Developing drug design through protein kinases

Well-characterised and capable of mediating the effects of various signalling factors, protein kinases hold great promise in terms of drug development. **Raimo Tuominen,** of the Protein Kinase Research Project, expands on his initiative's work in this crucial and rapidly evolving area

Accounting for almost 2 per cent of the proteins encoded by the human genome, the well characterised nature of protein kinases makes them excellent targets for drug development. Furthermore, the fact that they also play a central role in cell function, as well as mediating the effects of various growth factors, protein molecules – which promote cell proliferation and growth, means they could potentially be used to address a number of conditions, according to Raimo Tuominen of the Protein Kinase Research project. "If the effects of these signalling factors can be modified by inhibiting protein kinases – or general protein kinase activity – then cell proliferation can be stopped. This principle has already been utilised in the treatment of cancer, and it has great potential in the treatment of chronic inflammatory diseases, like rheumatoid arthritis, in which protein kinases are very important in the immune reaction," he says. Against this backdrop the Protein Kinase Research project's objective of developing protein kinase inhibitors and activators takes on real long-term significance. "The aim has really been to engage in basic research on protein kinases," continues Tuominen. "However, we are also working at the same time to achieve new drug discoveries and synthesise novel chemical entities, as well as to generate new knowledge and a basis for the future development of therapies."

Scientific work of this nature almost invariably builds on previous findings, and the Protein Kinase Research project is no exception. The success of imatinib and other drugs acting on protein kinases has been a real source of encouragement to the project; however, they have also branched out into less well-explored areas, and Tuominen is keen to stress that his project has achieved some significant breakthroughs. "We have found novel targets for the protein kinase inhibitors, such as Leishmaniasis, which is an infectious disease that mainly affects developing countries," he says. "There are similarities between leishmaniasis and malaria – not least that mosquitoes are also the vectors of the Leishmania parasite. It is also the case with Leishmania that there are protein kinases. However, these protein kinases are different from those that we have, and therefore it is the generally held view that it is much easier to find drugs which are targeted really specifically to these parasite protein kinases. In this way the disturbance of our own protein kinases will be minimised, possibly eradicated altogether. It is the same principle as using antibiotics – in bacteria there are many biochemical reactions which are, in principle, similar to human beings or mammalian cells. But still, the enzymes involved are different, and these differences are the basis of safe antibiotics."

Protein kinase inhibitors can be extracted from Nature...

.. or they can be designed using computer technology

The Prokinase Research Project Coordinator resides in Viikki Campus, University of Helsinki, Finland

Rational drug design

This kind of work brings the rapidly-evolving field of rational drug design – the discovery of new drugs based on the structural details of the molecules – into sharper focus. However, while recent scientific breakthroughs, including the sequencing of the human genome, have made it possible to develop drugs targeted specifically at certain diseases, significant challenges still remain. "No single technique will ever make drug discovery easy," acknowledges Tuominen. "It is

combining techniques, using the intelligence of people reading those results, and also taking physiological needs into account, that leads to research breakthroughs. You need to do research on the protein level, on the cellular level, on the tissue level, on the animal level and finally, on human subjects, to get the final information about a drug substance and to find out whether it is usable in therapy. We are both developing new methods and modifying existing ones. There are several partners in our consortium, including ourselves, who have developed new methods. Some SMEs that have generated new assays for protein kinases which are already being used – these are very important."

Ongoing improvement

Work in this area is ongoing, and there is always room for further improvement or more refined treatments. Indeed, although the consortium's term is nearing its end, the project partners are committed to pursuing further research in this area, and future collaborations could well include work aimed at adapting the Protein Kinase Research project's work to address other conditions. "It could be that in the future this kind of consortium will involve labs which are doing research on epilepsy, or doing research on alzheimers. They will have a specific target, or family of targets, that could then be used as the basis for drug discovery," predicts Tuominen, who says that with research advances bringing what were previously separate academic disciplines closer together, close collaboration holds the key to further development. "Many biomedicine labs are running high throughput screening to find chemical structures which anchor to a specific protein target," he explains. "At the same time, many chemistry labs are doing exactly the same. In our project we have had very fruitful interactions between sub-projects – of which we have five. These sub-projects range from looking at natural sources right through to utilising various disease models. This, together with the very sophisticated structural and synthetic chemistries, is really a combination which should be used in other projects like this, and hopefully will." ★

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With the project partners having already generated more than 200 protein kinase assays, and those assays representing the partners intellectual property, it is clear that this is work with real commercial potential. There are great reserves of knowledge in Europe's Universities, and although the suspicion that once existed between the commercial and academic sectors may have meant that business was unable to capitalise fully on this expertise, today the continent's policy-makers are keen to ensure that research breakthroughs are translated directly into commercial development. "The EU is really encouraging the commercialisation of these kinds of findings, and of the advances that are generated by research programmes like ours," says Tuominen. "Interaction between academic laboratories and commercial companies is very important, because we benefit from public funding from the EU – so the information that we share inside the consortium can also be used by companies," he says. "Of course, we need to follow agreements which have been signed, but really the companies are able to get benefits from work in academic laboratory. And the reverse is also the case, the academic labs can send their molecules to be tested by a company within the framework of this consortium."

At a glance

Full Project Title
Protein Kinases – Novel Drug Targets of Post Genomic Era

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Raimo Tuominen

Coordinator of Pro-KinaseResearch Consortium

Professor Raimo K. Tuominen, 53, made his M.D. in 1983, defended his PhD thesis in 1986, and became professor of Pharmacology and Toxicology in 1999 at the University of Helsinki, Helsinki, Finland. His research focuses on neuropharmacology, especially that of nicotine and neurotrophic factors, and intracellular signal transduction. Prof. Tuominen has been the Coordinator of Pro-KinaseResearch Consortium since 2004. This project "Protein kinases – Novel drug targets of post genomic era" is an Integrated Project of the European Union 6th Framework Program. The research has been carried out by 20 academic institutions and 5 SME partners in 12 countries.

PROTEIN KINASE RESEARCH