A new gene silencing platform -- silence is golden

February 8 2009

A team of researchers led by Rutgers' Samuel Gunderson has developed a novel gene silencing platform with very significant improvements over existing RNAi approaches. This may enable the development and discovery of a new class of drugs to treat a wide array of diseases. Critical to the technology is the approach this team took to specifically target RNA biosynthesis.

The research findings are reported in the journal *Nature Biotechnology*, published online in the February 8th issue.

Gunderson, an associate professor in the Department of Molecular Biology and Biochemistry at Rutgers, The State University of New Jersey, has created highly efficient gene silencing agents that function via a novel mechanism of action. The agents are single-stranded oligonucleotides, called U1 Adaptors, that have dual, and independent, functions. First is a target-gene binding domain that can be tailored to any gene. The second domain inhibits mRNA maturation by binding U1 snRNP, a component of the cellular splicing apparatus.

By combining both capabilities in the same molecule, the U1 Adaptor can inhibit the pre-mRNA maturation step of polyA tail addition in a gene specific manner. Further, the domains of the oligonucleotide are independent so transcript binding and U1 snRNP binding can be independently optimized and adapted to a wide array of genes associated with disease.

"The U1 Adaptor platform expands on early technologies that used 5'-end-mutated U1 snRNA," Gunderson explained. "The U1 Adaptor is an oligonucleotide version of this older method and instead targets the 3' end processing step. U1 Adaptors have high activity when used alone and are synergistic when used in combination with RNAi." Gunderson went on to say that the range of possible targets is very broad due to the mechanism of action in which inhibition occurs during the biosynthesis of mRNA at the near universal 3' end processing step. Perhaps the most interesting aspect of this technology is that U1 Adaptors can possibly inhibit genes that do not respond to current RNAi methods.

The applications of U1 Adaptors expand on those currently available using standard RNAi approaches. They can be used as a research tool to determine gene function and to validate gene targets. Gene silencing molecules also have potential prophylactic and therapeutic applications based upon ongoing clinical trials using RNAi and traditional antisense approaches. For some genes that cause disease, these other approaches may not be effective enough and U1 Adaptors may provide a novel solution.'

Source: Rutgers University