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Toward new cancer therapies

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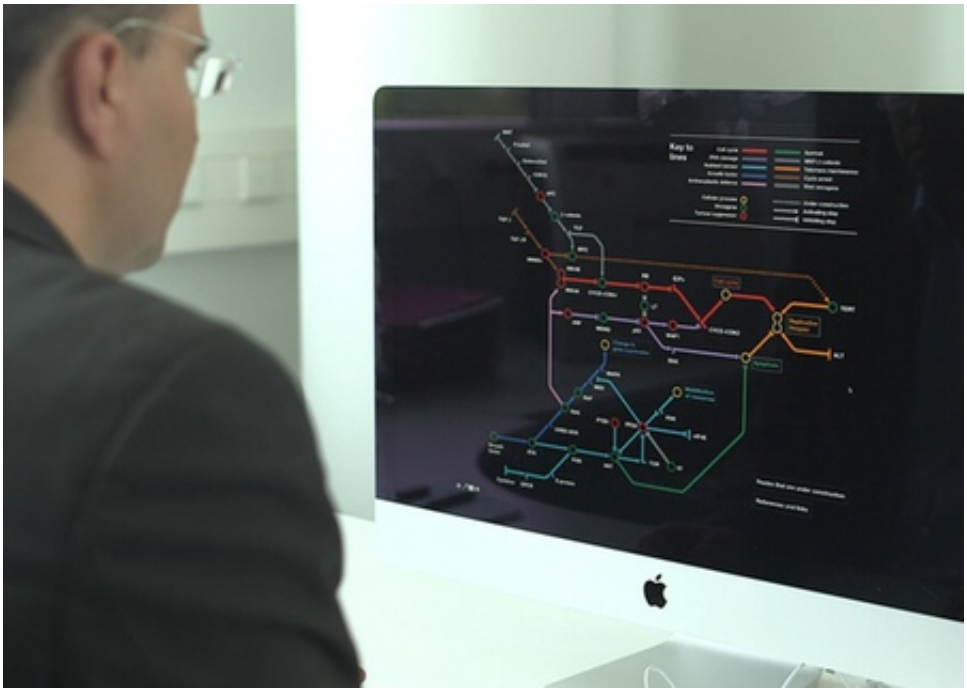

In 2012, about 8.2 million people died of cancer making the disease a major cause of death worldwide. According to the WHO World Cancer Report 2014, this figure is expected to rise within the next two decades. But new drugs are already in the pipeline. Since the end of last century, the success of targeted therapies has fuelled the research into so-called signalling pathways. In healthy cells, these pathways control cell growth, death and differentiation. If the pathways are perturbed, the cells may start to grow in an uncontrolled manner. Drugs targeting these

pathways have been successfully used. Among the most recently approved targeted drugs in Europe, there are, to name only a few,Caprelsa, which is used to treat a certain form of thyroid cancer and was approved in 2012, and Giotrif, indicated to treat a form of lung cancer, which was approved in 2013.

Identifying new potential targets for cancer therapy was the aim of an EU-funded project, called CancerPathways. To do so, the consortium turned to the old workhorse of genetics – the fruit fly. "Many of the signalling pathways where targeted therapies are entering clinical trials or clinical use have primarily been found in [the fruit fly] Drosophila and other model systems", says Michael Boutros, head of the division signalling and functional genomics at the German Cancer Research Center, in Heidelberg, who was also project coordinator. This is because "many of the genes that are mutated in cancer are highly conserved", Boutros adds. "The genome of Drosophila is much simpler and the genetic architecture easier to screen. The idea of this project was to take the power of genetic approaches in Drosophila and identify key components that control major signalling pathways", he says.

The project partners established "quantitative, very comprehensive assays for major cancer signalling pathways" Boutros tells youris.com. "The assortment of the group was done in a way that everybody worked on one of the major signalling pathways. My group, for example, is particularly interested in a signalling pathway called Wnt that is 90% mutated in colorectal cancers", he says. Using so-called siRNA (small interfering RNA), the researchers were able to knock down specific genes. The experimental results allowed the scientists to draw conclusions about the genes' function. Specifically, it helped them look for components of the pathways as potential therapeutic targets. "We found a couple of novel targets that we now pursue," Boutros says.

Experts acknowledge the value of the project's approach based on

Drosophila. "Signalling pathways in the fly are highly conserved relative to mammalian cells but there is less redundancy making it easier to dissect the pathway hierarchy and analyse their functional effects, and to discover new pathway members or interacting genes" saysHelena Richardson, group leader of the cancer cell biology program at the Peter MacCallum Cancer Centre in Melbourne, Australia. "The human homologues of these genes can be targeted to produce new anti-cancer therapies or used as diagnostic or prognostic markers", she explains.

Using siRNA technology is also seen by experts in the field as an advantage to provide a bigger picture. The siRNA technology applied in the project is a "very useful way for identifying new targets within signalling pathways," says Carl-Henrik Heldin, Director of the Ludwig Institute for Cancer Research, in Uppsala, Sweden. Moreover, "this is an example of an unbiased approach that gives a complete picture," allowing to specifically look for therapeutic targets, Heldin tells youris.com.

Heldin also points at the general advantage of targeting signalling pathways in cancer therapy. "In theory, the same medicine could be used to treat different tumours because they have the same mutations," he notes. However, since tumours differ greatly between individual patients, "we have to develop individualised treatments," Heldin says.

But he is optimistic. "All major tumorigenic pathways have probably been discovered", he says. "It is already fairly cheap to sequence DNA." This would allow medical doctors to look for mutations in individual persons and enable them to choose the ideal therapy. "This is still somewhat cumbersome and in an experimental state" according to Heldin. But "at some point we will have therapies for all cancers. The critical point that remains is the detection of cancer", he says.

Boutros himself regards the project's research as the "first step" on the

"long road" to new cancer therapies. "This project allowed us [to identify] four to five candidate [genes] that we are particularly interested in," he says. The researchers are now trying to modulate these also in human cancer cells and find ways to block cancer cell growth. "The project ended two years ago and we are still working on the follow-up experiments. It is a continuous endeavour", Boutros says.

Provided by Youris.com

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