where people are able to work seamlessly and inclusively together. In an environment where all doors are open, talent and diversity are celebrated, and every voice is heard.

We are always learning from people who live with the diseases our medicines treat. So we can understand their needs and make sure that great science born in the lab can make a real difference to their lives.

It's by creating and sustaining this culture that we are able to help unlock the power of what science can do. This is AstraZeneca R&D. This is what we are made of.

✓ Medical Chemist in our labs in Macclesfield, UK





Two organisations. One aim

We have two therapy-focused R&D organisations who lead all our work, from discovery through to late-stage development.

Oncology R&D is focused on cancer. BioPharmaceuticals R&D on Cardiovascular, Renal and Metabolism (CVRM); Respiratory and Immunology, and opportunistically, Neuroscience and Microbial Science.

The two organisations work both independently and together, sharing Functions specialising in key scientific capabilities from medicinal chemistry to biometrics, patient safety to data science and artificial intelligence (AI), and clinical innovation to device technology. All of which help us accelerate discovery and development in our efforts to bring new medicines to patients.

Our R&D groups are unified in their approach, and united in their purpose to deliver life-changing medicines to people who need them most.

Discovery

Oncology R&D

Lung, Breast, Ovarian, Haematology, Pancreatic, Bladder, Liver, Prostate

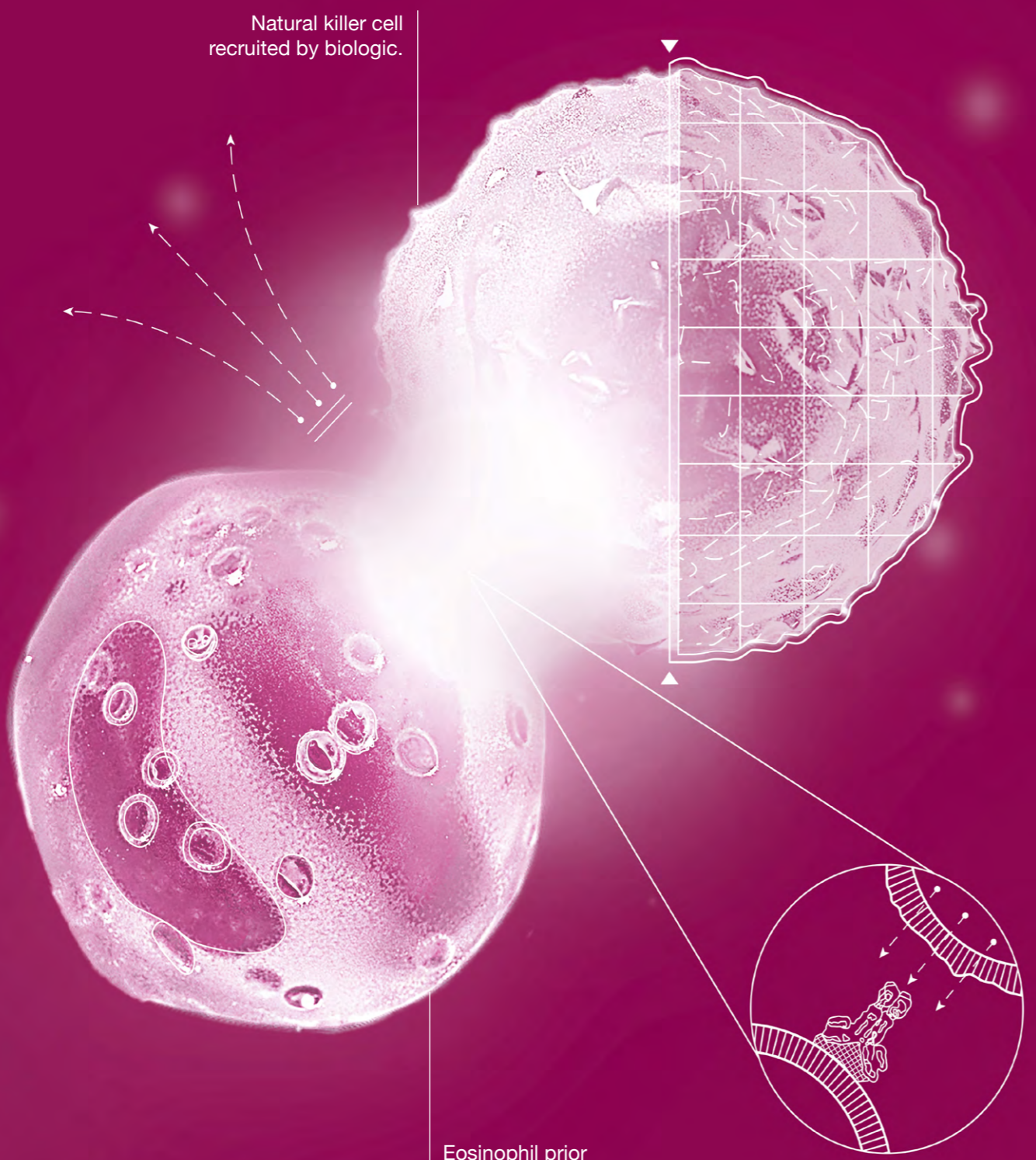
BioPharmaceuticals R&D

Cardiovascular, Renal & Metabolism
Respiratory & Immunology
Neuroscience
Microbial Science

Late stage development

Natural killer cell recruited by biologic.

Eosinophil prior to apoptosis.



Our therapy areas – Oncology

At AstraZeneca Oncology R&D, we are pushing the boundaries of science to change the practice of medicine and transform the lives of patients living with cancer, with the aim of eliminating cancer as a cause of death. We have one of the broadest and deepest oncology pipelines in the industry, based on six scientific platforms: Immuno-Oncology, DNA Damage Response, Antibody Drug Conjugates, Tumour Drivers and Resistance Mechanisms, Cell Therapies, and Epigenetics.

Our approach to eliminating cancer is to identify and treat patients earlier in the progress of their disease when there is potential for cure, and to improve the treatment of relapsed or refractory patients by addressing emerging resistant populations, particularly in later stages of disease. With a focus on monotherapy and combinations, biomarker-driven innovative clinical trials and digital technologies, we are confident that cures for cancer are within our grasp.



Antibody-drug conjugates (ADCs)
A cancer-killing drug is attached to the monoclonal antibody through a stable connection (the linker), creating the ADC. The ADC binds to specific proteins on the surface of cancer cells, it is then internalised into the cell. Once inside the cancer cell, the cytotoxic drug is released, destroying the cancer cell.



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Our therapy areas – Cardiovascular, Renal and Metabolism

We are committed to defining new standards of care for patients with cardiovascular disease, heart failure, metabolic diseases, such as diabetes and non-alcoholic steatohepatitis (NASH), and chronic kidney disease (CKD) - improving their outcomes and decreasing mortality rates.

We have built knowledge and invested in key technologies to develop both our pipeline and our level of scientific expertise. We couple this with a patient-centric approach aimed at better understanding the interplay and potential causal relationship between these diseases, which often present in the same patient. Our approach is opening up unprecedented opportunities for novel treatment paradigms to help more patients and strengthen our pipeline with further differentiated medicines.

Cardiovascular, renal and metabolic diseases

CVRM diseases such as heart failure, cardiovascular disease, diabetes and chronic kidney disease share common and distinct mechanisms. AstraZeneca is researching the interplay and potential causal relationship between these diseases with the aim of improving outcomes in patients with one specific diagnosis before co-morbidities emerge.



Our therapy areas – Respiratory and Immunology

We are aiming to transform the treatment of respiratory diseases, with our growing portfolio of inhaled combinations at the core of care, biologics for the unmet needs of specific patient populations, and scientific advancements in disease modification.

We have revolutionised our respiratory strategy with a focus on three core themes: lung epithelium, lung immunity and lung regeneration. Increasing our understanding of disease drivers forms the basis of our drug discovery programmes, and supports our vision to deliver disease modifying medicines that prevent, reverse or even cure these diseases.

Respiratory and immunology diseases
When lungs are stressed by allergens, pathogens or irritants, epithelial cells produce cytokines that trigger multiple downstream inflammatory pathways in the lungs. AstraZeneca is researching multiple drivers of respiratory and immunology disease areas with the aim of designing disease modifying medicines that prevent, reverse or even cure these diseases.



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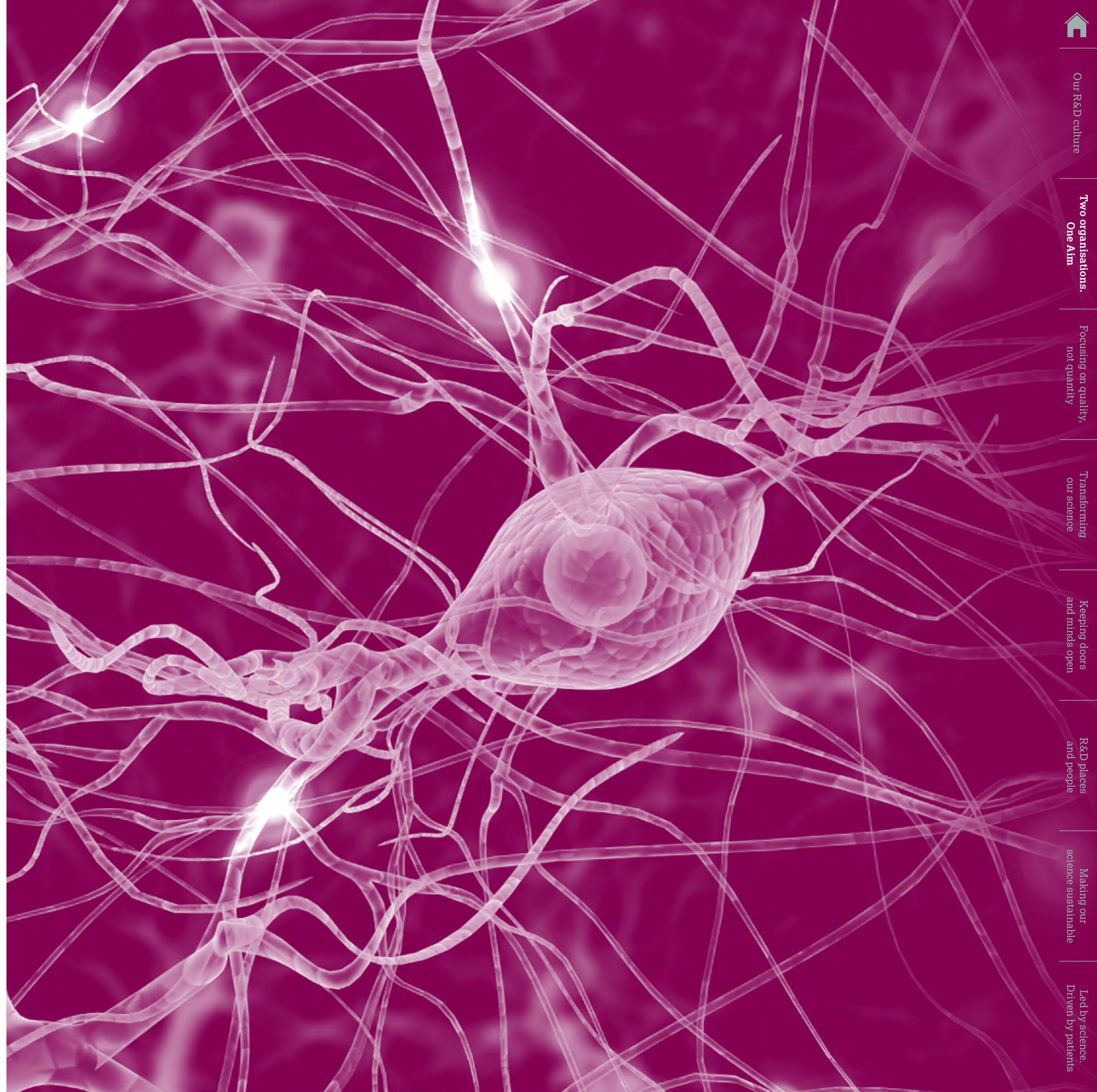
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Our therapy areas – Neuroscience and Microbial science

Additionally, we pursue opportunity driven projects in neuroscience and microbial science.

Our business model thrives on being dynamic and partly externalised, with a firm focus on driving science in our key areas of interest. Early, flexible partnering with the brightest and best in the world allows us to combine knowledge and progress clinical development, while managing the challenges associated with neuroscience and microbial science research.



Our expert functions

Discovery Sciences

Discovery Sciences applies deep technical expertise in specialist technologies to support the delivery of targets and molecules to the early AstraZeneca pipeline. Targets are identified through our human genomics and functional genomics efforts, employing the latest technologies in genome editing and advanced cell model development. Once identified and validated, we work with therapy area project teams to identify novel small molecules effectors of these targets using our integrated sample management and platform screening groups.

Antibody Discovery & Protein Engineering (ADPE)

The ADPE team leads the generation of biologic drug candidates and the development of new technologies with the aim of creating first or best in class therapeutics. As well as monoclonal antibodies, we are pioneering new drug formats, from antibody drug conjugates to multi-specific antibodies, therapeutic peptides, scaffolds, intracellular targeting, in vivo expressed biologics and cellular therapies.

Precision Medicine & Biosamples

Our vision is to transform patients' lives through personalising treatment, delivering innovative diagnostics with external partners aiming to match AstraZeneca drugs to patients most likely to benefit. Over 90% of our clinical pipeline takes a precision medicine approach. And our Biosamples team provides end-to-end expertise for the whole R&D portfolio across the Human Biological Samples lifecycle to meet our obligations to patients, including the lab analysis essential for safety.

Clinical Pharmacology & Safety Sciences (CPSS)

CPSS provides non-clinical safety, clinical pharmacology and quantitative modeling support to the R&D portfolio, with expertise in mechanistic discovery safety, regulatory toxicology, pathology, animal sciences, clinical pharmacology and pharmacometrics, quantitative modeling and data sciences. Our work impacts molecule design, selection, clinical study design, dosing regimens, regulatory approval of new medicines and life-cycle management.

Pharmaceutical Sciences

Pharmaceutical Sciences is responsible for key aspects of chemistry, manufacturing and control, from discovery to phase II trials. The function influence the intelligent design of medicines and delivery systems across all therapeutic areas, applying expertise in novel synthetic route and process design; data science and modelling; formulation and advanced drug delivery, as well as delivering to high standards from our drug substance and drug product manufacturing GMP facilities.

Biopharmaceutical Development (BPD)

Working across all our therapy areas, BPD integrates cell biology, process science, molecular structure and function, solution and solid-state chemistry, advanced data analytics and engineering to create industry-leading technologies. These in turn facilitate efficient production of novel biologics, stable formulations for delivering new medicines, new drug delivery systems and patient-friendly devices. All of which help us transform research into life-changing medicines.

Development Operations

Development Operations is here to deliver science through a wide range of specialist expertise, operational excellence and data driven innovation. These enable us to drive extensive clinical trial programmes from design to regulatory submission and approval. Providing the key connection between science and commercialisation, we deliver trials to the highest standards of quality, efficiency and ethics to thousands of patients globally.

Data Science & AI (DS&AI)

DS&AI works across R&D to drive innovative data science and AI applications. By drawing actionable insights from our data, DS&AI acts as data management and governance hub, helping bring transparency to discovery sciences and drug development. Together with our R&D and IT colleagues, we are harnessing new technologies to improve our disease understanding and accelerate the R&D process with an ambition to bring new medicines to patients faster and more effectively.

Digital Health R&D

Digital Health R&D leads the strategy and operational delivery of digital health solutions across R&D. Our aims are to help predict, prevent and treat patients' conditions more effectively. We'll do this using digital, data and analytics to improve and speed up portfolio development; improve patients' clinical trials experience and patient outcomes, and re-imagine the future of healthcare via partnerships and innovative digital solutions.

R&D Information Technology (IT)

R&D IT use technology to transform the speed and quality of our discovery and delivery of medicines to patients. The team helps optimise scientists' daily lives through the use of new IT technology but are also committed to transforming R&D by creating and building new digital and data science platforms to increase R&D success and reduce timelines. Expertise includes automation, analytics-ready data, scaled engineering, high quality digital applications, seamless integration and technology innovation.

Business Development & Licensing

Business Development & Licensing's remit includes search and evaluation, transactions, alliance management. Our role is to enrich the R&D pipeline and technological capability through external innovation from discovery to late clinical development by partnering with biotech companies, peer pharma and academic institutions. In this way, we can help ensure that both our science and portfolio are fit to meet future challenges by maximizing the value of our strategic partnerships.

Chief Medical Office (CMO)

The CMO works globally and is responsible for patient safety, regulatory excellence, quality assurance, clinical engagement and policy. Functioning across the enterprise, our priority is to continually improve the way we deliver our products and services. By creating opportunities for meaningful patient engagement, maximizing access to medicines, and strengthening our commitment to a safe science culture, we aim to create better experiences and outcomes.

Chief Operating Office (COO)

The COO's role is helping create world-class partnerships and work environments across all our sites, globally. We provide leadership in strategy; decision making; operational excellence; risk management, and specialist administration, as well as scorecards, reporting and publications compliance. We also nurture the pipeline of new scientists joining us through our global graduate, PhD and post doc programmes, helping make great science possible.

R&D Japan

R&D Japan has extensive capabilities in clinical development across all our therapy areas, driving studies from early development to life-cycle management. Supporting both local and global programmes, we are able to factor in local medical and regulatory requirements to help accelerate patient access, and lead global programmes for diseases prevalent in Asia, fostering partnerships and alliances to help create ground-breaking science.

R&D China

R&D China also has clinical development expertise across small molecules and biologics, helping accelerate the development of innovative medicines for Chinese patients, and lead the delivery of global programmes in all our therapy areas. Our strategic investments in China include a pharmaceutical development hub and local manufacturing facilities, and R&D China drives our portfolio locally, as well as supporting the global development of our most promising medicines.



Development chemists in our labs in Maihara, Japan



Focusing on quality, not quantity

Our drug discovery and development is guided by our '5R Framework', which champions quality over quantity, and has helped transform the culture of R&D and our business.

Over a 5-year period, it has enabled us to achieve a more than four-fold improvement in the proportion of pipeline molecules advancing from pre-clinical investigation to completion of Phase III clinical trials from 4% to 19%*.



* (Morgan et al., (2018) *Nature Reviews Drug Discovery*)



Circulating tumour DNA

AstraZeneca has pioneered the use of circulating tumour DNA (ctDNA) in the diagnosis of cancer. Pieces of DNA break off from a tumour and circulate in the bloodstream where they can be analysed to give genetic information about a patient's tumour. This allows healthcare professionals to determine the right treatment for the patient using a minimally invasive blood test.

Developments in diagnostics

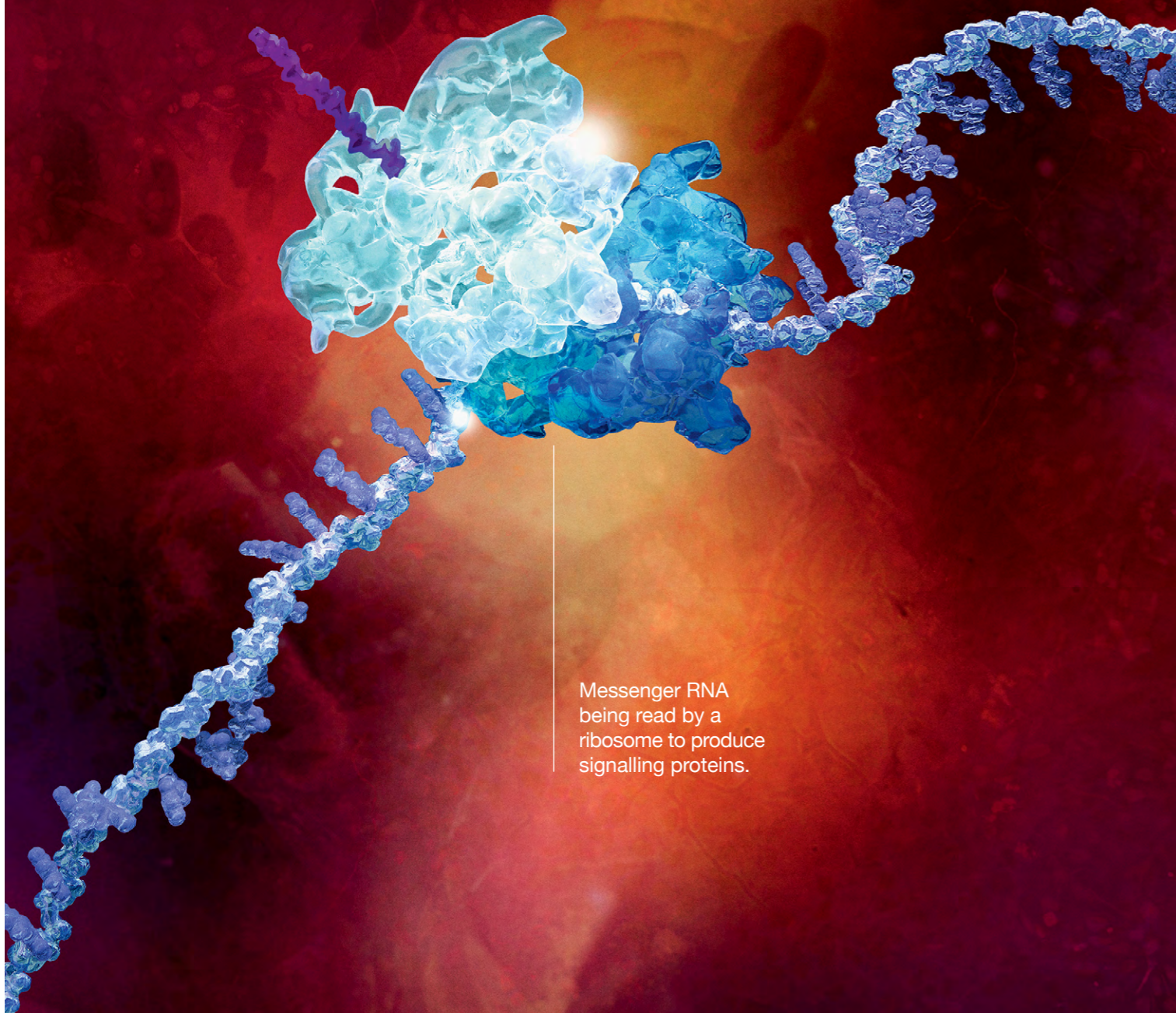
With 90% of our pipeline taking a precision medicine approach, compared to just 10% in 2009, we have been able to make significant steps forward in diagnostics. These include a broad range of cutting-edge technologies, such as tumour tissue diagnostics, molecular tests, and point-of-care diagnostics.

Since 2014, we have launched five precision medicine therapies linked to 35 different diagnostic tests, and are working towards developing technologies that can detect early disease. For instance, we are exploring tests based on circulating tumour DNA to measure minimal residual disease in colorectal cancer, which could lead to patients being treated with new treatments at an early stage, when response rates are higher.

Thinking beyond Oncology, we have developed point-of-care tests for respiratory disease to measure a biomarker for eosinophils with ChemBio Diagnostic Systems, and for inflammation, to measure serum uric acid with Nova Biomedical. And we are now exploring the use of CRISPR technology for diagnostics across many different disease areas.



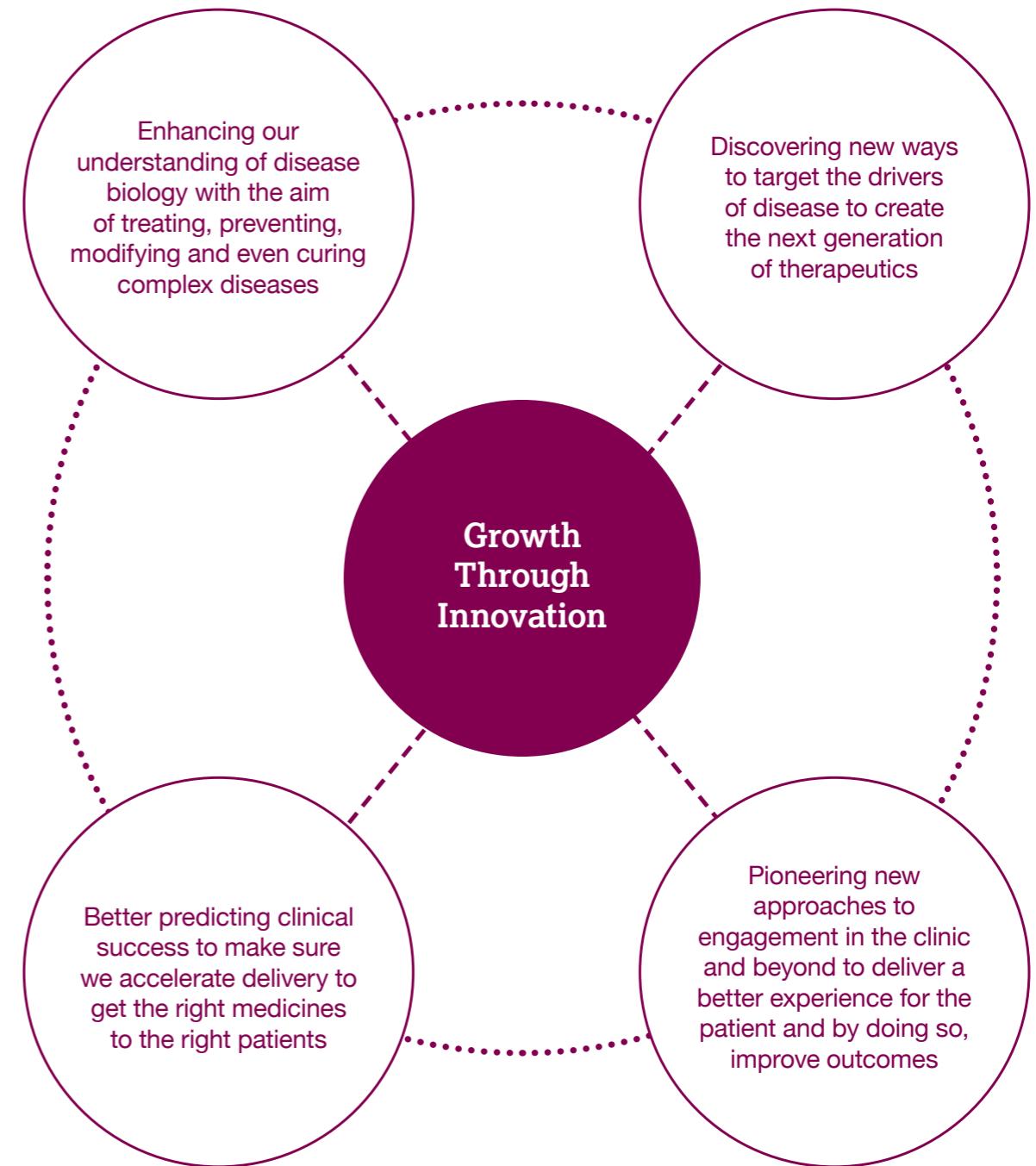
Transforming our science



Messenger RNA being read by a ribosome to produce signalling proteins.

We are never complacent about scientific discovery and development, always pushing our R&D productivity, searching for new knowledge and the next breakthrough.

Our 'Growth Through Innovation' strategy will guide our business to 2025 and beyond, supporting us in advancing our scientific knowledge to extend the possible and helping shape the future of healthcare. We are committed to investing in and embedding four key areas, which will help us in our aspiration to create the greatest and swiftest impact on disease.



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Data science & AI are transforming drug discovery and development

AI and machine learning have the potential to transform the way we discover and develop new medicines. We hope to be able to increase the probability of success and reduce timelines in our drug discovery and development process by applying advanced AI and machine learning across R&D.

We are embedding AI across all of our R&D activities, from target identification to early clinical trials to understand where we can harness new technologies and further automate processes. Our vision is one of freeing up more time for discovering and delivering as many new medicine programmes as we can from our innovative pipeline.

We are using AI to help us analyse and interpret huge quantities of data at all stages of drug discovery and development, with a number of aims in view. Gaining a better understanding of the diseases we want to treat; identifying new targets for novel medicines; speeding up the way we design, develop and make new drugs; designing and recruiting for better clinical trials, and driving personalised medicine strategies.

FAIR foundations, the right architecture and continuing investment

Today, we are generating and have access to more data than ever before. But the true value and transformational potential of scientific data can only be realised if it is 'FAIR' – Findable, Accessible, Interoperable and Reusable.

Making sure that we have the correct foundations for data science and AI is critical to our continued success. We have to get the data into the right shape, embed the right governance, implement the right analytical tools, and most importantly, get the right data into the hands of the right people to yield transformational benefits. This is why a concerted, cross-company effort around data and analytics is so important.

We are creating an enterprise-wide data and AI architecture. To achieve this, we are bringing the right people together – data scientists, bioinformaticians, data engineers and machine learning experts – to ensure that we are collecting, organising and using the right data, in the best way possible.

At the same time, we are also investing in internal training and education so that everyone in R&D understands our approach to data science and AI and can use or partner with the right experts to unlock data and apply it effectively.



Visualisation of a data network

Enhancing our understanding of disease biology

We are determined to advance our understanding of disease biology to uncover novel drivers for the diseases we aim to treat, prevent and in the future, cure. Selecting the right target remains the most important decision we make in the drug discovery process. We are investing in multiple approaches to improve this:

- Through our Genomics Initiative, we aim to analyse 2 million genomes by 2026 to identify rare genetic variants to uncover new targets and disease insights.
- We are investing in broader multi-omic technologies, such as transcriptomics, proteomics and metabolomics, to probe the more complex and transient molecular changes that underpin the course of disease and responses to drug treatment.
- Our use of precise gene and base editing technologies continues to help us create more relevant cell lines and animal models in a matter of weeks, as opposed to months or longer still.
- At our AstraZeneca-Cancer Research UK Functional Genomics Centre at the Milner Therapeutics Institute in Cambridge, in the UK, we aim to discover new targets by using CRISPR libraries to delete or upregulate every gene in the cell to understand the role of that gene in disease biology.
- We are combining these rich datasets with external data sources, and applying AI and machine learning to develop biomedical knowledge graphs to contextualise scientific data and the relationships between them in partnership with companies such as BenevolentAI.

Knowledge graphs

'Knowledge graphs' are networks of contextualised scientific data facts such as genes, proteins, diseases and compounds, and how they relate to each other. We are embarking on a long-term collaboration with BenevolentAI to use AI and machine learning to build knowledge graphs for chronic kidney disease (CKD) and idiopathic pulmonary fibrosis.



Creating the next generation of therapeutics

In our quest to transform disease, we believe it is essential to target novel biology we uncover. We are continuing to design new ways to target the drivers of disease to help us create the next generation of therapeutics – going beyond traditional small molecules, monoclonal antibodies and peptides.

By combining our distinctive medicinal and peptide chemistry skills and technologies with those of other leading companies in highly specialised fields, we are working towards our goal of addressing the unmet medical needs of patients.

The diversity of technologies applied in our early pipeline is exemplified by the increased number of new modalities entering clinical development. 30% of our early pipeline now consists of new drug modalities, including oligonucleotides, mRNA, bicyclic peptides and Anticalin® proteins.



Next generation therapeutics
Advancements in biotechnology have expanded our toolkit of drug modalities. This provides an opportunity to design therapeutics for disease mechanisms previously considered difficult, if not impossible, to target and enables our scientists to pioneer new approaches to drug discovery.



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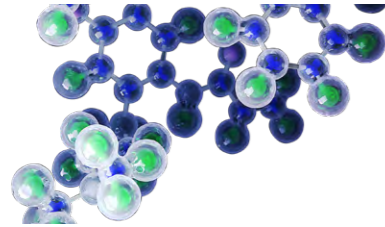
R&D places
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Drug modalities

Pioneering new approaches to drug discovery



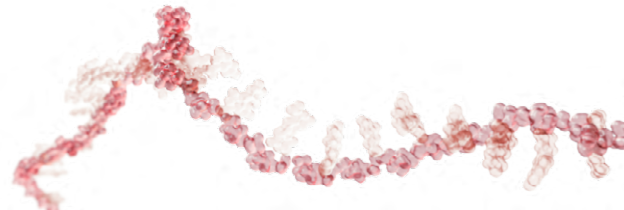
Small molecule

A small molecule is a low molecular weight (less than 900 daltons) organic compound.



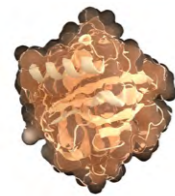
Antibody platforms

Antibodies target proteins with exceptional specificity and can be engineered to: target multiple proteins (bispecific antibodies), combine with linker molecules (antibody drug conjugates), reduce in size (fragment antibody) or modify delivery via mRNA or DNA (in vivo expressed biologics) to improve specificity, potency and targeting.



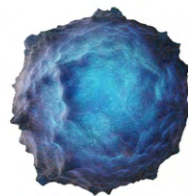
Oligonucleotides

Oligonucleotides are short DNA or RNA molecules that interact with messenger RNA to prevent translation of a targeted gene. Targeted delivery can be achieved through conjugation to a homing ligand.



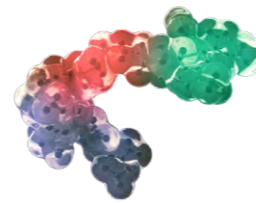
Anticalin® protein

Anticalin® proteins are artificial proteins derived from human lipocalins. They have a diversifiable amino acid sequence that results in four loops. These loops assemble into a cup like structure that can bind both smaller and larger molecules.



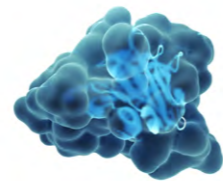
Cell therapy

Novel stem cell-based therapy aimed at regenerating damaged tissue.



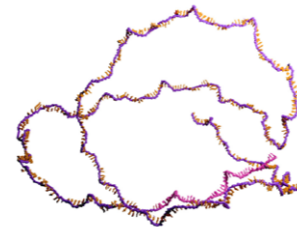
PROTAC

A proteolysis targeting chimera (PROTAC) is a hetero-bifunctional molecule containing two small molecule-binding ligands joined together by a linker.



Therapeutic protein

Proteins consist of one or more chains of amino acids, linked together by peptide bonds. There are 20 naturally occurring amino acids that make up the building blocks of proteins. Antibody-based drugs are an example of a group of therapeutic proteins.



Modified RNA

Modified RNA is a single stranded RNA that conveys genetic information from DNA to the ribosome, where it is translated into protein products.



Bicyclic peptide

Bicyclic peptides are synthetic, highly constrained peptides, typically between 9 and 15 amino acids in size.



CRISPR gene editing

CRISPR/Cas9 exploits a natural bacterial defense mechanism, to precisely edit the genome in somatic gene defects.

Transforming our science

Working in partnership to create the next generation of therapeutics

Ionis Pharmaceuticals – Antisense Technology – broadening our approach across therapy areas

Antisense oligonucleotides (ASO) are designed to bind precisely with specific RNAs thereby modifying the production of proteins potentially associated with disease. One of our molecules targets the mRNA for APOL1 and has shown encouraging results in preclinical models. Several variants of the APOL1 gene evolved in sub-Saharan West Africa providing protection from Trypanosoma infections, but people carrying two copies of these variants have an increased risk for developing chronic kidney disease (CKD)¹. APOL1 knockdown through ASOs is being explored with the aim of being a precision medicine in CKD and, if successful, would provide a novel treatment option for patients with APOL1-mediated CKD.

Transgene – innovative oncolytic virus immunotherapies

Oncolytic viruses are designed to both selectively kill tumour cells and activate the immune system against cancer cells. They have the potential to improve clinical response and survival when used in conjunction with Immuno-Oncology (IO) treatments in our pipeline.

We have a number of ongoing oncolytic virus programmes using different virus platforms across both pre-clinical and clinical stages of development.

Moderna – mRNA therapy passing a major milestone in cardiac regeneration

mRNA is the ‘mediator’ in the process by which genetic information contained in DNA in cells is transferred to make proteins. The beauty of mRNA-based therapy is that it can act locally and transiently, and doesn’t integrate into an individual’s genome. Instead, the aim is to augment the endogenous processes that prevail naturally in the body.

One of our mRNA therapies is designed to stimulate the formation of new blood vessels to protect heart muscle cells (cardiomyocytes) in patients with heart failure or after a heart attack, and other ischaemic vascular diseases. This asset has now entered the clinical phase of development.

Another mRNA therapy in clinical development is being tested in patients with advanced solid tumours. In this case, the therapy is injected directly into a tumour. Localising treatment in this manner may prevent systemic toxicity that may otherwise occur.

1. Dummer PD, Limou S, Rosenberg AZ *et al.* APOL1 kidney disease risk variants – an evolving landscape. *Semin Nephrol.* 2015. 35(3): 222–236.

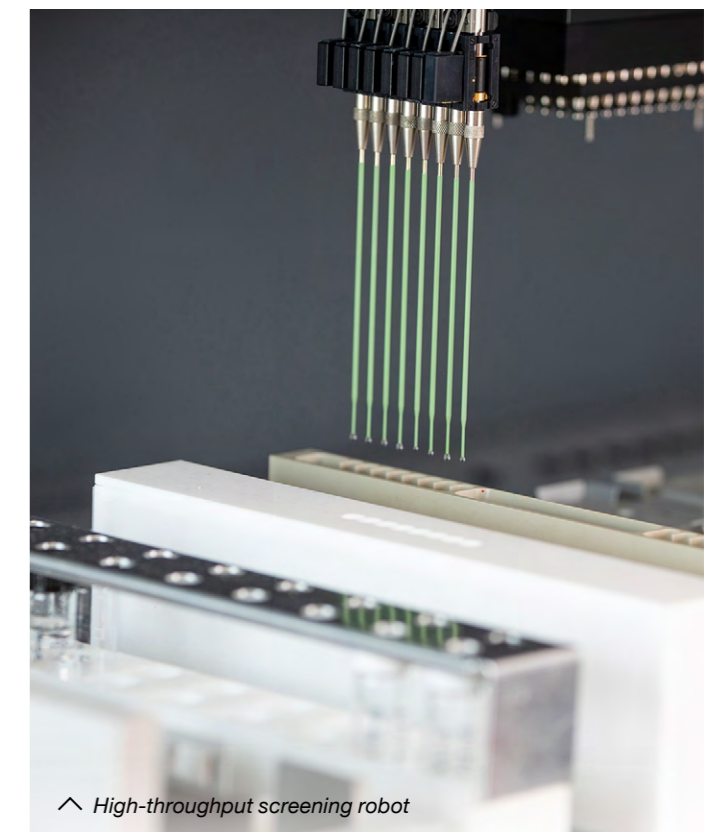
Pieris Pharmaceuticals – moving ahead with Anticalin® protein technology

This is designed to deliver engineered proteins which are significantly smaller than monoclonal antibodies, each tailored to bind with antibody-like potency and selectivity to a drug target of interest. Their small size makes them strong candidates for direct delivery by inhalation to the lung.

The lead molecule is an engineered Anticalin® protein designed to bind to the interleukin-4 receptor alpha and block the action of two key cytokines responsible for lung inflammation in asthma. It is in continuing clinical development.

Procella Therapeutics and the Karolinska Institute in Sweden – advancing regenerative medicine using stem cells

A new stem-cell technology that’s designed to direct the formation of specific cells and tissues using genetic markers. This highly selective approach is focusing on developing new stem-cell based therapies aimed at repairing parts of the heart that have been damaged by a heart attack. Human ventricular progenitor cells are implanted in the injured heart to form new ventricular tissue that becomes vascularised and supported by an extracellular matrix.



High-throughput screening robot



Better predicting clinical success

In our efforts to improve our ability to predict the clinical success of our candidate drug molecules, we are adopting a range of cutting-edge technologies.

Humanised models

Humanised models bridge the gap between animals and humans and are a big step forward compared to the conventional human cell cultures which have been in use for many years. These models provide an environment in which human cells behave more like they would in the body, generating data about toxicity, efficacy and other key effects that are more relevant to patients than previous methods.

- ‘Organ-Chips’ are helping us recreate what happens in full-size tissues and organs. Recently published research in collaboration with the Emulate, Inc. and the Wyss Institute at Harvard University, respectively, demonstrates the ability of the Liver-Chip to model the liver toxicity of eight previously-studied compounds, and the bone marrow chip to effectively replicate drug-induced toxicity responses observed in human patients at clinically relevant doses.
- 3D bioprinting and organoid models are helping us create complex structures for research into kidney and other diseases where pre-clinical to clinical translation is a challenge. Our collaboration with Harvard University created human vascularized renal proximal tubules to study cellular crosstalk and the behaviour of our compounds in the kidney.
- In the development of ‘miniature organs’ to recreate the mechanical and electrical properties in a beating heart, we are working with Novoheart, using their 3-D human ventricular cardiac organoid chamber. This ‘heart-in-a-jar’ technology is designed to reproduce key characteristics of heart failure with preserved ejection fractions.

CRISPR-Cas9 genome editing

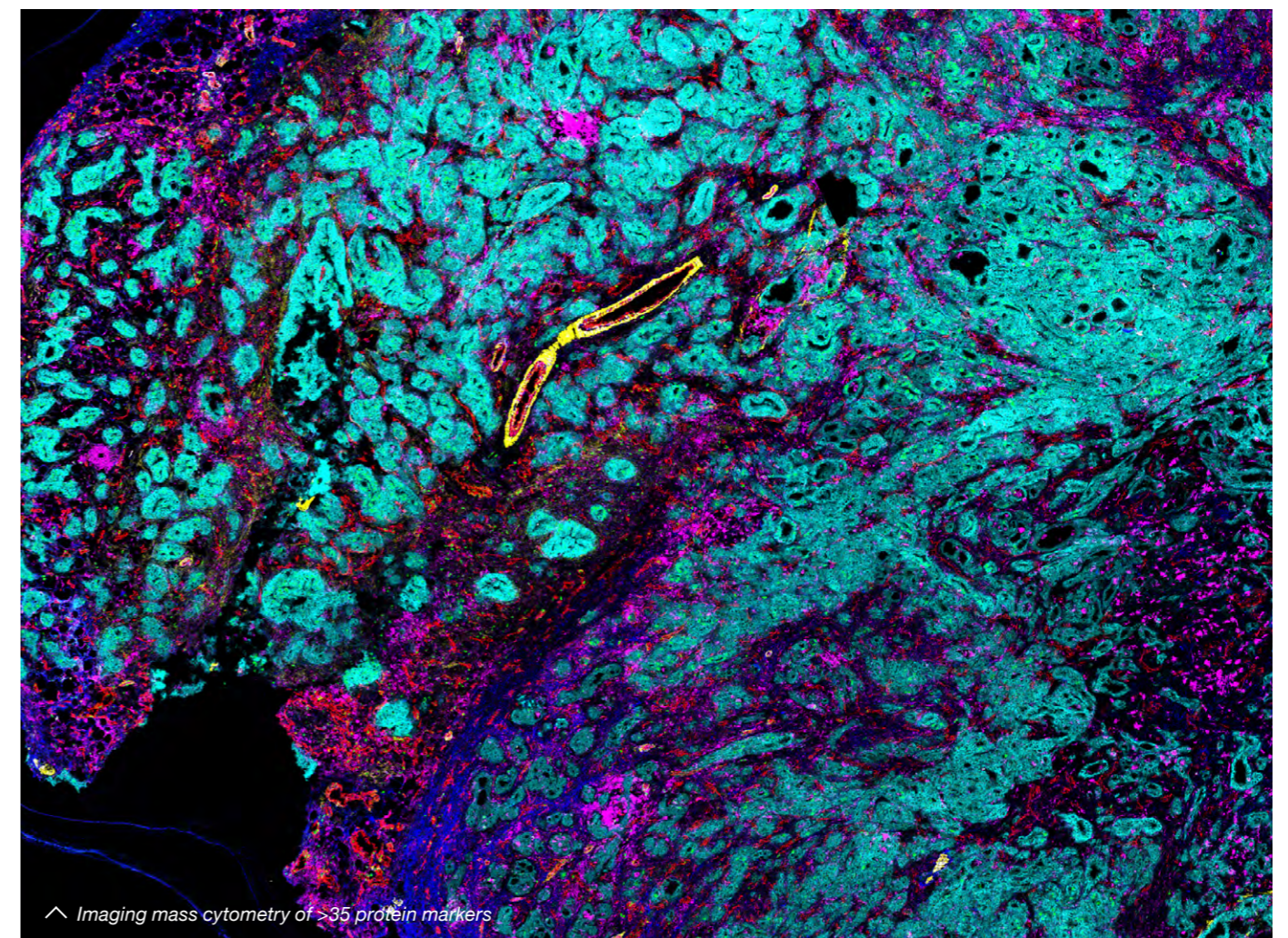
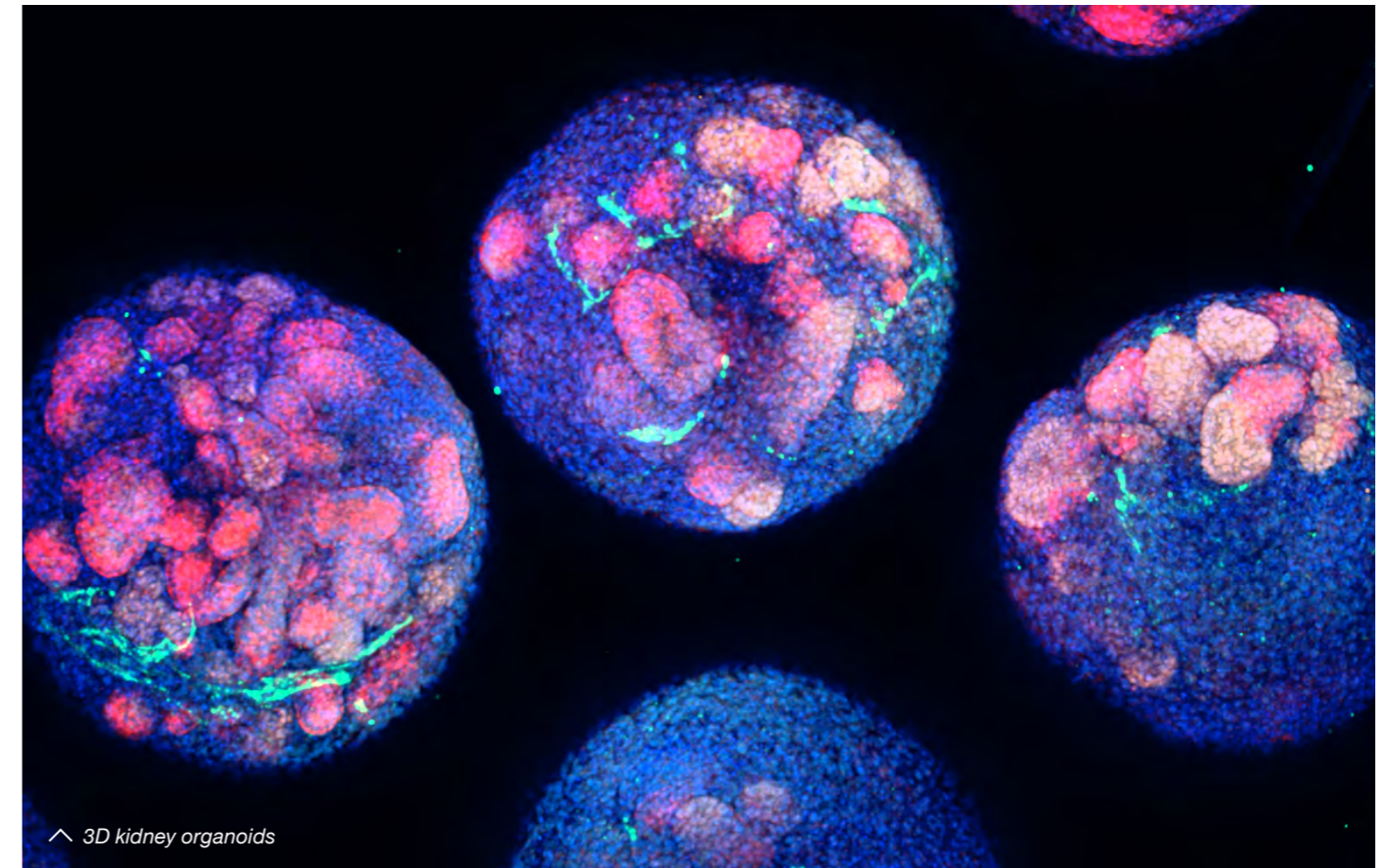
CRISPR is a powerful tool in target selection and validation. It can be used to create precise genetic disease models, often involving the change of a single nucleotide. We have applied CRISPR to create over 120 cellular disease models in which we have deleted or introduced single nucleotide changes to genes to examine the effect of specific genes on disease pathways.

Mass-spectrometry imaging

Mass-spectrometry imaging is helping us capture at a molecular level, the exquisite cellular interaction that can both define a disease, but also monitor for effective treatment. By retaining the spatial complexity in a tissue sample, we can monitor modulation of biomarkers in tissue in response to drug treatment, while simultaneously also quantifying drug biodistribution and immune cell populations. These technologies can give us a holistic view of our complex preclinical models that inform pre-clinical decision making.

Patient-derived xenograft models

Patient-derived xenograft models are helping us recreate the complexity and heterogeneity of a tumour for studying late-stage cancers, and for modelling mechanisms by which tumours become resistant to current therapies. With the University of Colorado in the US, we are continuing to show how different patient-derived xenograft models can help define new combination therapies in oncology.



Model-informed drug development

Quantitative pharmacology uses advanced analytical modelling to generate new and vital insights on drug efficacy and safety across the entire drug discovery and development continuum. Through modelling, simulation, systems pharmacology and advanced bio-analytics, we are interrogating how drug candidates interact within the human body to help inform decisions about the optimal balance between efficacy and safety. Working collaboratively with partners across AstraZeneca and beyond, we provide unique insights and expertise to ensure we deliver the right dose to the right patients.

With an extensive skill-base in clinical pharmacology, pharmacometrics, statistics and biometrics, our collective of expert scientists are pioneering new ways to extend our predictive modelling capabilities. By combining the latest computational technologies with the diverse expertise of our people, we deliver clinical programmes with greater speed, quality and efficiency.

Using extensive clinical pharmacology data, our teams are designing drug development models that can simulate virtual trials that:

- Examine how the benefit-risk profile of a potential drug candidate is impacted by real world variables such as age, sex or comorbidities.
- Offer insight into how a potential drug candidate may perform against current treatments or in combination with other therapies.
- Predict outcomes for efficacy and safety across different patient profiles, helping expand the reach of our drug candidates to additional patient populations who may benefit.

By providing these approaches, Quantitative Pharmacology is an important complement to the traditional toxicology and animal sciences methods in drug safety studies and is key to helping better predict and deliver clinical success for AstraZeneca and the patients we serve.



Minute pieces of tumour DNA circulating in the bloodstream.

Circulating tumour DNA (ctDNA) in Oncology

Circulating tumour DNA (ctDNA) are small DNA fragments that often leak from cancer cells into a patient's bloodstream. The detection and analysis of ctDNA may provide valuable insights about a patient's prognosis or information on how well a treatment is working. Researchers are investigating whether ctDNA measurements can identify patients with minimal residual disease (MRD) who may be at higher risk for disease recurrence post-surgery or post-adjuvant therapy.

Identifying MRD may enable physicians to intervene earlier and to offer personalised, effective treatments that could increase survival and improve quality of life. We are collaborating with diagnostics experts like ArcherDX to generate highly sensitive, personalised ctDNA assays to test for MRD, which has the potential to inform patient prognosis and to tailor individualised treatment options.





Pioneering new approaches to engagement in the clinic and beyond

Digital technologies are creating never-seen-before opportunities to improve clinical practice and engagement both in the clinic and beyond, helping to increase efficiencies and effectiveness for clinicians and support better experiences for patients.

In a typical year, we conduct over 240 global clinical trials, involving more than 123,000 patients, in around 60 countries. Digital is enabling us to improve their design and reduce set-up time. Electronic health records will help improve delivery, and more accurately forecasting drug supplies will avoid waste and delays. Trials will be more patient-centric, the patient burden lightened, and the value of the information trials give us increased, helping us make faster and more effective decisions.

Digital is helping patients optimise medication use, connect with medical staff, and manage or prevent adverse events during trials. Invasive monitoring is being replaced with digital – finger prick glucose monitoring, for example, with patches giving continuous readings. It is also helping us improve disease understanding and patient outcomes, and in early trials, we are exploring new digital markers, for instance, determining the relevance of Fractional Exhaled Nitrous Oxide (FeNO) as a biomarker in assessing lung inflammation.

As our digital capabilities grow, we are able to explore how we can help patients prevent, manage or treat their condition with evidence based, digital therapeutic solutions. For instance, with Voluntas and the National Cancer Institute, we are developing a digital therapeutic for women being treated for recurrent platinum-sensitive high-grade ovarian cancer. Currently in clinical trials, this aims to support patients through tolerability and management of adverse effects – recently winning the Prix Galien award for best patient engagement technology.



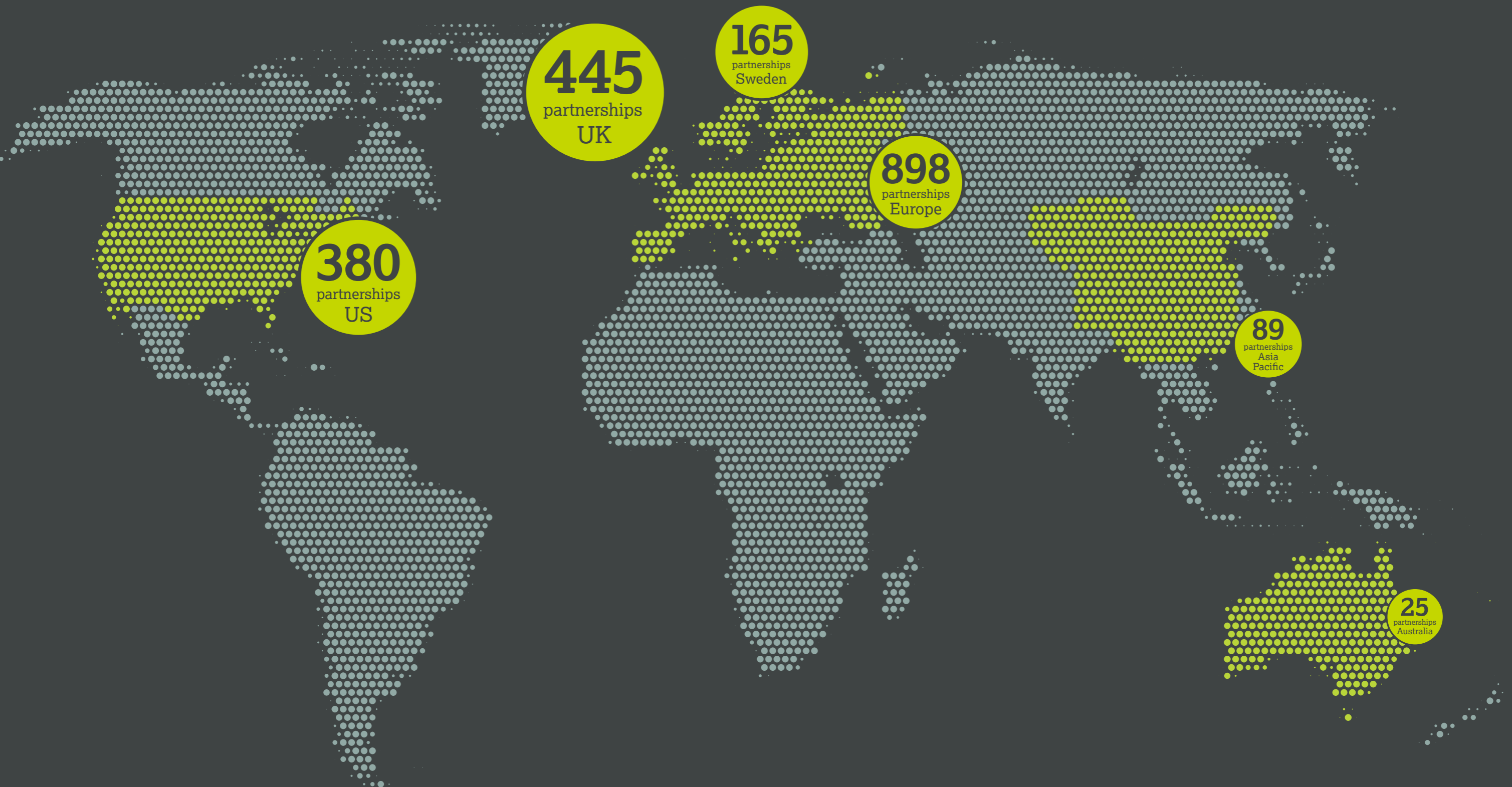
Keeping doors and minds open

We know that however innovative our science is, however effective our medicines and delivery, to achieve all we want to achieve, we cannot do it alone.

To address all the issues facing healthcare and achieve the scientific breakthroughs we aspire to, we need to work together, collaborating among ourselves and with others, bringing the best talent to bear on the toughest problems.

As a business, our teams are leading the way in creating open research environments that go beyond the usual collaborative models, with academia, biotech companies, industry peers, healthcare systems and governments.

We have over 1400 active partnerships and aim to lead the industry in partnership building over the coming years, believing it to be a powerful source of transformational potential.



Our R&D culture

Two organisations.
One Aim

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not quantity

Transforming
our science

Keeping doors
and minds open

R&D places
and people

Making our
science sustainable

Led by science.
Driven by patients

Working side-by-side with academic institutions

Our scientists work in collaboration with others in dedicated laboratories in universities and research institutions, aiming to generate high impact science to support possible future advances in life changing medicines.

These institutions include the AI Innovation Centre and the Karolinska Institute's Cardio Metabolic Centre in Sweden; the Max Planck Chemical Genomics Centre III in Germany, and in the UK, The Francis Crick Institute, the Functional Genomics Centre at the Milner Institute, the Antibody Alliance Laboratory with Cancer Research UK, the Medical Research Council Laboratory for Molecular Biology (MRC LMB), the Respiratory Hub at Imperial College and the University of Cambridge.

In addition, we have established a collaborative research initiative that brings together seven of the world's foremost oncology medical centres, each with strong translational research capabilities, to expedite research in some of the hardest-to-treat cancers. The partner institutions include: Institut Gustav Roussy (France), Johns Hopkins Medicine and Memorial Sloan Kettering Cancer Center (US), Universidad de Navarra and Vall D' Hebron Institute of Oncology (Spain), Peter MacCallum Cancer Centre (Australia) and Princess Margaret Cancer Center (Canada).



^ Bioscientists in our labs in Wuxi, China

Open innovation

Our open innovation programme is designed to offer a permeable research environment where scientists both inside and outside of AstraZeneca can share their ideas and collaborate on projects.

Since the programme was launched in 2014, we have reviewed more than 1000 proposals from scientists in 40 countries across six continents. Our Open Innovation collaborators have been awarded \$75 million in grant funding to support their research projects using our assets, and our Open Innovation portfolio now features 35 ongoing or planned clinical trials and more than 425 pre-clinical studies.

Our Open Innovation portal makes it easy for external scientists to access all the collaborative opportunities we offer to help find ways to advance medical science together:



Clinical compound bank

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



Pre-clinical toolbox

A preclinical toolbox of compounds with strong pharmacological properties and defined mechanisms of action.



Target innovation

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



Challenges

Research and development challenges to crowd source novel, innovative solutions.



Data library

A data library module offers access to preclinical data sets.



Drug delivery

Opportunities to access drug delivery, formulation and analytical technologies.



R&D places and people

AstraZeneca is profoundly committed to its purpose of pushing the boundaries of science to deliver life changing medicines and we have built our business around it.

We have three strategic R&D centres in Cambridge in the UK (which is also our Global HQ); Gaithersburg, Maryland, in the greater Washington region in the US, and Gothenburg in Sweden. We also have an active R&D presence in 40 other countries spanning the globe.

We have further integrated our R&D teams, accelerated our decision making processes, and are using our unique scientific capabilities to deliver what we believe to be one of the most productive pipelines in the industry.

Of our 68,000 employees, more than 10,000 work exclusively in R&D and in 2019, our scientists published a total of 870 manuscripts, with 111 in high impact peer-review journals, compared to 1 in 2010.

Our business and scientific culture is diverse, inclusive and collaborative, and we do everything in our power to enable all of our people to be the best they can be.

Strategic science centres

Cambridge

Our new facility at the Cambridge Biomedical Campus (CBC) will become AstraZeneca's largest research and development centre in the UK, with more than 2000 people working across all our therapy areas, drug discovery platforms, development and commercialisation.

The power of our physical proximity to our neighbours in academia, healthcare and industry creates a porous environment where ideas and talent can be shared to drive innovation. Already the scale of our collaboration with others in the city is considerable. We have well over 200 partnerships as part of the Cambridge ecosystem; hundreds more in the wider UK life sciences cluster.



^ New R&D centre and AstraZeneca headquarters in Cambridge, UK



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∨ R&D centre in Gaithersburg



∨ R&D centre in Gothenburg



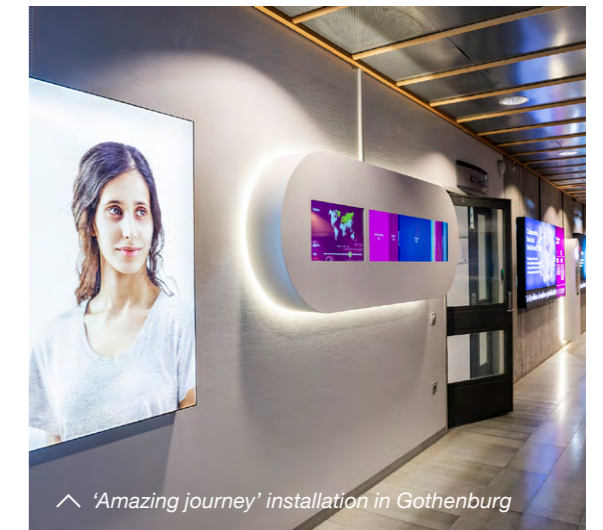
∧ Celebrating International Women's Day in Gaithersburg



∧ Team interaction spaces in Gaithersburg



∧ CoffeeLab meeting space in Gothenburg



∧ 'Amazing journey' installation in Gothenburg

Gaithersburg

A unique, innovative and inclusive modern campus, just a short drive away from Washington, DC, our Gaithersburg facility is home to a diverse community of some 3,500 people, with the capacity to discover, develop, manufacture, and commercialise life changing medicines – all on one site.

With a team of world-renowned scientists, cutting-edge technology, and a collaborative, interactive and cross-functional scientific culture, it's a great place to work and an exciting place to be. Our outstanding facilities and amenities promote wellness and a positive work-life balance, helping us attract and retain the best talent, while contributing to our business's values-led and sustainable approach to R&D.

Gothenburg

With more than 2,400 employees from 50 countries, our vibrant Gothenburg site helps support the entire life-cycle of AstraZeneca medicines, from drug discovery and clinical trials, through to global commercialisation and product maintenance. In 2017, we launched Lab4Life, creating an open and truly shared research environment that goes beyond the usual laboratory model. By breaking down traditional lab walls, automating processes and driving state-of-the-art IT, we are creating novel ways of working to speed up delivery of new medicines.

Looking to the future, Gothenburg has initiated the creation of a new, global cluster for health and life sciences, as part of the GoCo Health Innovation City project, which includes the Gothenburg BioVentureHub. There are currently more than 30 external companies and one academic group co-locating with AstraZeneca at the heart of the Gothenburg site. By facilitating interactions between drug, device, diagnostics and digital health companies, we are creating a dynamic, creative and fertile environment for helping unlock the power of what science can do.

Inspiring great scientists

Clearly, our ambition to take and sustain scientific leadership rests on our ability to attract and retain the best scientists. And nowhere is our determination to do this more evident than in the way we recruit, develop and inspire our people.

It's vital that we continue to attract the brightest minds, the best talent and the boldest innovators. People who share our passion for science and our belief in its potential to re-define the possible.

In return, we offer a working environment that truly reflects our ambition to push the boundaries of science. A place that empowers and inspires. Where curiosity, innovation and collaboration flourish; where drive and determination are rewarded, and where great science comes alive.

We believe that the best science almost always comes from teams with different backgrounds, different skills and experiences, and as a business, we are committed to maintaining a culture that is not only diverse and inclusive, but genuinely inspirational.

✓ AstraZeneca at the Pride in London event



**Our people impress and inspire us.
Our values define and guide us.**

- We follow the science
- We put patients first
- We play to win
- We do the right thing
- We are entrepreneurial





^ Scientist in our labs in Macclesfield, UK

Women as leaders

Our Women as Leaders programme supports our aim of increasing the number of female colleagues in senior scientific roles, and brings women together to discuss issues like career progression and personal development.

Since 2012, we have increased the number of women in senior roles from 25% to 44.6%. And in January 2019, AstraZeneca was the only major pharmaceutical company included in the Bloomberg Gender-Equality Index, which distinguishes companies committed to transparency in gender reporting and advancing gender equality.

AZPlus

Gender equality is also supported by AZplus, our employee resource group which aims to empower LGBTQIA+ colleagues to reach their full potential. With AZPride and the #thisisAZ campaign, AZplus has promoted inclusivity both internally and externally to encourage the recruitment of a diverse talent pipeline.

Its voluntary work led the launch of a groundbreaking cross-sector initiative, the Proud Science Alliance (PSA), which promotes LGBTQIA+ inclusion in life science and healthcare through a new website and social media channels, reaching thousands of scientists globally.

Development assignments

Providing our people with ready opportunities for development is high on our agenda and the majority of this comes from direct, on-the-job experience. From our Development Marketplace to cross-team secondments and shadowing opportunities, our programmes set out to make sure that we can continue developing the skills and capabilities to equip everyone in R&D to be the best they can be. And throughout 2019, we saw more than 80 colleagues take up assignments outside their core role to broaden their learning and experience.



^ Protein engineer in our labs in Cambridge, UK



^ Cell biologists in our labs in Gothenburg, Sweden

Chief scientist programme

As part of our drive to continue creating great science, we are keen to work with the best scientists, both in and outside of the pharmaceutical industry. To make sure that we are able to attract top science talent from academia, we have developed our flexible and versatile Chief Scientist Programme.

By tailoring individual arrangements to enable scientists to work with AstraZeneca R&D full time, part time, or on assignment from university, we promote a permeable research environment, designed to meet the needs of both individuals and institutions.

Being flexible in our approach enables scientists of the highest calibre to stay connected to their research and their universities, and work flexibly between commitments. This empowers them and us, enabling us to connect with the best scientific minds to work together in accelerating the discovery and development of life changing new medicines.

Early talent programmes

We have a portfolio of high-quality early career programmes supporting a diverse range of scientific talent. Every year, we support more than 500 young scientists – including apprentices, undergraduate and graduate placements, PhDs and post-doctoral scientists.

Postdoctoral programme

Our postdoctoral programme brings together motivated and innovative postdoctoral scientists who have a passion for ideas and a real desire to make a difference through an academic-style postdoctoral position in a global pharmaceutical setting.

The two to three-year programme funds postdoctoral projects originating with AstraZeneca scientists and clinicians from across our many different scientific disciplines and areas of research. These projects address fundamental scientific challenges that underpin drug discovery and development.

In addition, each postdoctoral scientist receives a tailored training and development programme, encompassing key skills such as presentation delivery and publication writing. So it's a very valuable and rounded experience.

Graduate programme

Our graduate programme offers graduates the opportunity to complete three different placements in two years across R&D, focusing on delivering breadth and depth of experience. Graduates are supported in each placement by a line manager and by a mentor who remains with them throughout the programme, providing career counselling and guidance.

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

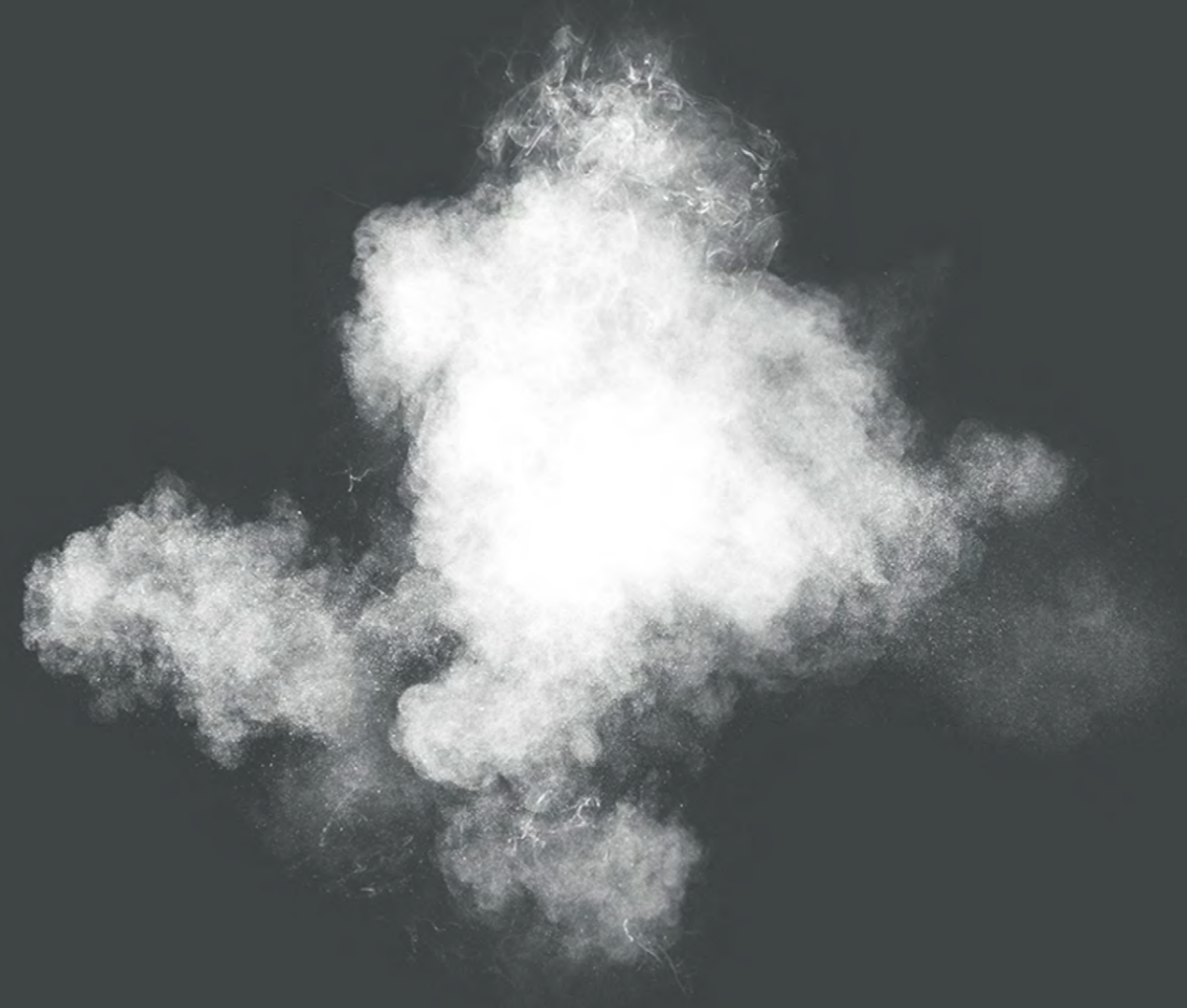
Making our science sustainable

We are a scientifically driven business with a strong global presence and as such, believe that we have a duty of care to help improve people's health and do as much as we can to contribute to the health of the planet.

Our approach to sustainability is built around three pillars: access to healthcare, environmental protection, and ethics and transparency.

Environmental protection

We set science-based emissions reduction targets to contribute to the global fight against climate change and the Science-Based Targets Initiative confirm that our Scope 1 and 2 targets are consistent with reductions required to keep global temperature increase below 1.5°C, the most ambitious goal of the Paris Agreement, with our Scope 3 targets in line with current best practice.



Environmental Protection

We appreciate the interconnection between our business and the wider world and strive to find innovative ways to make the most efficient use of resources and help protect our environment – aiming to manage our environmental impact across all our activities and products.

- For instance, we work in collaboration with the not-for-profit organisation, My Green Lab, to run a globally organised, locally delivered initiative, called Green Labs. Its aim is to improve the sustainability of our research labs, starting with surveys among people working in the lab environment to benchmark our current sustainability efforts. The initial phase began in 2019, with nearly 900 scientists across six different sites.
- We are also pioneering new approaches to reduce our dependence on natural resources and minimise the environmental impact of our products. Our Lab Plastics Recycling initiatives in Cambridge, for example, will save over 4.5 tonnes of plastic from incineration or landfill each year.



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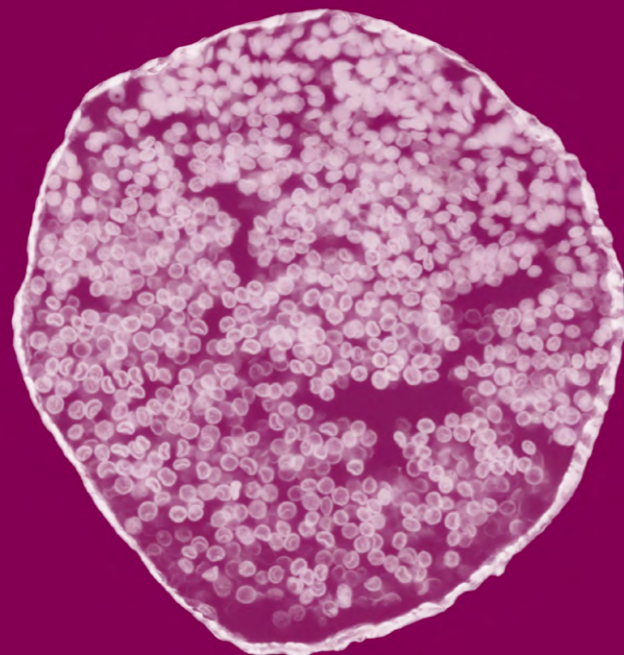
R&D places
and people

Making our
science sustainable

Led by science.
Driven by patients

Access to healthcare

Patients and healthcare professionals have a deeper understanding of the connections between products, waste, and pollution. We have created an innovative Green Chemistry tool to facilitate solvent selection, allowing our scientists to consider environmental properties alongside physical properties and regulatory needs.



Access to healthcare

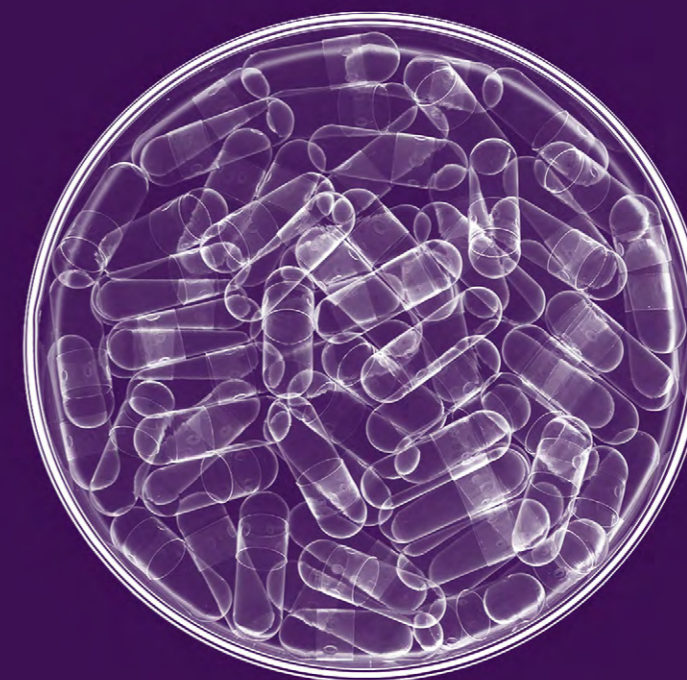
We are committed to improving access to healthcare by removing barriers, addressing the burden of disease across R&D, and via our ambition to make our medicines more accessible and affordable, and enable improved disease prevention and treatment.

- By maximising the value of health-related data we are moving towards accelerating our clinical trials and the delivery of potential new medicines. For example, through the adoption of Electronic Health Records (EHRs) we can access a vast and highly relevant data source with huge potential to refine or replace many clinical trial processes including patient identification, selection, trial conduct, and capture of data.
- Our ground-breaking DISCOVER CKD study uses real-world data from more than 100,000 chronic kidney disease patients across six countries to better understand the patient journey. This three-year study will analyse data which includes treatment patterns, quality of life and diet that are not captured using traditional tools. The study will help us identify gaps we may one day address with our emerging portfolio of renal therapies, shaping the future of care and reaching a broader number of patients.

- Another example of helping increase access to healthcare is [Emerging Markets Health Innovation Hubs](#) (EMHIH), an integrated, open science ecosystems, operating in partnership with academia, entrepreneurs, industry, medical professionals, governmental partners and venture capitalists. EMHIH are designed to improve access to resources and technology, improve capacity for local R&D, and boost AstraZeneca's capabilities to address local needs. The first Hub in Emerging Markets opened in Russia in July 2018, followed by Hubs in Brazil, Argentina, India, Singapore and the Gulf Cooperation Council countries, as well as mainland China, Taiwan, and Hong Kong. The Hubs have already produced tangible results, such as key cross-sector partnerships, and innovative new products, solutions and research opportunities. The connected ecosystems have also accelerated innovation by collaborating with local start-ups, complemented by a partnership with Slush - a global community of start-ups, entrepreneurs and investors.

Clinical trial transparency

The clinical trial phase is essential in the development of new medicines. As an ethical and transparent company, we apply our global policies and standards wherever trials take place and require all our sponsored trials to include patient engagement practices.



Ethics and transparency

We are building trust in our business and our science by continuing to pursue ethical practices and by bringing a high level of integrity to everything we do.

- Our research sites and bio-hubs are inclusive and dynamic centres for innovation, designed to enable science to thrive. A good example of this is the new, global cluster for health and life science that we created in Gothenburg as part of the GoCo Health Innovation City project (see 'R&D places and people' above), which includes our pioneering BioVentureHub. Numerous different companies and an academic group have joined us on the site, offering opportunities for cross-fertilising disciplines and ideas, and fostering progressive and holistic ways of working.
- A critical ethical issue for us is animal welfare, first because caring for animals' welfare is the right thing to do and second because good science depends on it. We have signed the Concordat on Openness on Animal Research in the UK, and apply the principles of openness and transparency globally. And we also follow the '3Rs' – Replacement, Reduction, and Refinement – meaning that, wherever possible, we replace the use of animals with non-animal alternatives; reduce the number of animals we use by designing animal studies optimally, and refine conditions for animals to maximise their welfare.

- We promote life-long learning and development across our employees, ensuring our workforce is equipped for the future. Our multi-year, multi-country investment in STEM (Science, Technology, Engineering and Mathematics) outreach programmes aims to inspire the next generation of scientist leaders and promote an understanding of the value and importance of global R&D towards creating a better, more sustainable society.



Some facts about R&D sustainability

Approximately

90%

of our pipeline has a precision medicine approach

We have the

largest R&D pipeline

for diseases in the scope of the 2018 Access to Medicine Index

61%

of our total electricity use is sourced or generated from renewable sources

We have achieved an

8%

reduction in our water use since 2015

93%

of active pharmaceutical ingredient discharges from our suppliers has been demonstrated as safe

Our Open Innovation programme has over

250,000

compounds available from our screening library

As well as iDREAM hubs in Russia, Taiwan and Brazil, we now have them in

China, Argentina, India and Hong Kong,

all designed to help improve the local capacity for R&D through collaboration



^ Solar panels on the roof of AstraZeneca Macclesfield



^ Electric car chargers at AstraZeneca Gothenburg



^ Our corporate beehive at AstraZeneca Gothenburg



Our R&D culture

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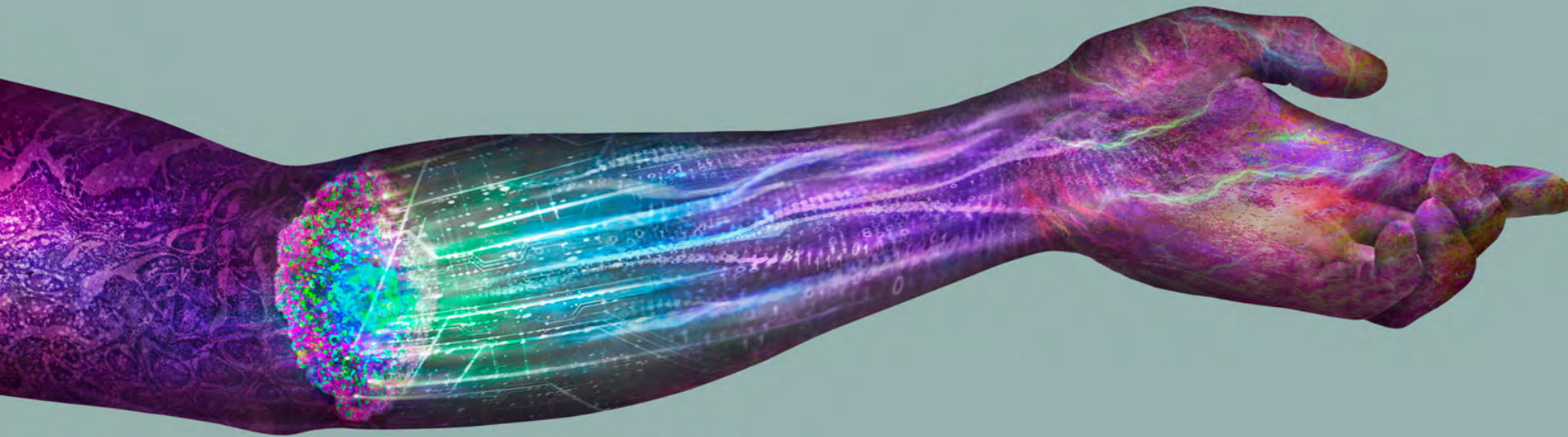
R&D places and people

Making our science sustainable

Led by science. Driven by patients.

Predicting clinical success

Humanised preclinical models are bridging the gap between animals and humans, from traditional cell cultures. AstraZeneca is adopting a range of cutting edge-technologies combined with advanced imaging to improve our ability to predict the clinical effectiveness of our candidate drug molecules.



Led by science. Driven by patients

The pace of change in healthcare is moving more rapidly than ever before, as patient populations and expectations rise, science advances, and data and technology dramatically accelerate progress.

We have always put patients first and are creating a patient-centric culture in every aspect of our work, from discovery to clinical trials, treatment delivery, and beyond. This is helping us achieve our aim of getting the right medicines to the right patients, faster than ever before.

We are transforming our business by using data, digital technologies and AI to increase the probability of success, and to discover new medicines more efficiently and deliver them more effectively.

At AstraZeneca's R&D, we will continue to help build our business's reputation for scientific leadership by inspiring people with curious minds, harnessing data and technology, working seamlessly and inclusively, and always learning from patients.

This in turn is how we'll attract and retain the best people and partners, to help us deliver life changing medicines. Building a diverse, inclusive, listening and inspiring culture, and making a real and sustainable difference to patients, healthcare and our wider society.

Our ambition is to transform the lives of patients with improved outcomes and a better quality of life, through more effective treatment and prevention, ultimately working toward a cure for some of the world's most complex diseases.



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