

Physician revolutionizes gene research

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A dramatic new study published in the most recent issue of *Nature* questions some of the mechanisms underlying a new class of drugs based on Nobel Prize-winning work designed to fight diseases ranging from macular degeneration to diabetes.

Dr. Jayakrishna Ambati, a University of Kentucky researcher and the paper's senior author, has for years been investigating gene silencing, a 1998 discovery that won a Nobel Prize in Physiology or Medicine in unusually quick fashion in 2006.

While the prize-winning discovery remains important, the findings made by Ambati's lab show the mechanisms behind it are not as scientists once believed. In fact, Ambati's work imparts the need for caution in current clinical trials using the technology, as it may have potentially harmful effects on subjects.

Gene Silencing Leads to New Class of Drugs

In short, researchers in 1998 discovered a class of double-stranded RNA (dsRNA) that possessed powerful gene-silencing capabilities, or the ability to "turn off" disease-causing genes in the body.

The technique of targeting these dsRNA for single genes was refined with synthetic molecules called small-interfering RNA (siRNA). siRNA were thought to have the capability to interfere with specific disease-causing genes and prevent them from being expressed.

Because gene-targeted silencing with siRNA does not involve permanent DNA mutations, this approach rapidly gained popularity throughout biomedical research. The breakthrough, with the powerful ability to turn off genes, has become a standard research tool for genetic studies and has resulted in a new class of 21st century drugs designed to silence disease-causing genes in the body or disarm an invading virus by knocking out its genes.

Many diseases including age-related macular degeneration, diabetes, kidney disease, cancer, Lou Gehrig's and Parkinson's have been heralded as candidates for siRNA therapy, creating a wave of on-going clinical trials.

New Discovery Shows Therapies Could Have Harmful Side Effects

Ambati, professor and vice chair of ophthalmology and visual sciences at the University of Kentucky College of Medicine, and his colleagues have made a critical discovery that challenges the view that siRNA's therapeutic effects are imparted solely through RNA interference.

Ambati and collaborators argue that siRNA functions generically rather than specifically, thus the new class of drugs being formulated may actually adversely affect blood vessel growth in a variety of organs.

"siRNAs are used in every area of biomedical research and are thought to be exquisitely specific in targeting a single gene," Ambati said. "My lab made the surprising discovery that siRNAs, including those in clinical trials, do not enter cells or trigger RNAi. Rather, we found that they generically, regardless of their sequence or target, bind a receptor known as TLR3 on cell surfaces and block blood vessel growth in the eye, skin and a variety of other organs."

Blocking blood vessel growth is beneficial in a variety of diseases. Prime examples include wet AMD, an eye disease hallmarked by the abnormal growth of blood vessels beneath the retina, as well as cancer. However, blocking blood vessel growth by administering siRNA intravenously could be detrimental if it impacts other organs, according to Ambati's study.

Ambati, however, quickly notes the Nobel Prize-winning discovery is still valid.

"RNA interference does, of course, exist," said Ambati, a University Research Professor and the Dr. E. Vernon Smith & Eloise C. Smith Endowed Chair in Macular Degeneration Research. "It is just that siRNA functions differently than commonly believed – not via RNA interference."

Ambati said the main implications of his research are two fold:

1. for researchers to understand how siRNAs actually work
2. for clinical trials of siRNA to be approached with great caution.

Ambati's lab also showed that people with a mutation in the TLR3 receptor would be resistant to the generic effects of siRNAs, thereby providing hope for personalized medicine in this population.

The next steps, Ambati said, are to better understand the generic mechanism of siRNA that inhibits blood vessel growth and to discover how to render it useful in creating treatments for the many conditions that would benefit from such effects. His lab also will work to refine siRNAs to potentially achieve their promise of precise gene targeting.

Source: University of Kentucky

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