The Innovative Medicines Initiative

As Big Pharma pulls back, IMI steps in

All those learning or practicing medicine are proud when their research papers are published by peer-reviewed publications. It was no different for the Innovative Medicines Initiative, Europe's largest public-private partnership, when research by one of its teams appeared in *Nature* in August 2012.

After studying the genomes of about 2,000 people in Iceland, including some people who had been diagnosed with autism or schizophrenia, the researchers discovered that for every one-year increase in a father's age at the time of conception, an additional two genetic mutations were passed on to his offspring. Not all mutations are harmful. But the findings help clarify some of the risk factors for important diseases such as autism and schizophrenia.[1]

The publication was important for the IMI because it illustrated for the first time that it is possible to deliver a rigorous scientific study from a diverse group of industrial and academic researchers who hadn't previously worked together. Collaboration by itself is not new. Scientists have been working together for years to try and solve problems related to disease and the development of new drugs. But until the IMI was launched on 30 April 2008, coalitions involving several Big Pharma companies, together with biotech and academia, had never been tried in Europe before.

"What is very different here is that we actually work together," said Tine Bryan Stensbøl, director of synaptic transmission research at H. Lundbeck A/S, in a telephone interview. Dr Stensbøl is coordinator of an IMI consortium called NewMeds that is investigating new treatments for depression and schizophrenia. The autism paper arose from another consortium called EU-Aims. The principles governing all of the consortia are the same.

Dr Stensbøl explained that collaboration under the IMI involves sharing information with other members of a consortium, leading to a better analysis of a scientific problem. This is information that wouldn't usually be disclosed between commercial rivals – even at a scientific conference.

The IMI is a 'public-private partnership' that is jointly funded and managed by the European Commission and the European Federation of Pharmaceutical Industries and Associations (Efpia), a trade body representing the world's largest pharmaceutical companies. It has its origins in discussions that took place nearly a decade ago between industry leaders and policymakers who were seeking to reverse a drop in pharmaceutical productivity. At the time, the output of new medicines across the industry was in a steep decline. Yet, record amounts of money were being spent on pharmaceutical research and development.

The initial goal of the new partnership was to bring the parties together to create new tools for drug development. Looking ahead, the partnership has an ambitious goal of helping to discover and develop new antibiotics, a huge public health need.

The IMI was launched with a budget of €2 billion that covers a period from 2009 to the end of 2017. This is shared between the Commission and industry. The Commission contributes cash, drawn from the Seventh Framework Programme (FP67) for research, while industry makes in-kind contributions such as laboratory tools and staff.

According to Michel Goldman, the IMI's executive director, some €1.2 billion has been committed thus far for a total of 37 projects. The projects include work on biomarkers, diabetes research, neuroscience and pharmacovigilance, to name just a few. With some €800 million still to be allocated, the remaining projects are expected to be fewer in number, but bigger. Besides work on antibiotics, the upcoming projects will seek to formulate a new taxonomy of disease as well as set up a Europe-wide storage and distribution centre for induced pluripotent stem (iPS) cells. Induced pluripotent stem cells are adult cells that have been reprogrammed to become embryo-like cells capable of regeneration. Such a repository would support drug research as well as stimulate the development of personalised medicines.

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>
> *Michel Goldman*

According to Dr Stensbøl, the culture of cooperation that has developed under IMI owes a lot to the clarity of the partnership's intellectual property policy. Under IMI, IP falls into one of three categories: background IP is intellectual property that a participant brings to a project; foreground IP is data developed during a project and is related to that project's objectives; and side-ground IP is data that is generated outside the project's objectives.

Characterising the IP "is done proactively," said Prof Goldman in an interview at his office in Brussels. "We don't fund any project if they [the companies] don't have a clear plan for intellectual property."

Dr Stensbøl said the IP policy essentially means that "everything that you bring into the consortium is your IP but everything that comes out is the IP of the people working on it". She said this clear-cut definition made it easier to recruit people into the NewMeds consortium – and to encourage collaboration.

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NewMeds ("novel methods leading to new medications in depression and schizophrenia") is one of several projects underway in the field of neuroscience.

Neuroscience is an area that has received a lot of attention lately – mostly for negative reasons.

In late August, Eli Lilly and Company announced that it was stopping Phase 3 development of what was thought to be a promising drug for schizophrenia after a futility analysis showed that the second of two studies was unlikely to reach its primary endpoint. Months earlier, both AstraZeneca Plc and GlaxoSmithKline Plc announced huge pull-backs in neuroscience because of the complexity and cost of the research. Both AstraZeneca and Lilly are members of NewMeds.

"Indeed some companies consider neuroscience as too risky and that is exactly why for them IMI is a way of continuing some of this research. I think this will be the future. And I anticipate that companies that were leaving [neuroscience] will come back if they can continue their research in the context of pre-competitive research and collaboration with academia," Prof Goldman commented.

Dr Stensbøl said that research in NewMeds has recently produced some interesting results, though it is still too early to say how these will play out in the clinic. Some of the first results come from a retrospective analysis of schizophrenia trials carried out by five pharmaceutical companies. The analysis showed that in trials lasting six weeks or longer, results could already be observed by week four or five. Secondly, women in the trials had a better response than men. The implications from the research are twofold. First that schizophrenia trials might be shortened and still obtain meaningful results and second, that trials with a higher concentration of women might be more optimal for testing early proof-of-concept.

"We speak so much about personalised medicine but one thing that we have never done in CNS [central nervous system disorders] before is to group patients based on whether they are women or men. When you are testing a new drug you need to know whether it works….If you enrol more women you might get a better and more robust answer," Dr Stensbøl commented. The consortium is now collecting data on trials in depression to find out whether this observation holds true for depression as well.

Second project

One of the issues that frequently arises in neuroscience, particularly in schizophrenia, is finding ways of engineering animal models that are predictive of the way the disease affects humans. Animals are widely used in drug research but it is very difficult to simulate human neurological disorders. To address this problem, NewMeds is currently working with three genetic animal models developed by Lundbeck to find out whether the animals can give clues as to how cognition is impaired in schizophrenia. There are currently no drugs approved for cognition in schizophrenia. The experimental animals carry copy number variants that correlate with a predisposition towards schizophrenia in humans.

Through DeCODE genetics Inc of Iceland, NewMed scientists have gained access to people in Iceland with similar mutations. With the assistance of an ethics committee, they have obtained consent from the relevant individuals to scan their brains to see if there are any structural differences in the brains of the people concerned. This, and other information, is being used to gain a fuller picture of how schizophrenia develops.

"Hopefully by the end of the consortium we will have found some of the features on which we can test novel concepts that will help the patient. In the end, our goal is to find novel ways, novel tools, that will enable our drug hunt in industry," Dr Stensbøl said. The NewMeds consortium has been funded until 30 August 2014.

Since IMI project funding got underway in 2009, there has been an exponential rise in published IMI research. By mid-November, more than 220 papers had been published in scientific and medical journals and every week new studies are added to the list. Eventually this new knowledge is expected to find its way into drug development, particularly if new targets are identified.

"As soon as there is enough evidence that a target is really interesting, and actually there are drugs that are being tested in autism, it is clear that the companies will move forward using the classical approach," Prof Goldman commented.

In the meantime, the IMI is considering funding what the executive director called 'quite ambitious' projects in the future. These are the antibiotic, the taxonomy and the iPS cell repository projects.

Speaking about the antibiotic proposal, Prof Goldman said: "The point is that there is a big gap between the huge public health needs and the efforts of the industry so that's why there has been this programme launched with the support of the Council [of Ministers], the Parliament of the European Union, to use the IMI to join public and private forces to speed up the development of new antibiotics."

The plan pushes the IMI into new territory in that it will go beyond researching 'tools' for drug discovery to actually conducting clinical trials of new agents particularly those targeting Gram-negative bacteria.

According to statistics issued in 2011 by the Infectious Diseases Society of America, seven out of 11 Big Pharma companies have no antibiotics in clinical development at all. And in October 2012, GSK discontinued development of one of the few agents that was targeting Gram-negative infections.

Looking to the future, Prof Goldman said the antibiotic problem needs to be tackled, along with the structure of healthcare systems generally. "There is an urgency to revisit in depth the way the healthcare systems are organised; if we don't do this I would predict that we will have many major problems in our society because people will not accept that the advances in research for which they pay is not translated into new drugs accessible to everyone."

Reference: 1. Kong, A. *et al. Nature* 488, 471-475 (2012).

The editor of *MedNous* interviewed Prof Michel Goldman, executive director of the IMI, and Tine Bryan Stensbøl, director for synaptic transmission research at H. Lundbeck A/S.

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