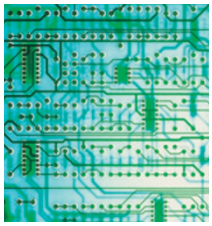

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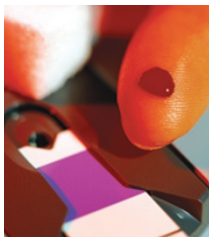

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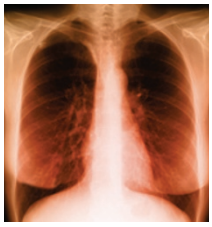

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Vaccine partnerships to tackle neglected diseases

Novartis launches a research institute that aims to aid the development of vaccines through public–private partnerships.

Bethan Hughes

At the end of February, the non-profit Novartis Vaccines Institute for Global Health (NVGH) was launched in Siena. The institute, which is offering access to Novartis' technology and expertise in vaccine development to potential academic and industry partners with vaccine inventions, will initially focus on the prevention of diarrhoeal diseases.

"There are 3 types of neglected diseases," says Rino Rappuoli, Global Head of Novartis Vaccines and Diagnostics in Siena, Italy, "the first category includes diseases where more basic research is needed before a candidate vaccine can be generated, the second includes diseases for which a candidate vaccine can be created but drugs already exist that could cure the disease and the third — which is where we have put our priorities — are diseases with high mortality, without good drug treatment options, that we believe we can address with available vaccine technology."

Novartis already has experience with such non-profit ventures — in 2002, it set up the Novartis Institute for Tropical Diseases (NITD), a drug discovery research institute that is currently engaged in ~27 public–private partnerships (PPPs). Paul Herrling, Head of Corporate Research at Novartis and Chairman of the NITD Board, attributes the high number of collaborators to the appeal of accessing Novartis' technology. "The fact that a pharma company makes available their drug discovery or vaccine knowledge for non-profit indications makes it very attractive for some of the funding agencies who have the money and the mission but don't usually have access to a professional organization." ▸

Regina Rabinovich, director of infectious diseases development at the Gates Foundation, USA, agrees that industry is an important partner. "Traditionally, innovation has come out of academia but turning that into a product requires corporate partnership," she says.

The Gates Foundation has been instrumental in the development of PPPs to tackle global health problems. "This method of activity probably began 8 or 9 years ago," says John Boslego, director of vaccine development at the non-profit organization PATH (Program for Appropriate Technology in Health) in the USA, "but started much more in earnest in the past 3 or 4 years … driven by the presence of funding from the Gates Foundation."

Rabinovich's portfolio alone includes more than US$1 billion in grants for product development partnerships for the prevention, treatment, and research of infectious diseases. When selecting projects, Rabinovich follows set criteria to ensure that the disease to be tackled is a global health priority, followed by 'landscape analysis' which looks at how the proposed solution compares with technology in that area. Finally, the potential partner is evaluated to determine what their organizational viability is in terms of management and if they are able to deliver project commitments. Rabinovich explains, "Money is an important ingredient that allows everyone to participate in a project, but without leadership commitments projects will not succeed."

For corporate partners, leadership is particularly important because, even if a product has received grant funding or non-diluting capital, it is a challenge to keep progressing non-profit projects. PATH addresses this issue by focusing on development of products that have value in the developed and developing world. Boslego says, "We think it is a win-win situation to help a company to develop a commercially viable product that would also be an addition to the health armamentarium for the developing world."

Like the NVGH, PATH aims to translate academic inventions into products. Boslego continues, "We work with established manufacturers and sponsors such as big pharma or smaller biotechnology companies to get the technology developed and advanced to a point where it can either be manufactured large-scale by the developed world or transferred to the developing world for eventual manufacture for those populations."

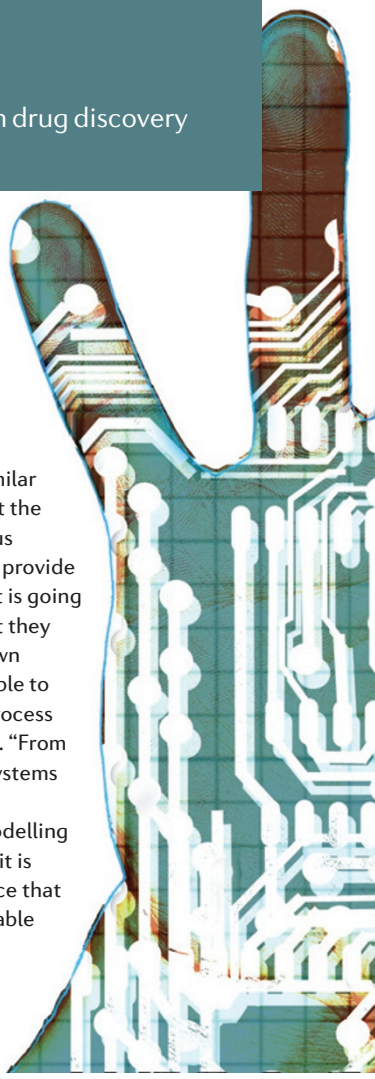
Although PPPs such as NVGH and PATH aim to create proof-of-concept products that can be manufactured large-scale by other sponsors, Alice Dautry — President of the Pasteur Institute in Paris — cautions that, even if you have a fantastic vaccine, without concurrent capacity building in the countries there will not be long-term sustainability. This includes building research in the countries, training local doctors and researchers to run clinical trials and follow the impact of vaccination campaigns, and working with the ministries of health to ensure there will be take-up of the vaccines. From his extensive experience in vaccine development, Rappuoli is aware of the importance of engaging governments, "If you don't, you get to a point where you have a vaccine but nobody will use it," he explains.

Dautry also emphasizes that it is critical to correctly diagnose the infectious disease and feels that diagnosis is another area that has been neglected. Citing an example from the Sahel region in Africa, where there are regularly epidemics of meningitis due to different strains, she notes that misdiagnosis could result in people being vaccinated against the wrong strain, which would lead to lost money, effort and credibility. "Once you have convinced mothers to bring their children and the vaccine does not work, you will not get them back next time — you have lost a generation." She concludes, "We must not be blinded by the idea that a big foundation or pharmaceutical company alone will solve these problems. Building a new vaccine is very important but in the long term it is not enough … it must be a global effort of all players, public, private and governments."

NEWS FEATURE

All systems go

How might systems biology approaches be applied in drug discovery and development? Dan Jones investigates.



In February of this year, researchers at a workshop held in Tokyo announced a bold project: to create, over the next 30 years, a 'virtual human' based on the burgeoning field of systems biology. This molecule-based computational model would describe the systems or networks of interactions between the tens of thousands of genes and proteins that underpin biological processes in both health and disease.

Systems biology is a rapidly developing field, and currently means different things to different people. "You could almost write a dictionary of the different uses of 'systems biology'," says Adrianno Henney, Director of Global Discovery Enabling Capabilities & Sciences at AstraZeneca. However, all definitions share a move away from the reductionist focus on single genes or proteins.

Systems approaches, such as genomics, proteomics and metabolomics, measure the effects of drugs or other environmental perturbations on the activities of large-scale biological networks. Although informative, some researchers think that these approaches have limitations for guiding drug discovery and development. "They are great technologies, but the data they produce have to be interpreted and integrated with a proper theoretical and conceptual framework," says Hiroaki Kitano, Director of the Systems Biology Institute in Tokyo.

Henney has similar reservations about the value of the various 'omics'. "They can provide signatures of what is going on in a system, but they are not on their own predictive of, or able to simulate, how a process operates," he says. "From my perspective, systems biology is about computational modelling and simulation — it is a predictive science that can generate testable hypotheses."

Modelling biological networks could provide

insights into why some drugs fail in clinical trials or produce unexpected side effects, argues Kitano. A crucial factor that underlies the efficacy of a drug is the 'robustness' of the network that the compound targets. Various mechanisms have evolved that allow biological networks to cope with a range of perturbations.

For example, redundancy ensures that a biological system, in health or disease, can remain stable even if some components are missing or targeted with a drug, and modularity in networks means that affecting one module does not have knock-on effects to the system as a whole. On top of this, a range of feedback mechanisms enable pathological networks to maintain a steady state in the face of various drug interventions.

As such, altering the system-wide activity of the robust networks that underlie disease states is frequently difficult to achieve by targeting single elements within the network. For complex diseases, the key is to hit numerous parts of the network to overcome the intrinsic robustness. Modelling these networks could lead to new ways to rationally design multi-target or multi-component therapies, suggests Kitano. "A robustness-based approach combined with an analysis of network structure and dynamics should enable us to predict the likelihood that certain combinations will generate desirable synergistic effects," he says.

Although generally robust, networks can also exhibit fragility at certain key points. Again, computational modelling can help to identify which parts of the network give rise to robustness and which parts are more fragile. "If we're going to succeed in treating complex disease, we have to gain an understanding of the dynamics of the complex network that underlies the pathology, and the points of fragility that exist within these networks," says Henney.

Developing predictive models of biological networks poses some pressing intellectual challenges. One task is to establish better ways of describing and understanding the control and regulation of complex networks. Traditional control theory typically assumes that systems can be regulated through one or a few control points, argues Kitano. In biological systems, by contrast, multiple control points might need to be perturbed to induce a desired network state while avoiding adverse effects. "We need to develop a powerful mathematical and computational foundation so that we can design a set of perturbations to control the state of networks," says Kitano.

Another challenge is to overcome the intellectual and conceptual inertia of established target-driven approaches to drug discovery. According to Henney, there is still some way to go in convincing people of the usefulness of systems-oriented approaches. "The drug development industry is in some respects risk averse and conservative," he says, "and it is hard for people to confidently get on board with what we're talking about."

One reservation Henney has encountered about computational models is that they do not completely capture biological reality. Some biologists say, 'The model can't be right because it doesn't contain my favourite protein or this latest bit of data!' But all models, including animal models, are imperfect, argues Henney: "They are representations, not duplications or replications."

For Henney, the key feature of computer simulations is that if you run them and validate them in the context of particular questions then they are fit for purpose. It's not a case of devising a model, running it, and automatically believing everything it tells you. "It's about generating hypotheses, checking them out, and refining the model — an iterative process to reach the point where it is sufficiently validated to run a particular set of simulations," he says.

Not everyone is convinced that computational modelling of biological networks is set to make a big impact on drug discovery any time soon. "I believe this is primarily an academic endeavour at the moment," says Eugene Butcher, Professor of Pathology at Stanford University. Butcher suggests that although there are examples in which the approach can be used to address specific, focused issues, it will be many years before we can model the response of even a single human cell to diverse environments.

> "Systems biology is about computational modelling and simulation — it is a predictive science that can generate testable hypotheses."

Leroy Hood, president of the Systems Biology Institute in Seattle, Washington, agrees. "We're very short of the experimental data to understand how biological networks function, and there's a long way to go to in developing the experimental and modelling tools to give us a view of disease-perturbed networks," he says. This, suggests Hood, means that many current modelling attempts have little contact with biological reality. "The first part of the cycle is to begin with a detailed understanding of experimental data, and this is where the progress in developing predictive models is now being made."

Even if systems biology and computational modelling could eventually boost productivity in the pharmaceutical industry, particularly in the discovery of truly innovative therapies, might it not push up development costs as well? Kitano suggests that it might, particularly in the development of combination therapies that systems-oriented approaches suggest are likely to have a greater chance of success in the clinic; these require testing and validation in various combinations, and at various doses and time schedules.

Henney, however, thinks that computational systems biology can actually help direct experimental resources more effectively, by allowing hypotheses to be ranked in advance of any wet biology. "You can ask 'Is this a reasonable experiment to run?' before you've even picked up a pipette," he says.