New treatments for viral and other diseases by blocking genes

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The elusive goal of developing effective treatments for viral diseases such as AIDS and influenza has been brought closer by dramatic progress in the ability to interfere with viral genetic machinery. The stage was set for a coordinated European effort to accelerate research and stimulate development of new treatments against viral diseases at a recent research conference organised by the European Science Foundation (ESF).

It has been possible for many years to protect against some viral diseases such as polio in advance by vaccination, but there is still no effective treatment for patients once infection has occurred. Furthermore vaccination has not been possible so far against some diseases such as AIDS, and is only partially successful against some others, such as influenza. However there is now the possibility of developing treatments potentially against all viral diseases through drugs based on the recently discovered phenomenon of RNA interference (RNAi), as was discussed at the ESF conference. The interference is performed by small RNA molecules known as siRNAs (small interfering RNAs).

RNA is produced when genes are expressed, normally as an intermediate step in the production of the end product, proteins. In some cases though expression stops with short RNA molecules, which in turn regulate the activity of other genes. Such molecules are called microRNAs, of which siRNAs can be considered a sub-category. It has already been shown that siRNAs occur naturally in plants as a defence mechanism against viral infection, but it is not known whether they occur in animals as Jens

Kurreck pointed out, who organized the conference together with Ben Berkhout,. “An important question is whether RNAi is a natural cellular defense mechanism in mammals including humans,” said Kurreck.

If it turns out that siRNAs do occur naturally in humans, researchers will attempt to stimulate or reinforce them to treat viral diseases more effectively than they normally do. If they do not occur naturally, then the line would be to create artificial siRNA molecules exploiting knowledge of how plants produce and apply them in their innate immune defences.

Although the basic mechanisms of RNA interference are now quite well understood, significant challenges remain in applying the technique in treatment of disease. A major issue lies in the ability of viruses to “escape” siRNA molecules by mutating so that they are no longer susceptible, according to Kurreck. These mutations prevent siRNA molecules from binding to relevant sites on the virus, so that it can reproduce without interference.

One solution to prevent viruses escaping from RNAi in this way would be to combine several different treatments. “In analogy with the combination of several drugs in conventional virus therapy, various siRNAs against the virus can be combined to prevent viral escape,” said Kurreck. The idea is that the virus might be able to evade one siRNA, but could not duck the combined effect of several.

Another challenge lies in ensuring that siRNAs are specific and inhibit the genetic machinery just of the target virus, without impairing vital cellular processes, with knock on effects for the immune system as a whole perhaps.

RNAi treatments are not just for the future – some are close to reality, particularly against respiratory diseases, since it is easier to deliver the drugs into the lung. “Two clinical trials to use RNAi against viruses are

ongoing," said Kurreck. "There is a phase II trial with siRNAs against the Respiratory Syncitial Virus, and a phase I trial to treat patients infected with HIV." Phase I trials are usually conducted on small groups of people to assess safety, while in Phase II larger numbers of volunteers are recruited, typically around 300, to assess the effectiveness of the drug.

While the most immediate promise of RNAi is for treating viral diseases, it has equally exciting potential against other diseases such as macular degeneration, and some cancers. Here too real progress has been made. "Three clinical trials are ongoing to treat patients with age-related macular degeneration. Furthermore, one talk at the conferences was about the use of RNAi against cancer. A clinical trial for that was announced to begin at the end of 2008," said Kurreck.

Source: European Science Foundation