AN AUDIENCE WITH...

Francis S. Collins

Francis S. Collins, Director of the National Human Genome Research Institute (NHGRI), National Institutes of Health, Bethesda, Maryland, USA

Dr Francis S. Collins is renowned for his outstanding contributions to determining the genetic basis of disease, including identifying the genes responsible for cystic fibrosis and Huntington's disease, the development of positional cloning and, perhaps most famously, his leadership of the Human Genome Project. Collins now leads NHGRI's effort to exploit genomic data and develop innovative new tools to advance biological knowledge and improve human health. As part of this, he is a keen proponent of the National Institutes of Health (NIH) Molecular Libraries Initiative — part of the NIH Roadmap — which he says "aims to empower investigators in the academic sector to have access to high-throughput screening of libraries of small molecules, in order to develop chemical probes for basic research."

What are the criteria for the small molecules that comprise the Molecular Library — will they be drug-like?
Although investigators in universities and non-profit institutes are regular users of other biological tools for probing biology, the ability to identify small organic compounds to interrogate targets or pathways has not generally been within their reach. We now have the genomic targets and the technology to screen hundreds of thousands of compounds quickly, and the NIH has the opportunity to catalyse this. But this is not an attempt to turn the NIH into a drug development company. If a small percentage of the identified compounds turn out to have potential as drugs, follow up would be carried out by the private sector.

Considerable discussion has gone into the decision about what compounds will be included in the library. It will include combinatorial compounds with as many independent scaffolds as possible (to thoroughly represent chemical space), natural products, all current FDA-approved drugs, and other compounds obtained from private and public sources. Because the goal is to generate research tools, there will be less constraint on the types of molecules included than if the compound had to be used *in vivo*.

Might the potential rewards of discovering a drug mean that academic researchers choose to focus more on using drug-like compounds in their studies to the detriment of basic research?
The compounds in the library will not be entirely up to the individual centre or researcher who submits an assay. Although individuals could add certain compounds, the core composition will be decided by a distinguished group of experts from the public and private sectors. Criteria will include: the representation of as many independent scaffolds as possible, high purity, adequate quantity, ready re-synthesis, and the ability to make a family of derivatives rapidly once an initial hit has been identified. This core component of the library will be used by all of the screening centres, with constant efforts by the advisory group to improve it over time. Drug-like compounds will not drive the process disproportionately — but obviously if it is possible to represent chemical space with compounds that have a higher than average chance of being useful *in vivo*, it would be silly not to do that. However, even a drug-like compound identified in a screen has a small chance of becoming a drug.

It has been quoted that it costs pharma ~$200 per 15 mg of high-quality sample. How will the government fund the acquisition of one million high-quality compounds in quantities large enough to enable follow-up studies?
The initial budget is sufficient for populating the collection with 100,000 compounds, and it is expected that the repository will grow to a million compounds over several years, both from commercial purchases and syntheses through grant and contract mechanisms.

What will be the intellectual property (IP) situation if researchers using this library discover a potential drug?
We are considering carefully what IP protection, if any, will be sought on the probe compounds used by the screening centres, in order to maximize their use in both basic research and therapeutic development applications. Most of the compounds used have little chance of directly becoming drugs, because substantial optimization of the initial hit will almost always be necessary. So we are continuing to consult with those we hope will use the probe compounds — large pharmas, biotechnology companies, disease foundations, academics and others — to determine whether IP on the probes would encourage or hinder their use, but our philosophy would favour the lack of encumbrances.

It has been suggested that critics of big pharma and its drug-pricing policy are using the threat of the government discovering drugs to score points in an election year. What are your thoughts on this?
Being in Washington for more than a decade has helped me realize that even the purest scientific motives can be seen as having dark political roots, but this particular conspiracy theory takes my breath away. It could only arise from someone who misunderstands the goals of the initiative. The origins of this initiative are purely scientific. With the human genome and proteome now largely laid out in front of us, the urgency of understanding function compels us to consider all possible new additions to the tool kit — and the small-molecule approach is a powerful one. This initiative is not about 'the government discovering drugs' but is an effort to enable academic investigators to identify small molecules that are useful for *in vitro* research. The likelihood of any particular compound becoming a therapeutic agent is low and is likely to happen only if biotech or pharma companies decided to follow up on these early hints of function. My conversations in both the public and private sectors suggest that there is much interest in this initiative to catalyse important advances in biology and medicine.