The newest of the new in gene therapy: 'Tag and target and exchange'

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A combination of two techniques promises to improve the efficiency and effectiveness of experimental gene therapies, while also reducing potential side effects says a new research report published in the December 2011 issue of the *FASEB Journal*. The report describes how scientists from Germany combined two techniques involving the use of site-specific recombinases, or enzymes that facilitate the exchange of genetic material between DNA strands, to help guide exactly where new genetic material is inserted into a cell's DNA. This experimental approach to gene therapy represents an important advance, as successful gene therapy has the potential to correct the root cause of numerous illnesses and health conditions.

"The central outcome of these and related techniques is the predictability and safety of a therapeutic regimen," said Juergen Bode, a researcher involved in the work from the Institute of Experimental Hematology at Hanover Medical School in Hanover, Germany. "These novel strategies will obviate the majority of animal experiments that are presently needed; it will enhance the effectiveness and shorten the timeline."

To make this discovery, Bode and colleagues identified two types of site-specific recombinases (SSR), one from yeast (Flp recombinase) and one from phages (PhiC31 recombinase), which are capable of tagging and targeting specific areas in a DNA strand. Specifically, the tagging process involves mounting a distinct address within a genome, whereas the targeting process covers the delivery of genetic material to this address. PhiC31was identified as an ideal enzyme for tagging because it

recognizes just a limited number of pre-existent genomic addresses with well-known and mostly beneficial characteristics, allows for only a one-way transfer of genetic material, and is basically irreversible. In contrast, Flp recombinase acts in a reversible manner, meaning that a given target can be modified over and over again to study the role of slight changes in the structure of therapeutic proteins. Although both techniques have particular properties, they complement one another and may even be used in conjunction to obtain ultimate results.

"Successful gene therapy has been called the Holy Grail of biomedical research. It could revolutionize medicine as much, if not more, than the development of antibiotics," said Gerald Weissmann, M.D., Editor-in-Chief of the FASEB Journal. "While we have a long way to go, this report is an important advance. It shows us how to insert important genetic material exactly where it is needed, rather than blindly popping it into a cell and hoping for the best."

More information: Soeren Turan andJuergen Bode. Site-specific recombinases: from tag-and-target- to tag-and-exchange-based genomic modifications. *FASEB J.* December 2011 25:4088-4107; doi:10.1096/fj.11-186940

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