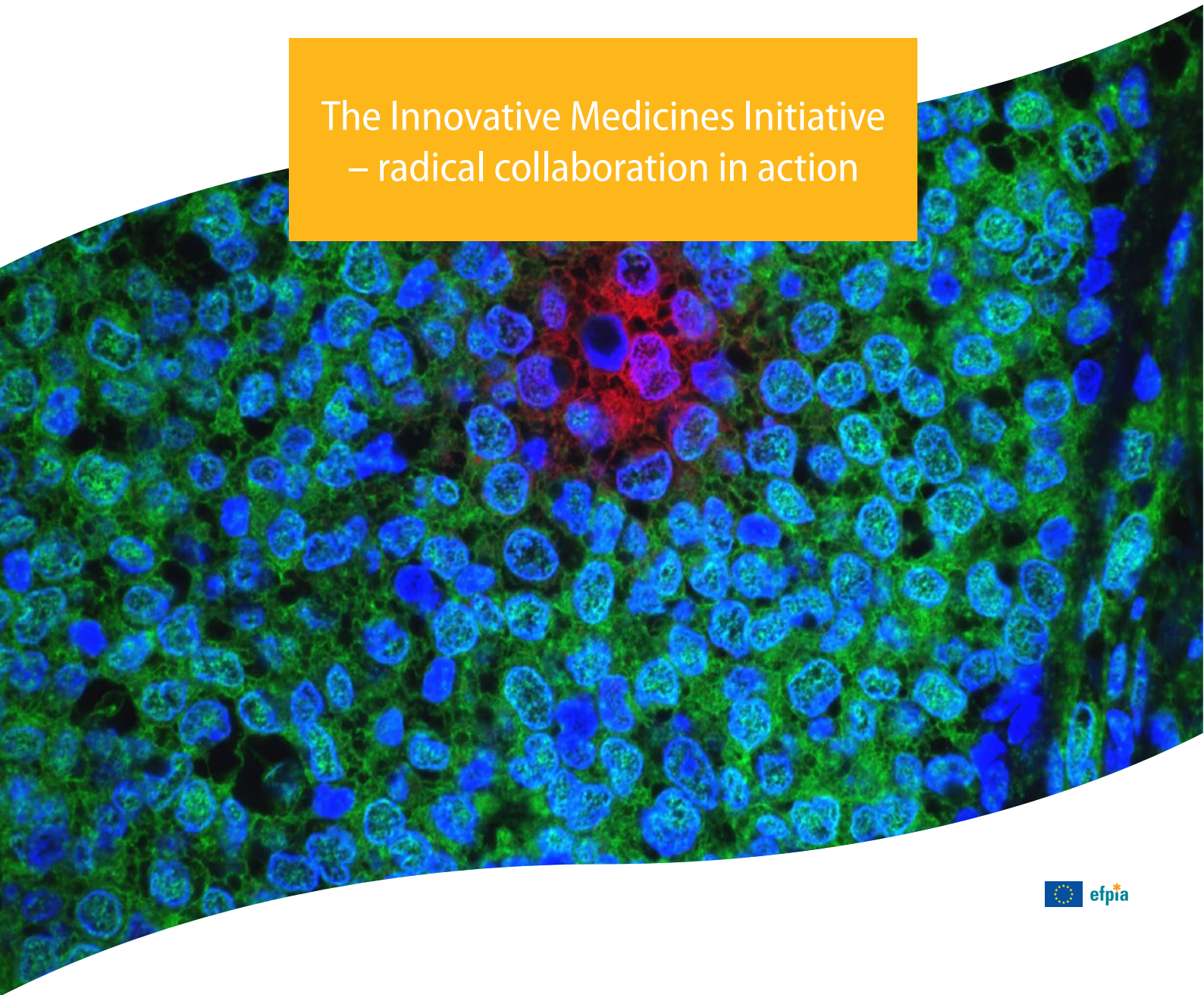
innovative medicines initiative

The Innovative Medicines Initiative – radical collaboration in action



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This brochure contains a snapshot of the latest IMI project achievements, many of which are recorded in the IMI Annual Activity Report (AAR) 2019. The AAR 2019 is online at **bit.ly/IMIAAR2019**.

More project results can be found via the 'success stories' page of our website (**bit.ly/IMIsuccesses**) and in previous editions of our Annual Activity Reports (online at **bit.ly/2ysOhVK**).

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FOREWORD

As we are now in the final year of the Horizon 2020 programme, it is interesting to reflect on Europe's position regarding its innovation ecosystem. This ecosystem has been criticised as being fragmented, yet if we look at the European Joint Undertakings, we can be proud of what has been achieved in a relatively short period of time.

The public-private partnership (PPP) networks in healthcare, advanced rail systems, new generation aircraft and air traffic control systems, electronic systems, clean energy and so on, are world class and have been developed at a scale that is the envy of the world. These PPP networks are challenging to create, develop and maintain, and indeed the model has not been replicated on this scale elsewhere. Why is that? In my view, it's because of the EU, and the European culture of collaboration which is by nature cross border, cross institutional and cross disciplinary.

Thus in the Innovative Medicines Initiative (IMI), we have created a neutral platform where the relevant actors can collaborate, co-create and accelerate the knowledge needed to advance innovation, whether that be in infectious diseases, dementia, diabetes, cancer, etc. Today, IMI is a true partnering machine and we are truly at the cutting edge of 'radical collaboration'.

No wonder therefore the IMI project portfolio is full of high-risk projects. Europe needs these PPPs in order to share risk and in turn, incentivise investment in the most scientifically complex areas – which are also incredibly important for public health and thus for the European citizen. The significance of our projects has been amply demonstrated during the COVID-19 pandemic, as many IMI projects have quickly adapted their results to contribute to the fight against the disease. The contributions include knowledge, tools and expertise, and while some come from projects in the infectious disease field, projects working in other areas, such as data management and Alzheimer's disease, are also stepping up to the plate.

In 2019, we saw some remarkable achievements directly attributable to IMI projects. A vaccine for Ebola has now been given authorisation to be used by the European Commission, and several rapid diagnostic kits are in field trials in the Democratic Republic of Congo (DRC) and neighbouring countries. A new anti-microbial from our ENABLE project has entered into clinical assessment. And, crucially, IMI's outbreak preparedness project ZAPI delivered results on coronaviruses that are now proving valuable in the quest to develop vaccines and treatments for COVID-19.

As we move towards the end of the IMI2 programme, the added value of public-private partnerships in key areas for our societies and the economy remains as clear as ever.

Pierre Meulien
IMI Executive Director

INTRODUCING IMI

What is IMI?

The Innovative Medicines Initiative (IMI) was set up in 2008 as a public-private partnership (PPP) between the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations).

At IMI, our goal is to improve the medicines development process and make it more efficient, and to ensure that patients will have faster access to better and safer medicines.

We do this by funding collaborative projects that bring together all key groups involved in life science research, including universities, large pharmaceutical companies, small and medium-sized enterprises (SMEs), patient groups, medicines regulators, and companies in other health-related sectors, such as diagnostics, imaging, and IT.

By bringing these diverse groups together around one table, our projects are able to accelerate the development of innovative solutions to the most pressing medical burdens of our time, including antimicrobial resistance, dementia, diabetes and cancer. The relationships forged in our projects often last beyond the lifetime of the project and are helping to transform the wider medical research ecosystem, making it more open and collaborative.

Over a decade in, we are globally recognised as a pioneer of open innovation and an attractive model for successful PPPs in research.

How we work – a partnering machine

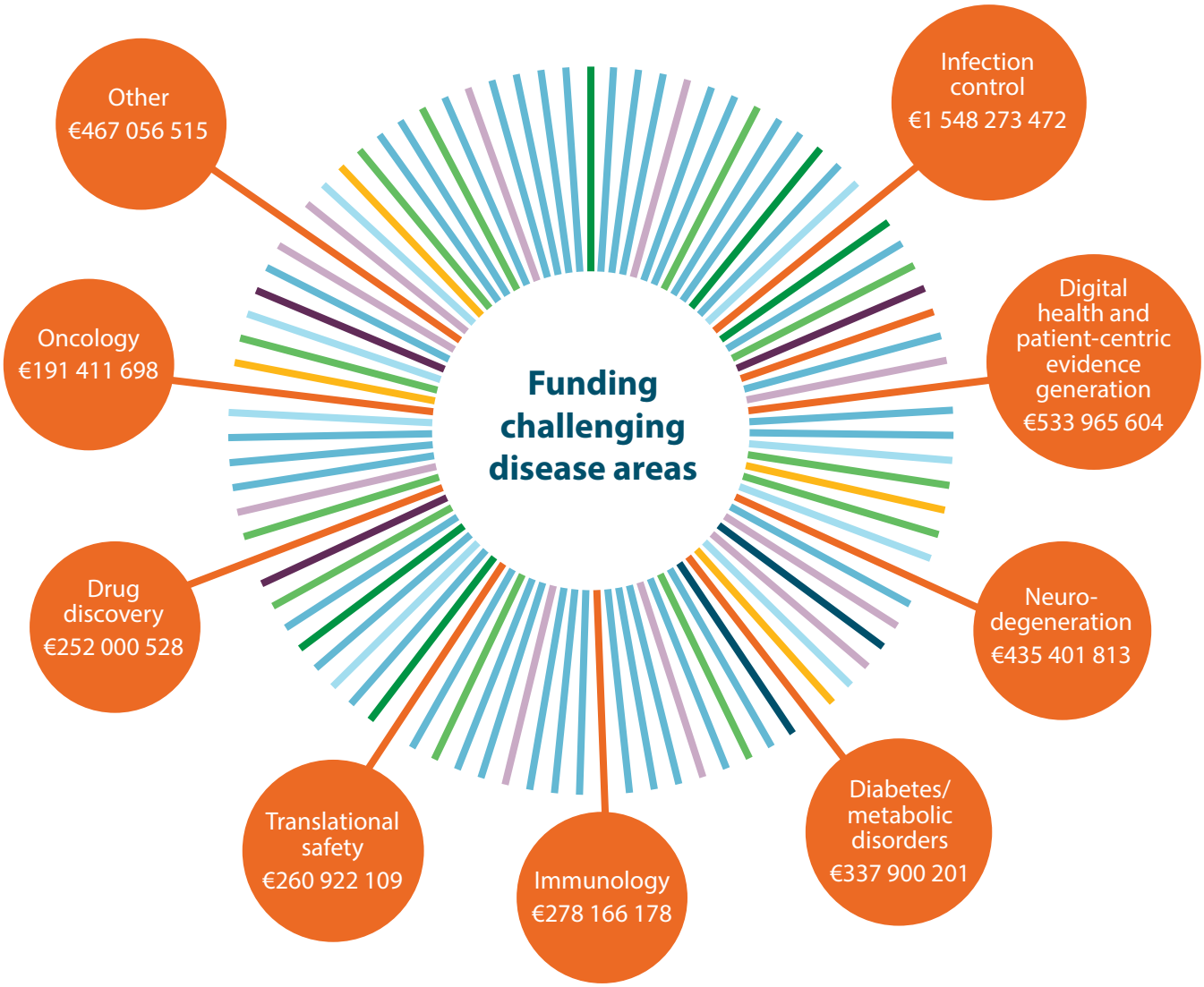
Our projects are born out of open, competitive Calls for proposals, through which consortia of researchers from diverse sectors can apply to be part of new collaborative projects and receive

funding. The proposals are evaluated by independent experts, who ensure that we get the very best teams for our projects.

Each Call for proposals usually includes a number of topics. The topics are based on our top level objectives (as set out in the legislation creating the IMI programmes) and our multi-annual Strategic Research Agenda (SRA). The European Commission, the IMI States Representatives Group (SRG) and the IMI Scientific Committee provide their input on the proposed topics, and the Calls also have to be signed off by our Governing Board.

What areas do we address?

IMI projects cover the full spectrum of drug discovery and development, from understanding the underlying causes of disease and identifying potential drugs and drug targets, through the creation of tools to identify toxicity or efficacy issues early in drug development, to clinical trial design and monitoring the benefits and risks of medicines and vaccines once they are in use. Many of the tools developed by our projects contribute to the '3Rs', i.e. replacing, reducing and refining the use of animals in research. We also have a growing number of projects grappling with the use of big data in research. The infographic below shows the breakdown of our funding by area.



THE IMI FUNDING MODEL – A TRUE PUBLIC-PRIVATE PARTNERSHIP

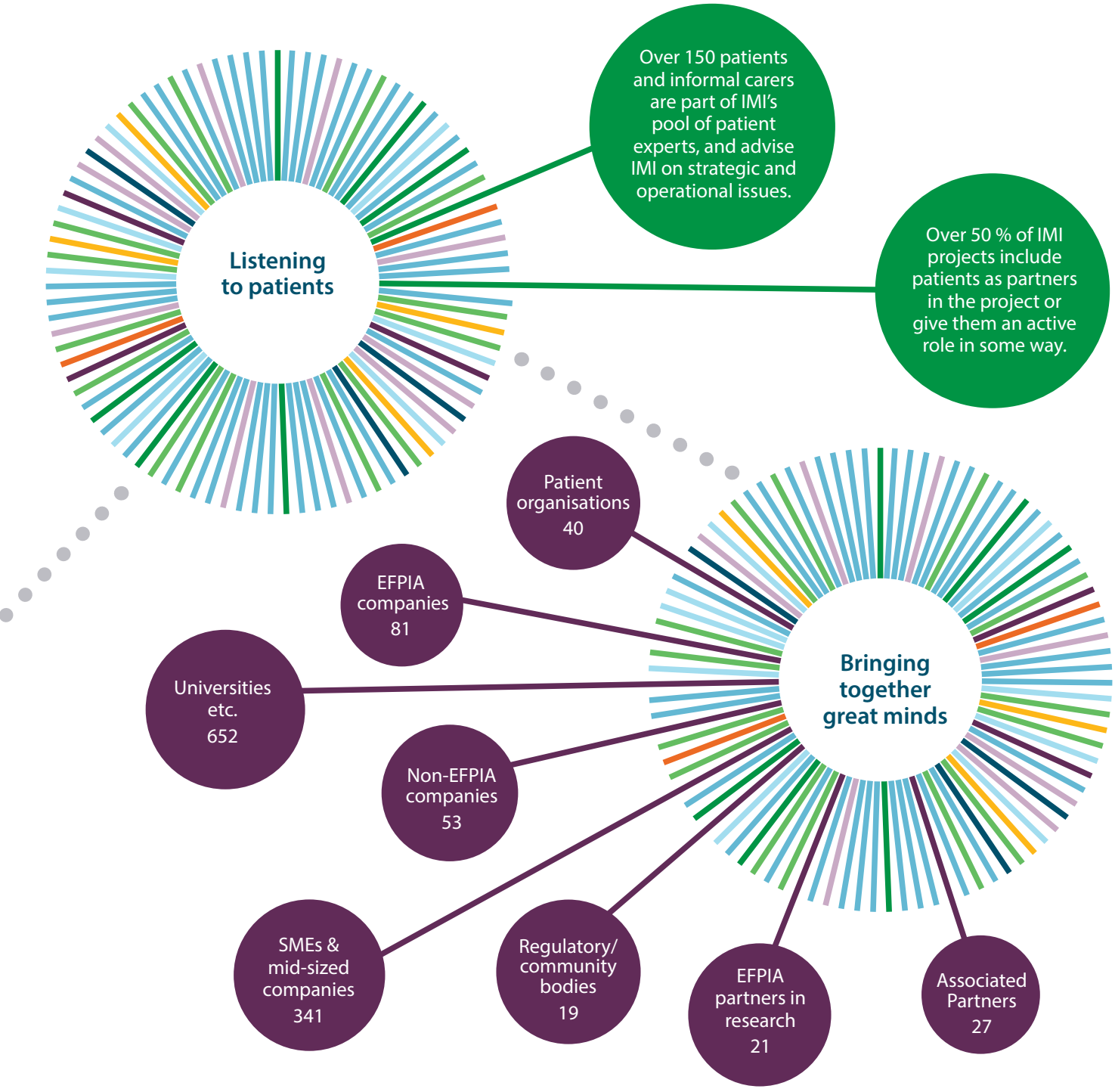
For period 2014-2020, IMI's total budget is EUR 3.276 billion.

Of this, EUR 1.638 billion (half the budget) comes from Horizon 2020, the European Union's funding programme for research and innovation. This funds the participation in our projects of eligible organisations like universities, small companies and patient groups.

EFPIA companies have committed EUR 1.425 billion to the program, and up to EUR 213 million can be committed by other organisations that decide to contribute to IMI as Associated Partners in individual projects.

EFPIA companies and IMI Associated Partners do not receive any EU funding through IMI, but contribute to IMI through 'in-kind' contributions. These contributions are mostly in the form of personnel costs (the time their staff spend working on IMI projects); other direct costs (e.g. samples, compounds, data); a financial contribution (e.g. to a university in the consortium); or through subcontracting (e.g. for data management, communication, and project management services).

These investments, particularly those from Associated Partners, show how IMI has become a magnet for partners who both see their contribution leveraged and get to join a project involving some of the best minds in their field.



INFECTIOUS DISEASES

What's the problem?

Recent decades have seen major advances in our ability to tackle infectious diseases. Vaccines now protect billions of people worldwide from a swathe of serious diseases, and antibiotics have cured millions of infectious that would have been life-threatening just 100 years ago.

Yet infectious diseases continue to pose a serious threat to public health worldwide. Antimicrobial resistance (AMR) is on the rise, and kills 33 000 people annually in Europe alone. New diseases like COVID-19 and Ebola continue to emerge, often by making the leap from animals to humans, and the linked-up nature of our world means they can spread rapidly around the planet. And old diseases like tuberculosis still defy our attempts to consign them to the history books. Meanwhile conspiracy theories are encouraging many to avoid vaccinations, placing growing numbers of people (including many children) at risk of entirely preventable diseases.

What's IMI doing about it?

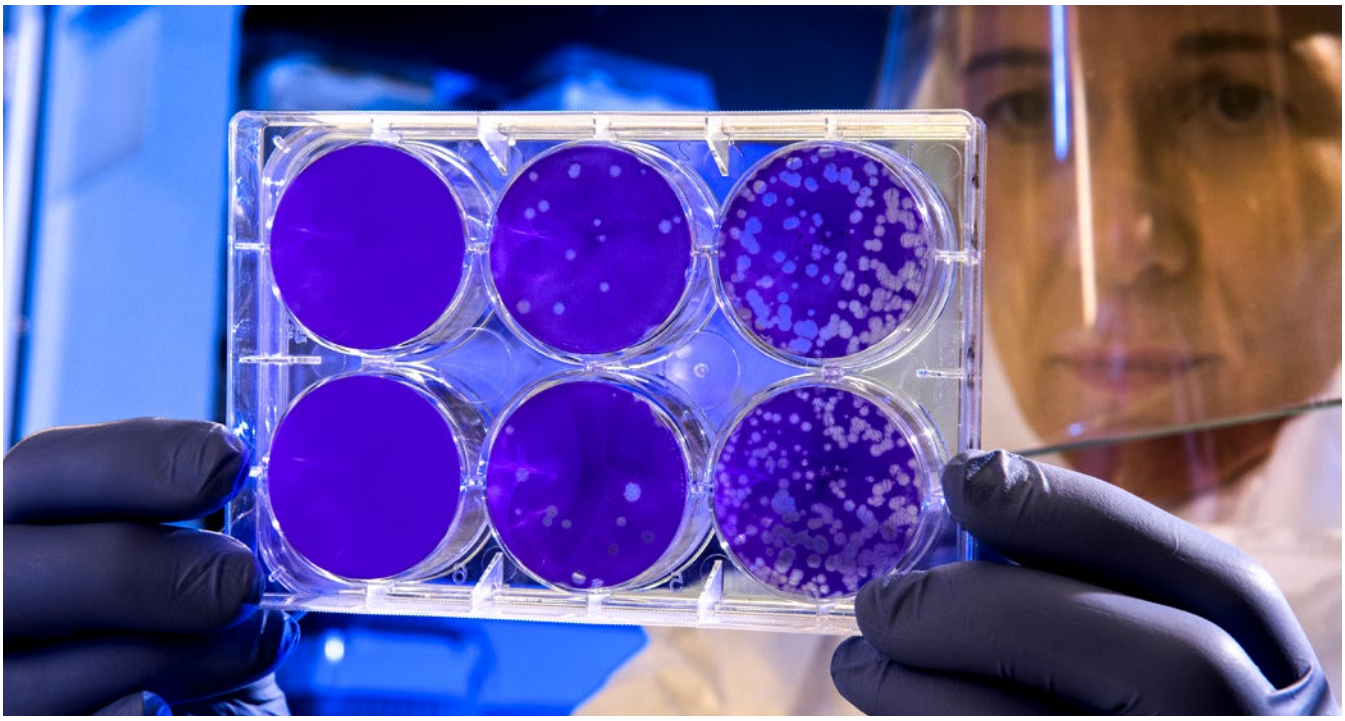
Infectious diseases have been a priority for IMI since the beginning; we now have over 40 projects in the area, covering AMR, Ebola and related diseases, vaccines, tuberculosis, diagnostics, respiratory infections and zoonoses (diseases transmitted between animals and humans). The total value of our infectious disease portfolio is over EUR 1.5 billion, equivalent to over a third of our budget.

Our project successes demonstrate the impact a PPP can have in this highly challenging area. For example, our TRANSLOCATION project added to our understanding of how bacteria defend themselves from antibiotics – knowledge that is essential for the development of new antibiotics. Our COMBACTE projects are making it easier to set up clinical trials of new antibiotics. And our DRIVE-AB project developed recommendations for policy makers on how to incentivise the development of new antibiotics while ensuring they are used responsibly.

Furthermore, IMI is able to respond rapidly to emerging health threats and launch new projects in a very short space of time, as demonstrated during the Ebola outbreak in western Africa in 2014-2016, and more recently during the COVID-19 pandemic. Our ongoing projects have also responded rapidly to the COVID-19 outbreak, with many contributing their skills, resources and knowledge to the fight against this new disease.

Be prepared! Getting ready for the next disease outbreak

The COVID-19 outbreak has put the spotlight on coronaviruses, a large family of viruses which includes the common cold as well as more serious diseases such as SARS (severe acute respiratory



syndrome) and MERS (Middle East respiratory syndrome). Coronaviruses are also found in many animals, and outbreaks occur when a virus jumps from animals to humans and mutates to allow direct transmission between humans.

IMI's ZAPI project was set up to deliver a platform and technologies to facilitate a rapid response to future disease outbreaks. One of the diseases chosen by ZAPI as a case study is MERS, which is closely related to SARS-CoV-2, the virus that causes COVID-19.

The surface of the MERS virus features 'spike proteins' which help the virus to break into cells and infect them. ZAPI developed antibodies that block the spike proteins; tests in animals showed that these could be effective as treatments for MERS. The team also drew on a MERS spike protein to create a vaccine; again, tests in animals showed that it appears to be effective. Studies suggest that these results could be useful in the hunt for treatments for COVID-19, and this work is being taken forward in the EU-funded MANCO project and one of IMI's new coronavirus projects, CARE.

ZAPI has also advanced the development of a biomanufacturing platform that means production of vaccines or therapeutic antibodies can be rapidly scaled up. Finally, they have compiled a master file to facilitate the fast-track regulatory approval of vaccines and therapeutics in emergency situations. This has been shared with regulatory and other authorities.

Early antibiotic development gets a much-needed boost

The goal of IMI's ENABLE project is to advance the development of potential antibiotics against Gram-negative bacteria, such as ***Escherichia coli***. The project has set up a platform that gives universities and SMEs the opportunity to advance promising potential antibiotics through the highly-challenging early stages of antibiotic development.

One goal of the project was to get at least one drug candidate into Phase I clinical trials, when the drug is tested in humans for the first time. In 2019, it achieved this with Juvabis's apramycin. In pre-clinical tests, apramycin proved effective against a variety of drug-resistant bacteria that are classified as priority pathogens by the World Health Organization (WHO).

The project has also selected Mutabilis's oral combination including MUT485 as a candidate drug. This means that if the results of the final pre-clinical tests are positive, it too can be advanced to a Phase I clinical trial. MUT485 could be used to treat urinary tract and kidney infections caused by bacteria that are resistant to other antibiotics.

Clinical trials of novel antimicrobials offer hope in fight against drug-resistant bugs

When setting up a clinical trial of a new antibiotic, one major challenge is finding enough patients with the resistant infection under study. IMI's COMBACTE family of projects has established a network of over 900 hospitals and 800 laboratories across Europe that are ready to participate in clinical trials of novel antibiotics. So far, over 350 sites have participated in 23 trials involving 21 000 patients. The first trials delivered initial results in 2019.

More recently, COMBACTE has joined the EU-funded COVID project RECOVER, and its hospital and laboratory networks have supported clinical trials of COVID-19 treatments.

Another key output is an online platform which allows users to explore and visualise data on antibiotic resistant infections in humans and animals across Europe. The website brings together epidemiology data from 32 European countries on the World Health Organization's priority list of pathogens, as well as data on more recent outbreaks and emerging cases of resistance to newly-developed antibiotics.

Building capacity in Africa to deal with Ebola outbreaks

Two major Ebola outbreaks have struck Africa in recent years. In 2014-2016, an outbreak in western Africa infected over 28 000 people and killed 11 000. Throughout the outbreak, IMI's Ebola+

programme played a major role in supporting clinical trials of Ebola vaccine regimens and the development of rapid diagnostic tests. In 2018-2020, an outbreak in the Democratic Republic of the Congo (DRC) saw over 3 000 infections and 2 300 deaths. In 2019, both the DRC and Rwanda started using the Johnson & Johnson Ebola vaccine regimen which had been developed with significant support from IMI. By the middle of 2020, nearly 100 000 people had started the vaccine regimen.

The clinical trials showed that the vaccine regimen was safe and induced a long-lasting immune response. In July 2020, the European Commission granted marketing authorisation to the vaccine regimen. Meanwhile, up to 1.5 million vaccine regimens are stockpiled, meaning the world is better placed than ever to respond to the next Ebola outbreak.

IMI's Ebola+ projects have also devoted a lot of energy to building the capacity of local scientists and healthcare workers to run clinical trials. In 2019, the EBOVAC projects ran over 130 training courses in the DRC, Guinea, Liberia, Mali and Sierra Leone covering a range of topics relating to clinical trials.

In addition, the EBODAC project trained close on 10 000 people in DRC, Rwanda, Sierra Leone, and Uganda in community engagement tools and techniques, including the use of biometric tools and rumour management. EBODAC has also shared its expertise through an online handbook entitled 'Community engagement, communications, and technology for clinical trials in outbreak settings'. It includes chapters on ethics, the social context, engagement, rumours, and enabling technologies.

Analysing the safety and efficacy of vaccines

Only medicines and vaccines that have been demonstrated to be safe and effective (through clinical trials) are allowed onto the market. Once a medicine or vaccine is on the market and being used by the general public, manufacturers and regulators continue to monitor safety and efficacy. The ADVANCE project focused on the safety and efficacy of vaccines that are already on the market.

Vaccinations are a highly successful public health intervention. However, as they are used primarily in healthy people (often children), expectations on their safety and effectiveness are particularly high. The project published a blueprint of a framework to rapidly provide scientific evidence of the benefits and risks of vaccines that are on the market. The document is the culmination of the project's work and it underwent a comprehensive consultation process with representatives of the main stakeholders interested in the assessment of benefits and risks of vaccines, as well as a public consultation.

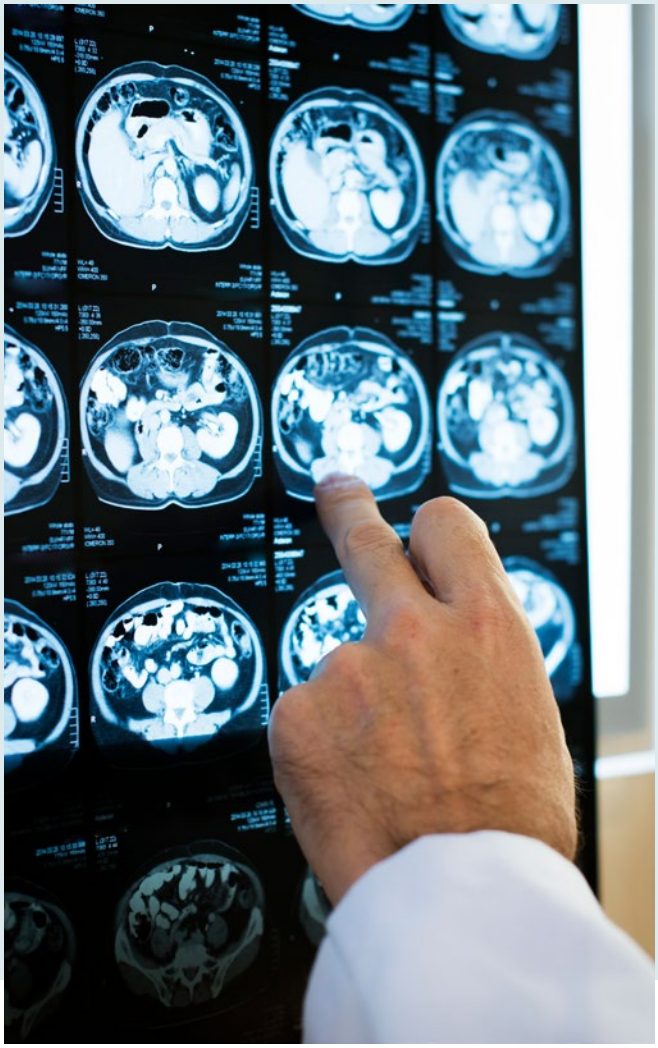
The document sets out the steps needed to use the framework, the tools that can be used, and how to disseminate the results. The hope is that it will help health professionals, regulatory agencies, public health institutions, vaccine manufacturers and the general public make more informed decisions on the benefits and risks of vaccines.

ADVANCE's work is being carried forward by VAC4EU (Vaccine monitoring Collaboration for Europe), a multi-stakeholder, international association. VAC4EU, along with two other IMI projects (CONCEPTION and EHDEN) will help the European Medicines Agency (EMA) gather real world data on COVID-19 vaccines and treatments once they are approved and being used in day-to-day clinical practice. This is a major success story for the sustainability of major EU initiatives which is always challenging to achieve.

BATTLING BRAIN DISORDERS THROUGH COLLABORATION

What's the problem?

Brain diseases affect millions worldwide, yet there is a dire lack of treatments for these diseases. This is not for want of trying; pharmaceutical companies spent years, and upwards of EUR 10 billion, looking for an effective treatment for Alzheimer's disease, without success. And while treatments do exist for other diseases such as depression, they do not work in all patients.

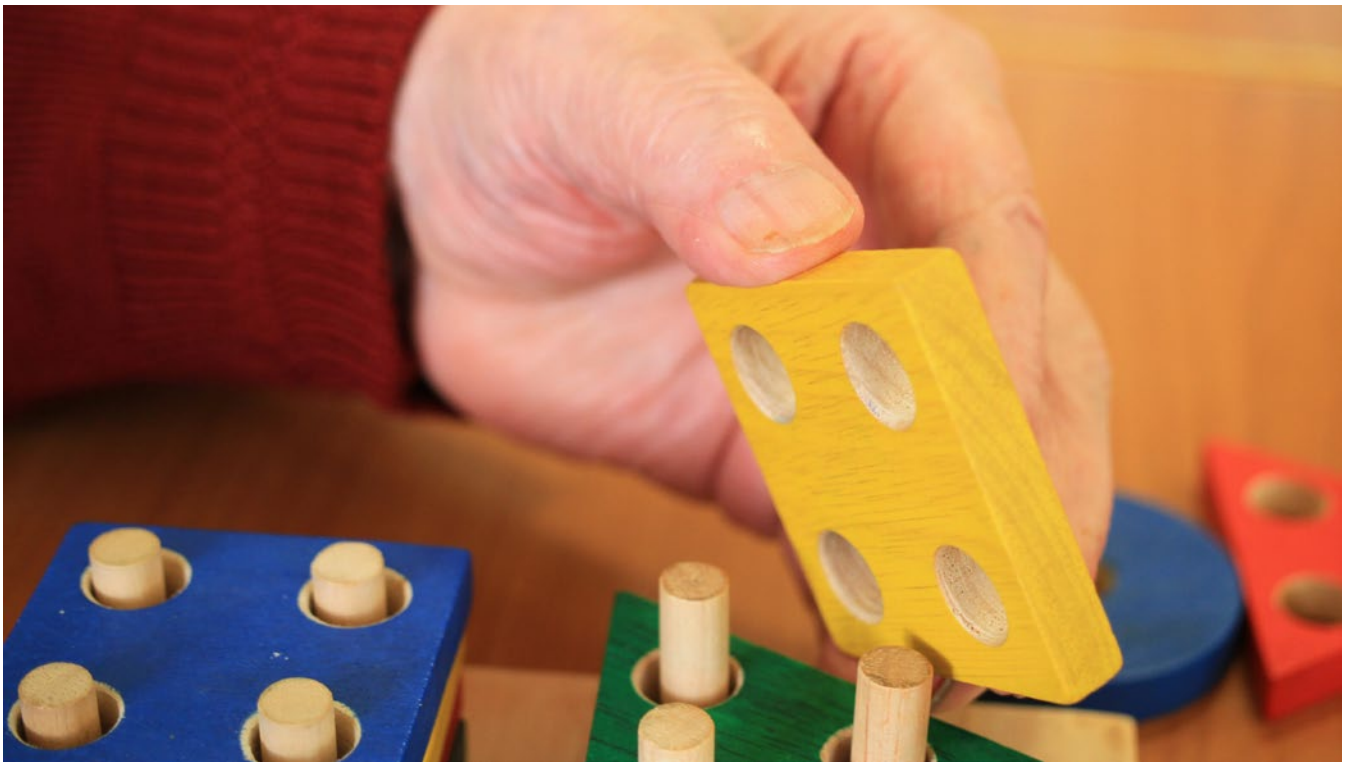


What's IMI doing about it?

IMI has over 20 projects in this area accounting for around 10 % of IMI's budget. Most focus on Alzheimer's disease and other forms of dementia, but we also have projects on Parkinson's disease, pain, and multiple sclerosis, for example. The projects cover the whole spectrum of medical research and drug development, and patients play an active role in many projects, bringing their knowledge and experience of their disease to the table.

Given the complexity of the brain and nervous system, it is unsurprising that many of our projects are unravelling the role of specific genes and proteins in disease. Other projects are exploring ways of identifying people at greatest risk of developing diseases. We also have projects using a 'big data' approach to study brain disorders.

The PPP approach to brain research is bearing fruit. Our AETIONOMY project came up with an innovative way to classify Alzheimer's and Parkinson's diseases based on the mechanism, i.e. cause(s) of disease. EUROPAIN delivered tools that accurately assess whether a potential pain drug is likely to work in humans. NEWMEDS shed new light on the brain circuits involved in schizophrenia and applied this knowledge for further research and drug development. And EPAD is revolutionising clinical trials of drugs designed to treat dementia in the earliest stages, before any symptoms have appeared.



New tools to study the role of ApoE in Alzheimer's disease

We know that people with the ApoE4 version of the ApoE gene have a considerably higher risk of developing Alzheimer's disease and are also more likely to develop the disease much earlier in life. However, we don't know why this is, and IMI's ADAPTED project is working to change this. The project has developed tools to make it easier to study the role and activity of the ApoE gene in the lab. These include nerve cells derived from human induced pluripotent stem cells with different versions of the ApoE gene, and a method to study the effect of ApoE on inflammation in Alzheimer's disease.

Unravelling the role of misfolded proteins in dementia associated with head injuries

Scientists have unravelled the structure of the abnormal tau filaments associated with chronic traumatic encephalopathy (CTE), a type of dementia associated with repeated blows to the head. Furthermore, the tau filaments associated with CTE are different to those found in people with Alzheimer's disease. The findings add to our understandings of how different forms of dementia develop, and could pave the way for future treatments for CTE and other diseases associated with abnormal tau filaments. The work, which was published in the prestigious journal Nature, was funded in part by IMI through the IMPRiND project.

Study reveals complex role of TREM2 gene in Alzheimer's disease

Clumps of proteins in the brain called amyloid plaques are a hallmark of Alzheimer's disease, and very often specialised immune cells cluster around these plaques. Research has shown that two genes involved in the immune system, TREM2 and CD33, appear to be involved in this immune response to Alzheimer's disease and could therefore be targets for drugs. However,

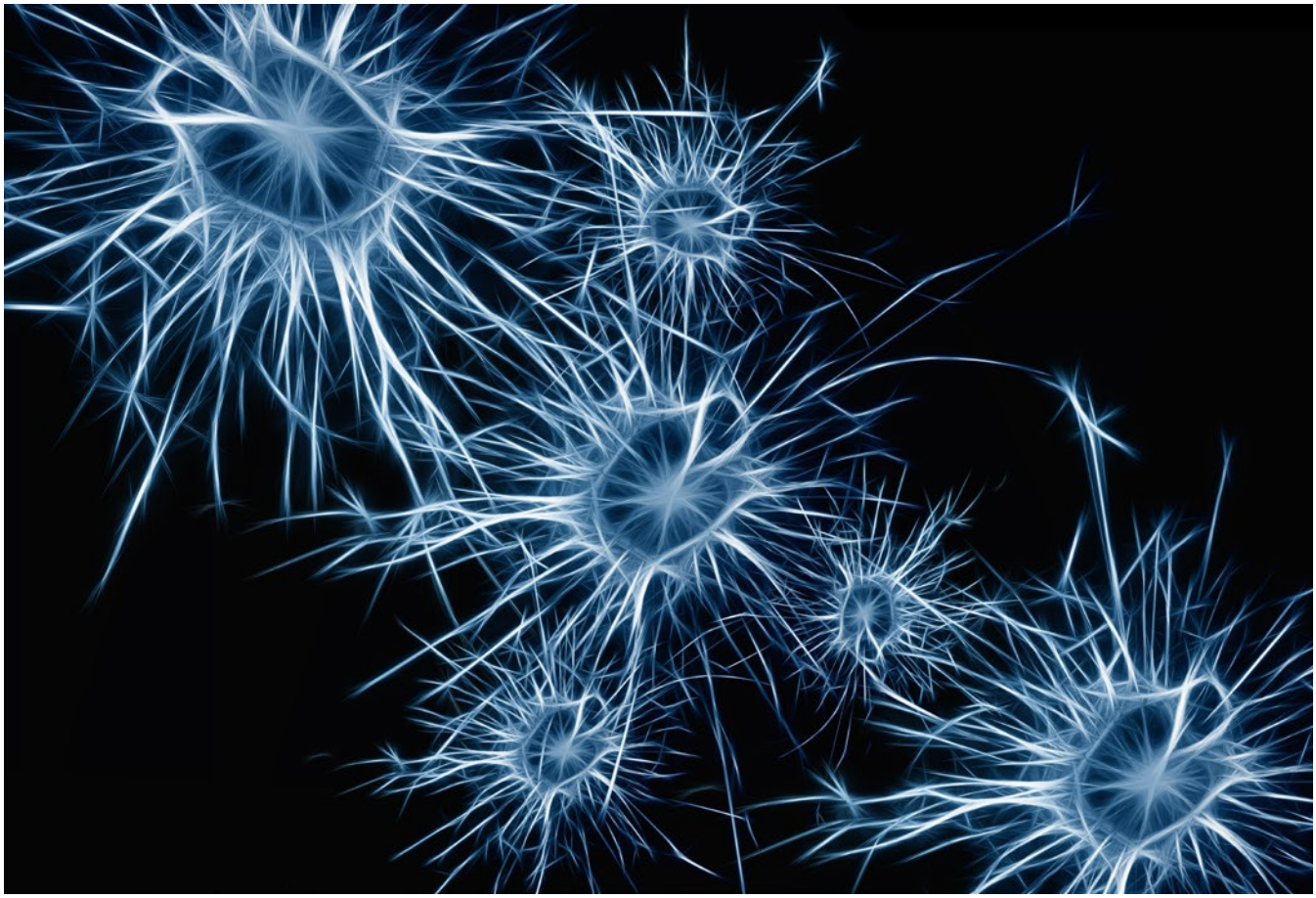
their exact role in the disease is still poorly understood. A study published in Nature Neuroscience, funded partly through IMI's PHAGO project, sheds new light on how the TREM2 gene influences the progression of Alzheimer's disease in different ways in the early and later stages.

The TREM2 gene codes for the TREM2 protein, which activates immune cells in the brain called microglia. Microglia play a vital role in the removal of amyloid plaques. In this study, the researchers showed that in mice with early signs of plaque deposition (and a functioning TREM2 gene), microglia cluster around small plaques and cause them to disintegrate. In mice lacking a functional TREM2 gene, the microglia were not able to break up the amyloid plaques. This suggests that in early stage Alzheimer's disease, activating TREM2 could help to prevent the build-up of toxic amyloid plaques and this could be a useful treatment strategy for patients in the early phases of the disease.

However, the results of a similar test in mice with more advanced plaque deposition paint a different picture. There, the amyloid plaques grew faster in mice with a functioning TREM2 gene than in mice without it. Further analyses showed that in the microglia, TREM2 also stimulates the production of a protein called ApoE, which is by far the strongest genetic risk factor for developing sporadic Alzheimer's disease, and is thought to promote the aggregation of amyloid plaques.

Alzheimer's project EPAD releases first wave of data to research community

IMI's EPAD project has recruited 2 000 over-50s from across Europe to participate in a long-term study that will help to improve our understanding of the very earliest stages of Alzheimer's dementia – before people have any symptoms. Participants undergo multiple assessments including regular health checks, standardised tests and brain scans over several years.



In 2019, the project made data from the first visit of the first 500 participants available to the scientific community. The data has been de-identified to protect participants' privacy, and quality controlled. Access is provided via secure online tools; researchers who want to use it have to apply via the EPAD website. As the project progresses, further data will be made available to the wider research community.

According to project coordinator, the research participants are enthusiastic about the move to make their data available to researchers - they want as much knowledge to be gained as possible from their contribution.

ROADMAP Data Cube allows interactive visualisation of Alzheimer's data

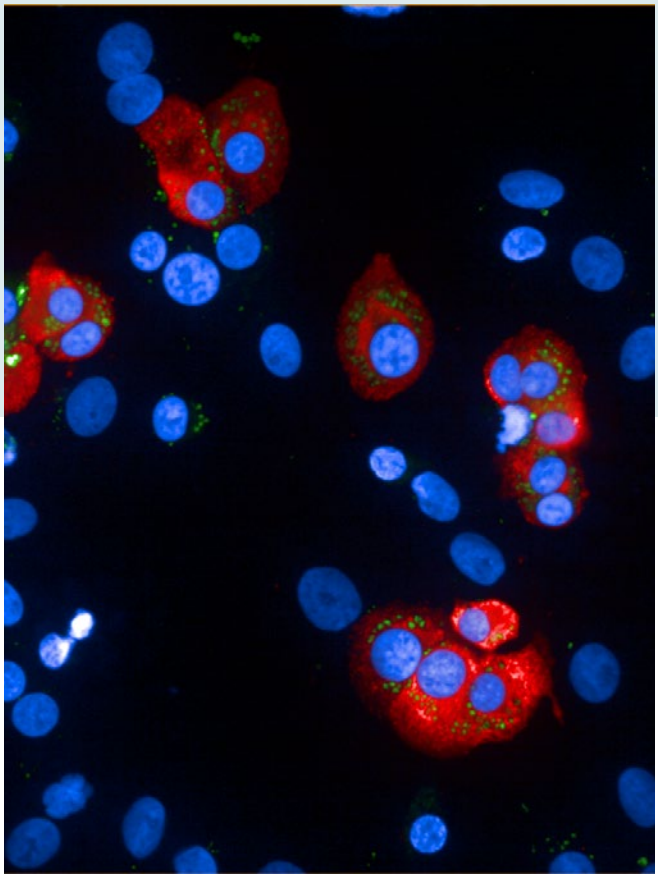
IMI's ROADMAP project has released its **Data Cube**, an online, three-dimensional 'heat map' that allows users to visualise how different data sources capture different Alzheimer's disease outcomes at different disease stages. Furthermore, users can switch between the perspectives of people with dementia, carers, and health professionals. The Data Cube makes it easy to see what data sources are available, and where there are gaps. It comprises information from 65 data sources, including electronic health records, clinical trials, and cohorts, but does not provide access to any underlying data.

According to the project, 'Enabling the visualisation of the AD-related data availability in different types of European data sources and the intrinsic gaps has proven to be a powerful tool for the design, planning and validation of the models and strategies used to guide future recommendations to enhance AD research.' ROADMAP is part of IMI's Big Data for Better Outcomes programme.

REVOLUTIONISING THE WAY WE THINK ABOUT DIABETES

What's the problem?

Diabetes occurs when the body is unable to regulate blood sugar levels properly because the pancreas does not make enough of the hormone insulin, or because other organs do not respond to insulin as they should. According to the International Diabetes Federation, diabetes currently affects 463 million adults, and by 2045 this will rise to 700 million. Despite decades of research, there is still no cure for diabetes, and many patients still have to inject themselves with insulin to manage their condition. Furthermore, many people with diabetes experience complications such as heart, kidney and eye problems.



What's IMI doing about it?

IMI has a strong diabetes project portfolio, with 11 projects addressing different aspects of the disease. Some are studying the underlying causes of the disease and the internal processes that lead to the destruction of the cells in the pancreas that produce insulin. Others aim to detect clues as to how the disease will progress in different patients. Finally, many projects focus on detecting, preventing and treating the complications associated with diabetes.

One of IMI's first projects, IMIDIA, delivered a scientific breakthrough when it generated the world's first human pancreatic beta cell line that could be studied in the lab. As these are the cells that produce insulin, this is a valuable new tool for diabetes researchers. Our DIRECT project developed tests that offer clues as to who will get diabetes, whose condition will deteriorate rapidly after diagnosis, and who will respond well or badly to certain drugs. SUMMIT developed a non-invasive imaging technique that can identify patients at imminent risk of a heart attack or stroke.

IMI projects put forward new classification of diabetes subtypes and pave way for use in the clinic

Currently, two main types of diabetes are recognised, and diagnosis is through a measurement of a patient's blood sugar levels. However, research funded in part through IMI's BEAT-DKD and RHAPSODY projects suggests that there are in fact five subtypes. The team monitored over

13 000 newly-diagnosed diabetes patients, analysing blood sugar levels, insulin resistance, insulin secretion, and age of onset among other things.

This revealed five distinct groups of patients with different risk levels for certain complications associated with diabetes. For example, patients with 'severe insulin-deficient diabetes' are at greatest risk of eye disease, while patients with 'severe insulin-resistant diabetes' had the highest incidence of kidney damage. The projects validated these initial findings in additional patient populations and uncovered new clues as to the best treatment options for the different groups. For example, one study demonstrated that patients with 'severe insulin-resistant diabetes' who undergo bariatric surgery show the best recovery from diabetes and the greatest improvement in kidney function. This is important as kidney disease is a common complication in diabetes.

Now, BEAT-DKD is working on a software package that would allow doctors to identify which diabetes subtype a patient has. The doctor would simply have to enter information on the six variables used for clustering. As well as indicating the subtype that is the best match for the patient, the tool would generate information on the best choice of treatment. The tool is under development and will be formally tested as a medical device for use in clinics.

DIRECT study on personalised treatments

Further results that pave the way towards personalised treatments for diabetes came from the project DIRECT. Here, the project found that people with altered ARRB1 and GLP-1R genes respond better to certain injectable anti-diabetic drugs. Around 5 % of the population has been found to have one or more copies of the altered ARRB1 gene. They show a much better response to GLP-1RA drug treatments, equivalent to an extra 0.6mg of Liraglutide or 10µg of Exenetide. The study suggests that in future, doctors may need to test patients' genetic make-up before prescribing these drugs.

New tool could predict risk of diabetes drugs for kidneys

People with diabetes are already at greater risk of heart and kidney problems. The BEAT-DKD project has developed a tool that indicates whether

long-term use of a drug could harm the heart or kidneys. The tool could prove helpful to those developing new drugs. It could also be used by doctors to assess which patients would benefit from certain medicines and which patients should use alternative treatments.

INNODIA research gets to grips with the underlying causes of type 1 diabetes

The INNODIA project focuses on type 1 diabetes, which occurs when the immune system attacks the beta cells in the pancreas responsible for producing the hormone insulin. INNODIA researchers analysed the molecules on the surface of the pancreatic beta cells and how immune cells called T lymphocytes respond to them. They found that in both healthy people and diabetes patients, T lymphocytes recognised these molecules when they encountered them in the blood. However, in diabetes patients, the immune cells also recognised them in the pancreas.

The team will use this new-found knowledge to develop vaccines to prevent and treat type 1 diabetes. However, while conventional vaccines seek to boost the immune response, the aim here will be to neutralise it. The research was published in the journal Cell Metabolism.

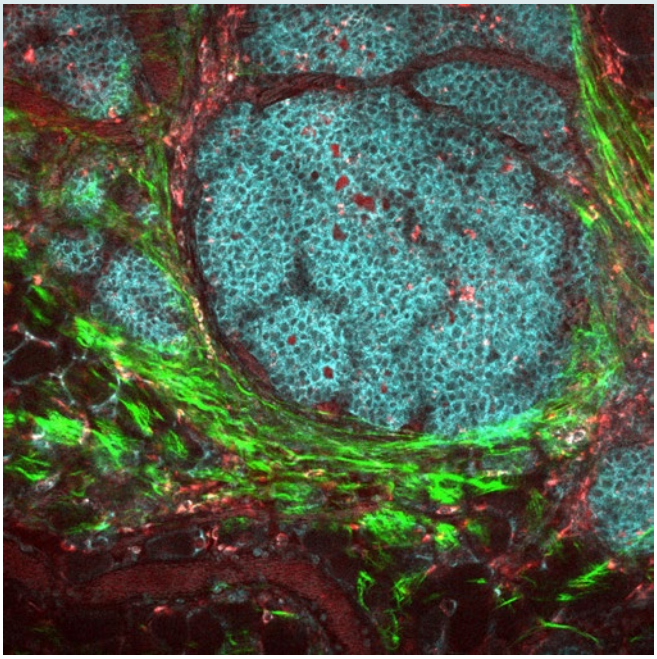
The project is also studying the genetics of type 1 diabetes. Writing in the journal Nature Genetics, scientists from the project explain how they have identified some of the genes involved in the beta cells' response to attacks by the immune system. The findings add to our understanding of the molecular basis of the disease and could pave the way for future treatments.

IMI AND CANCER RESEARCH: NEW PARTNERSHIPS TO TACKLE AN OLD ENEMY

What's the problem?

According to the European Journal of Cancer, in 2018 there were an estimated 3.9 million new cases of cancer in Europe. And although advances in treatments mean survival rates are on the up for some types of cancer, the disease killed 1.9 million people in Europe in the same year. Meanwhile many survivors experience long-term health problems resulting not only from the disease, but from the aggressive treatments used. There is therefore a clear need for better, more targeted treatments for many cancers.

The challenge is so great that 'conquering cancer' has been selected one of five 'missions' to be launched under Horizon Europe, the EU's next framework programme for research and innovation.



What's IMI doing about it?

IMI's older projects have delivered a range of tools and resources to advance cancer research. These include the PREDECT project's laboratory models of some common tumours that more accurately mimic the three-dimensional complexity of tumours, and their behaviour within the patient's body. OncoTrack identified molecular 'fingerprints' of different types of colorectal cancers and correlated them to how the tumours respond to different drugs, information that is helping to choose the right treatment for the right patient.

IMI's cancer portfolio has grown a lot in recent years, and now includes 9 projects with a total budget of just over EUR 190 million. These new projects are investigating immune therapies, childhood cancer, and the use of big data to advance drug discovery for prostate cancer and bone cancers.

First steps on the path to new treatments for colon and skin cancers

IMI's European Lead Factory project has created a vast library of over 500 000 compounds that were contributed to the project by large pharmaceutical companies as well as other organisations. Researchers from universities and SMEs can apply to access the compound collection to hunt for compounds that could be useful in their own drug development projects. Scientists at the German Cancer Research Centre (DKFZ) had

discovered that a protein called kallikrein-related peptidase 6 (KLK6) appears to be involved in the development and spread of some cancers, including colon cancer and melanoma (skin cancer).

The team turned to the European Lead Factory in their hunt for potential drugs that could block the activity of KLK6. With the help of the project, they screened the collection and identified a number of compounds that could fit the bill. Further work on the 'hit list' narrowed the list down, and one of the compounds blocked the spread of the cancer in laboratory tests. The findings were published in the journal ChemMedChem.

Carrying on the legacy of an innovative cancer project

Today, many cancer patients have to undergo biopsy surgery to provide doctors with the cell samples they need to diagnose the disease, determine the treatment needed, and then monitor how well a treatment is working. Needless to say, doctors cannot carry out biopsies too often because they are invasive, costly, and risky to the patient. Yet cancer is a dynamic disease, and patients would benefit immensely from more regular analyses of their condition.

Cancerous tumours shed cells and fragments of DNA into the bloodstream, and IMI's CANCER-ID project was set up to see if these 'circulating tumour cells' (CTCs) and DNA could be detected and analysed in blood samples – a so-called 'liquid biopsy'. The project picked two cancers as case studies: lung cancer (where biopsies are particularly hard to obtain on a regular basis) and breast cancer (where there is an urgent need for tests that detect early on when a tumour has become resistant to certain medicines).

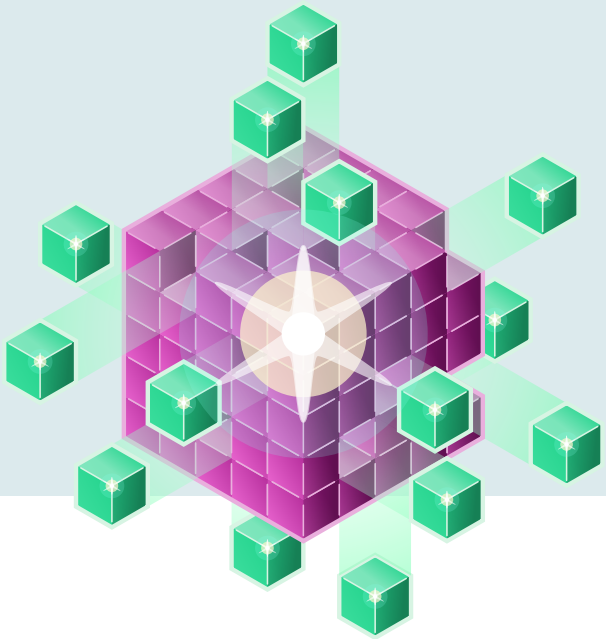
The project has developed and validated a range of methods and protocols to extract these cells and fragments of genetic material from blood samples and then analyse them. This is no mean feat. The levels of tumour cells and DNA in the blood are low. The levels of rare genetic mutations in the circulating tumour DNA are even lower, and detecting them requires a special, faster centrifuge that is not available in all clinical labs. In addition, even small changes in the way a blood sample is handled can affect the results. The CANCER-ID team validated its methods and protocols by testing them in different laboratories.

In 2019, the project coordinator set up the European Liquid Biopsy Society (ELBS) to continue the work of the project once the IMI funding period is over. The ELBS brings together many project partners and already has strong ties with the global liquid biopsy research community. This can ensure the sustainability of a major asset for Europe and the world.

PUTTING BIG DATA INTO PRACTICE TO ADVANCE HEALTH RESEARCH

What's the problem?

Medical researchers and healthcare systems generate vast amounts of data every single day. If linked up and harnessed, it could revolutionise medicines development and healthcare. However, most of this 'big data' remains in silos, inaccessible to most researchers, its potential untapped. Meanwhile digital technologies and wearable devices offer new and more efficient ways of gathering data, but question marks remain about how to address issues like patient privacy and how these devices fit in with patients' lives.



What's IMI doing about it?

IMI has had 'big data' projects since its creation. Project outputs include the EHR4CR project's platform that enables controlled access to hospitals' data for the preparation of clinical trials. The platform has demonstrated its usefulness in speeding up the recruitment of patients, while ensuring that patient privacy is respected. The Open PHACTS Discovery Platform links up existing data sources and allows scientists to rapidly answer complex questions in drug development. And the EMIF project used existing data to generate new insights into Alzheimer's disease.

Today, IMI's Big Data for Better Outcomes programme is addressing the technical, legal and ethical issues that currently prevent researchers from making full use of the data that is out there. What's more, the projects are putting 'big data' principles into practice to advance research in the fields of cardiovascular disease, haematological malignancies (blood cancers), Alzheimer's disease, and prostate cancer. IMI also boasts a number of projects working on health-related mobile and digital technologies.

Can real world data replicate a clinical trial? EHDEN study suggests yes

IMI's EHDEN project has dramatically demonstrated the power of using clinical data in research by replicating, during a five-day 'study-a-thon', the results of a systematic review covering 20 years of research, and a multi-year clinical trial. The findings, which focus on the pros and cons of different types of knee replacement surgery, were published in the journal Lancet Rheumatology. They show that it is possible to harness clinical data (such as electronic health records) from different sources and use it to generate information that could help patients and doctors to make better decisions about their care.

'Randomised controlled trials remain the gold standard for establishing efficacy,' the EHDEN team

concludes in the paper. 'However, we feel that this study shows the value of real world evidence for complementing the evidence produced from randomised trials.'

Today, EHDEN is applying its skills to tackling COVID-19. The project launched a Call for proposals which identified 25 data partners across Europe with data from 1 million SARS-COV-2-tested patients; 228 000 of whom tested positive. EHDEN is now harmonising the data to the OMOP Common Data Model so that meaningful insights and evidence can be generated in the coming months that will ultimately improve patient care. Furthermore, EHDEN is one of three IMI projects contributing to the EMA's efforts to gather real world data on COVID-19 treatments and vaccines once they are approved.

Want to make your data FAIR? Follow the recipes in the FAIRplus cookbook!

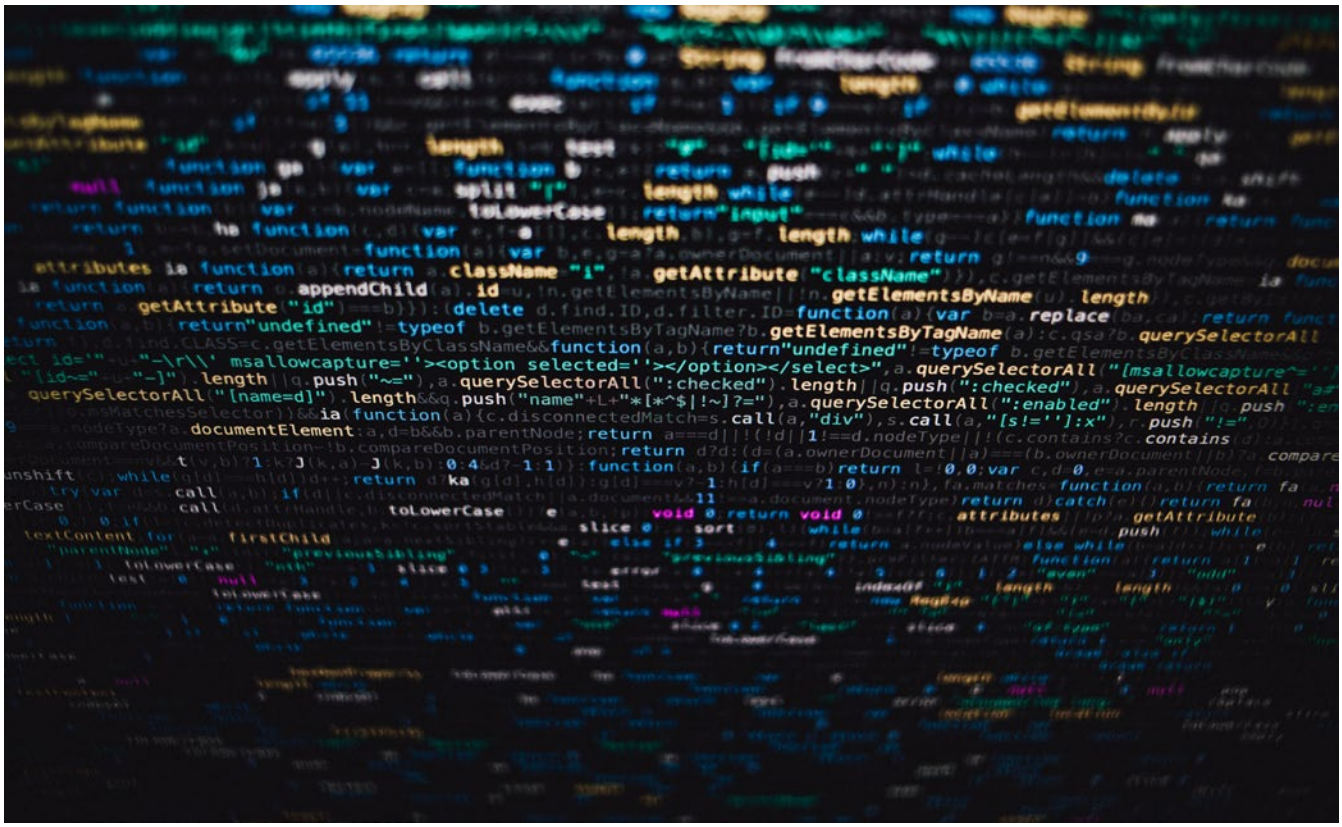
The vast amounts of data generated in life science research have the potential to add to our understanding of disease and help advance drug development. Yet most data is hidden away in proprietary databases and stored in different formats. The goal of FAIRplus is to deliver guidelines and tools to facilitate the application of 'FAIR' principles to data from certain IMI projects and datasets from pharmaceutical companies. FAIR stands for 'findable, accessible, interoperable, reusable'. In 2019, the project published a FAIR 'cookbook', an open access resource designed to help researchers ensure their data is 'FAIR'. The cookbook, which will continue to evolve throughout the project, sets out step-by-step 'recipes' on what researchers need to do. The project has already used the 'recipes' in the cookbook to FAIRify datasets from four IMI projects, and their data is now in the IMI data catalogue:

RADAR-CNS study reveals factors influencing digital technology use for depression

IMI's RADAR-CNS project is working to develop new ways of monitoring major depressive disorder, epilepsy, and multiple sclerosis using wearable devices and smartphone technology. The hope is that these technologies would make it possible to detect changes in behaviour, sleep, or mood before the individual themselves is aware of it. This could help them to predict – or even avoid – a relapse.

The project is working with patients to discuss their attitude towards the use of these technologies to monitor their condition. In a recent study, the project discussed the technologies with adults with experience of depression from Spain, Italy and the UK. In all three countries, the patients raised issues regarding their motivation levels, the potential impact of the technologies on mood and anxiety, aspects of inconvenience, and ease of use. These findings will help the project to deliver technologies that fit in with patients' lives.

Underlying much of the project's work with mobile and wearable devices is the RADAR-BASE



software platform, which integrates data from different sources, stores it, and makes it available to those who need it, all while respecting users' privacy and security. The platform has been open source since 2018 and is now being used by over 13 additional studies involving more than 13 500 participants. These include a study on emerging infectious diseases in Africa, and a study to track how recovery from poor mental health 'unfolds' over time.

Ensuring key clinical trial paperwork is GDPR compliant

Before taking part in a clinical trial, participants must sign an informed consent form which addresses, among other things, how their data is used. However, for the people running the trial, navigating the complex rules around data protection and ensuring the trial complies with the EU's General Data Protection Regulation (GDPR) can be difficult.

The DO-IT project has delivered a template for harmonised informed consent forms to make it easier for researchers to collect data and use it for both the clinical study and (if permission is granted) future research, while adhering to GDPR rules. The forms were developed by experts in data privacy, law and health care, who also gathered input from of data privacy and ethics representatives from data protection authorities, ethics committees and other regulatory bodies.

The freely available templates cover all information required by the GDPR, and address the processing of personal data for the conduct of a clinical study within a drug development programme; and future scientific research on personal data and biosamples collected in clinical studies, i.e. research beyond the original drug development programme.

TOOLS AND RESOURCES TO ADVANCE MEDICAL RESEARCH AND DRUG DEVELOPMENT

What's the problem?

A lot of the challenges in drug development are shared across multiple disease areas. For example, all potential drugs undergo toxicity tests in the lab. However, these tests are not always reliable and toxicity issues are often only picked up late in development. Other challenges for researchers include gaining access to resources such as libraries of compounds that can be screened for drug development; or stem cells derived from adults that can be used to study diseases.

What is IMI doing about it?

Many IMI projects are providing practical solutions to some these general challenges in medical research and drug development. What's more, in a number of cases, IMI projects are making these tools available to the wider scientific community.

For example, the European Lead Factory set up a vast collection of 500 000 compounds and a state of the art screening centre; researchers can apply to screen the collection for compounds that could be useful for their own research. This has delivered results in fields as diverse as cancer, metabolic disorders, neurodegenerative diseases, antimicrobial resistance and neglected tropical diseases.

Our EUPATI project provides training to patients who want to get involved in research; patients who understand the medicines development lifecycle and associated jargon are well placed to contribute to research and drug development in myriad ways.

On medicines safety, our eTOX project developed tools that allow scientists to detect toxicity issues with potential medicines in the earlier stages of drug development.

Making clinical trials of medicines for children easier

Currently half of all medicines used in children have never actually been tested in children; c4c is working to change this by creating a pan-European network for paediatric clinical trials. The project has now selected four studies that will leverage the fledgling network and implement new ways to integrate children's and young people's views in clinical trial design. They will also apply novel ways of evaluating medicines. The four studies address a range of disease areas and age groups.

One will assess the effectiveness of paracetamol in premature babies with a serious heart defect called patent ductus arteriosus. Another will investigate the use of steroids in children with Kawasaki disease, which mainly affects the under 5's and is characterised by a high temperature, rash, swollen glands in the neck, dry, cracked lips, and red eyes, fingers or toes. The third study focuses on posaconazole in children and young people with cystic fibrosis and an Aspergillus (fungal) infection. Finally, the project will run a trial on losartan in children and youngsters with osteogenesis imperfecta, a genetic disorder which results in fragile bones.

WEB-RADR medicines side effects reporting apps go global

Traditionally, reporting a suspected side effect of a medicine entails filling in a paper form. However, thanks to the WEB-RADR project, patients and healthcare workers alike can now report side effects quickly and easily via an app. The first version of the app was launched in the UK in 2015, and Dutch and Croatian apps followed a year later. The project then collaborated with the World Health Organization to create special versions of the app designed to support anti-malaria programmes in Burkina Faso and Zambia. In 2018, the United Arab Emirates started using the app, and in 2019 Armenia, Botswana, Cote d'Ivoire, Ethiopia and Ghana joined the list of nations

with a WEB-RADR app. The reports received via the app have already contributed to the identification of new safety issues with various medicines, enabling regulatory authorities in relevant countries to take appropriate action.

RESOLUTE provides open access to treasure trove of materials on understudied proteins

Open access is a principle of IMI projects, and this is embodied by the RESOLUTE project, which is making its results available to the wider research community. RESOLUTE is studying proteins called solute carriers, which act as gatekeepers to our cells, controlling what molecules are allowed to enter and leave the cell. Although they have been implicated in diseases ranging from Alzheimer's disease and amyotrophic lateral sclerosis (ALS) to schizophrenia, solute carriers have never been studied in detail.

The goal of RESOLUTE is to deliver knowledge and resources on these under-studied proteins, and make the information available to the scientific community.

The project has already made available the DNA sequence of approximately 400 solute carriers. The RESOLUTE plasmid repository is available via **Addgene.org**, a not-for-profit repository for this kind of material. Within weeks of the material becoming available, several labs worldwide had placed orders. In the future, more DNA sequences will be added to this collection.

The project has also published the RESOLUTE '**knowledgebase**', which brings together in one place high quality, reliable information on solute carrier proteins from publicly available sources. The RESOLUTE knowledgebase is freely accessible and the project will add information to it from both public sources as well as the project's own results.

Getting to grips with pharmaceuticals in the environment

When we take a medicine, much of it will be broken down by the body. However, very often some of the active ingredient remains intact and is excreted when we go to the toilet. After that, it travels in the sewage system to a wastewater treatment plant and if it is not removed during the sewage treatment process, it is released into the environment. Although the concentrations of medicines in the environment are generally low, in some cases they could still be potentially harmful to wildlife and ecosystems. A first step in assessing the environmental risk of chemicals is estimating the levels of the chemical in the environment. IMI's iPiE project has developed a **technical model** that draws on national drug consumption data to estimate the concentrations of pharmaceuticals in the environment across Europe. Previously, iPiE released an online tool, iPiE*SUM ('iPiE Summary Database Search'),

that summarises the properties, environmental toxicity and characteristics of active pharmaceutical ingredients.

Stem cell bank on track for sustainability

Induced pluripotent stem cells (iPSCs) are key tools for early drug development and disease modelling. IPSCs are mature adult cells that have been reprogrammed to make them 'pluripotent', i.e. able to differentiate into any type of cell found in the human body. IMI's EBiSC project was established to provide researchers across academia and the pharmaceutical industry with disease-relevant, quality-controlled, research-grade iPSC lines, data and cell services. Now, the EBiSC2 project is building on the work carried out under EBiSC to ensure the long-term sustainability of the infrastructure. During 2019, EBiSC2 continued to add new cell lines to the **catalogue**, and distributed cell lines to over 20 users in more than 10 countries. These numbers show that the iPSC repository is expanding, and is therefore well placed to meet future demands from both the industry and the wider research community.

New start up facilitates access to IMI project outputs

Publicly-available outputs of three early IMI projects – eTOX, K4DD and Open PHACTS – are now available through a newly-launched start-up company called Phenaris. The projects delivered a wealth of tools and resources in the areas of toxicology (eTOX); the analysis of interactions between a drug and its target (K4DD); and data management across diverse sources (Open PHACTS). The start-up is the brainchild of an IMI project coordinator, and it provides researchers with data, models, and decision support in all aspects of ***in silico*** (i.e. computer-based) toxicology.

RADICAL COLLABORATION - THE BENEFITS OF IMI

The term 'radical collaboration' was coined by the former Commissioner for Research and Innovation, Carlos Moedas during the 10th anniversary celebrations of IMI in 2018. He was pointing out that, in addition to the impactful results (only a fraction of which are highlighted in this brochure), IMI had driven a new collaborative model for novel medicines R&D and as a result, transformed the biomedical ecosystem.

Indeed, since 2008, IMI has catalysed the transformation of the biomedical R&D landscape to the extent that this way of working is the norm. No more silos between upstream and downstream players; precompetitive collaboration amongst industry players; inclusion of SMEs; involvement of regulators from the beginning; and, of course, the involvement of patients throughout the medicines R&D lifecycle. Some of the results documented here would simply not have been possible at all without the PPP model, or would have taken a lot longer to generate.

Measures of success

Measuring the success of a programme like IMI is far from easy, and entails looking at all stages of the R&D process. IMI's evaluation framework, built over several years of constant learning, measures indicators of performance such as:

- scientific output (a detailed annual analysis that clearly demonstrates the world class nature of the research output of IMI funded projects);
- tools, models, databases etc. that our projects are sharing with the wider scientific community (a list of these can be found on the IMI website);
- impacts on regulatory frameworks - these are numerous and vary between specific qualification opinions on clinical outcomes to profound discussions on how to evolve the clinical trial design depending on the disease setting;
- impacts on industry practice – harmonisation of model systems and standards across industry etc.

The list is long, but all of these impacts are important and mean that we have created in Europe a rich, diverse ecosystem that incentivises industry to continue to invest in European R&D. This, taken collectively, represents the added value of the PPP model.

An integrated ecosystem for medical research

Researchers world-wide have been criticised for not being interested in the translational aspects, which would see their work being used for societal benefit. IMI gives them the opportunity to integrate themselves into a new, connected ecosystem, where their work can be easily taken up by industry and other stakeholders. As well as enhancing researchers' huge value to society, this ecosystem opens the doors to new ways of partnering, all of this on a scale never implemented before.

The IMI concept has never been more clearly validated than with the COVID-19 pandemic, where IMI has played a key role in the European response. Ongoing IMI projects have been critical in organising a swift response, and our collective ability to mobilise industry and reprioritise public funding allowed us to rapidly launch new projects to develop new treatments and diagnostic tests.

Through IMI's portfolio of over 150 projects (and counting) this new ecosystem is alive, is being sustained and, as we look to the future proposed programme under Horizon Europe, will undergo a significant expansion to include several other industry sectors involved in healthcare such as diagnostics, medical imaging, health informatics and medical devices. Further integration of these and other new players across the public –private divide is urgently required to reap the true benefit of past investments and optimise the impact on society.

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The Innovative Medicines Initiative (IMI) is a partnership between the European Union and the European pharmaceutical industry. We support collaborative research and innovation projects designed to improve the medicines development process and make it more efficient, so that patients will have faster access to better and safer medicines.

Our projects are delivering innovative solutions to the most pressing medical burdens of our time, including antimicrobial resistance, dementia, diabetes and cancer. More broadly, we are transforming the medical research ecosystem by making it more open and collaborative, and today we are globally recognised as a pioneer of open innovation.

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