Advancing the search for new cancer drugs

June 11 2014

Targeted therapies have revolutionised the treatment of cancer since they were first introduced. Amongst the first medications approved in Europe, was the breast cancer drug Herceptin, which was approved in 2000. Then, the drug Glivec, was initially introduced to treat a certain form of leukaemia, and approved in 2001. Targeted therapies specifically inhibit molecules within so-called signalling pathways that usually control cell growth, death and differentiation. If they are altered, for example falsely inactivated or activated, the cells may start growing in an uncontrolled manner.

Identifying potential new targets for cancer therapy by looking at signalling pathways in the fruit fly, Drosophila melanogaster, was the aim of the EU-funded project Cancerpathways, which ended in 2011. Here, project coordinator Michael Boutros of the German Cancer Research Center in Heidelberg talks to youris.com about the effort it takes to develop new drugs, and what has happened since the project completion.

What strategy are you adopting to fight cancer?

Our involvement in the European project was to develop novel ways to advance our understanding of cancer biology and how the disease can be attacked. A major aim was to develop novel methods, so-called high-throughput bioassays, to measure the activity of signalling pathways. The partners made use of the model organism Drosophila with its highly conserved signalling pathways. Many are very similar to signalling pathways in humans.

Why are signalling pathways important as targets for cancer therapy?

Cancer is often considered to be a pathway disease. This means that there is an aberrant regulation of the same pathway found in different cancers. For example, if you look at a particular type of brain cancer, you can find the same genes mutated as in breast cancer or in colon cancer. A lot of endeavours are taken to target, for example, the so-called Hedgehog pathway in different cancers with the same type of drug. Most recently, drugs that target the Hedgehog pathway entered clinical practice to treat basal cell carcinoma [a form of skin cancer] and medulloblastoma [a brain tumour mainly affecting children].

What did you find?

The project screened through large libraries of so-called siRNA (small interfering RNAs) to identify gene products that were linked to the activity of [signalling] pathways and which may constitute novel targets for cancer. The participants ran thousands of experiments and developed new techniques to organise and analyse this huge amount of data. The team analysed many of the key signalling pathways and identified potential candidate target genes. For example, we looked for novel genes in the so-called JAK-STAT pathways, often modulated in haematological tumours. We also asked which additional genes that were previously not found are part of this signalling pathway.

What was particularly challenging?

One major challenge was: how can one run tens of thousands experiments in parallel? How can one integrate such quantitative data sets with other available genome-wide data to find the few most interesting pathway genes. Other challenges had to do with automation

and miniaturisation of experiments. The groups closely worked together to develop the technologies from small-scale to high-throughput genome-scale.

How long does it take until new medical therapies are developed based on these results?

Drug development is a long-term project. It often takes ten to twenty years from fundamental discoveries to new therapies. Of course many drug development efforts fail. In preclinical research, targets are identified. These are then validated in different disease model systems and in tumours. Then, inhibitors are designed and tested against these targets in clinical studies. This is a very complicated and expensive process. Based on the research done in the project, we are currently pursuing targets in the so-called Wnt signalling pathway. It is often mutated in colorectal cancer but also many other cancers. We are currently trying to identify inhibitors that might interfere with their activity.

What are the next steps?

Identifying targets in signalling pathways is only the first step. The different groups in the consortium are now taking the project findings further by independently following up specific gene products. This will allow them to understand these gene products' function and mechanism of action, possibly identifying new ways how to modulate their activity.

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