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A promising cancer therapy

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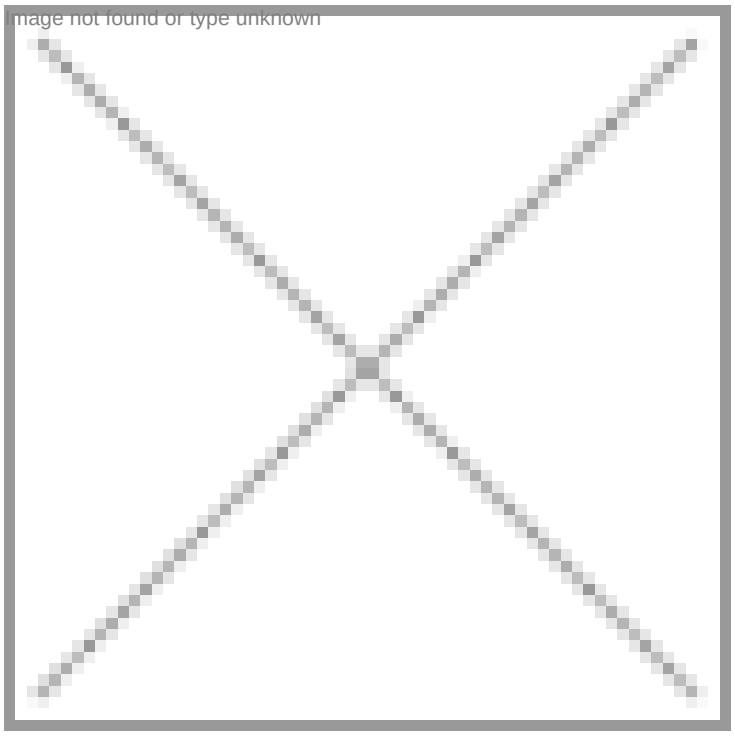
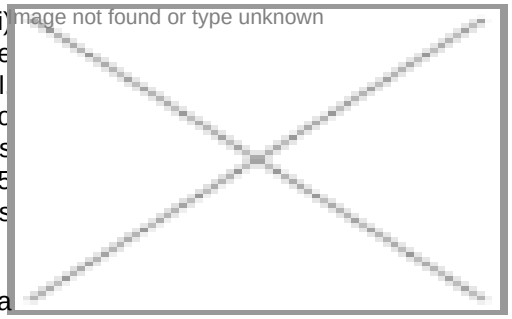




A revolutionary new technology to treat cancer called RNA interference (RNAi) which can selectively deactivate disease-causing genes is making waves in the scientific world. Anila Madiraju, a student at the Marianopolis College, Montreal Canada, has used this technology successfully to show that it was possible to turn off some cancer causing cells in humans and swept the Intel Science Awards 2003 in a global competition in mid-May from among 1,300 participants from 35 countries. She gets a $ 50,000 (Rs 25 lakh) scholarship to pursue higher studies and a high performance computer.

Anila, daughter of Murthy and Padma Madiraju, hailing from Guntur in Andhra Pradesh, was selected one of the top three young scientists in the world by an international panel of judges. Her father is a cancer researcher at a biotechnology company in Montreal. She was also selected for the Seaborg award to attend the Stockholm International Youth Science Seminar and the Nobel Prize ceremonies in 2003. Another student of Indian origin, Anant Ramesh Patel at the Astronaut High School, Titusville, Florida, was the second winner for the trip to Stockholm.

Anila has also won two cash prizes in the medical projects category.

"I want to do further research on this and help people with cancer," Anila told BioSpectrum minutes after becoming the star of the annual science show.

RNA interference (RNAi) is a phenomenon used by most living organisms as a defense against viral attacks. The process

involves the use of "small-interfering" RNAs (siRNAs) that selectively bind with complementary mRNAs and target them for degradation by inhibiting the proteins required for its growth.

Several researchers have shown that synthetic siRNAs can be constructed and used to induce RNAi in human cells. Usually cells in organisms die due to a process called apoptosis. This process is triggered in cells that have completed their lifespan or fulfilled their physiological functions. The proteins that control this process are products of oncogenes.

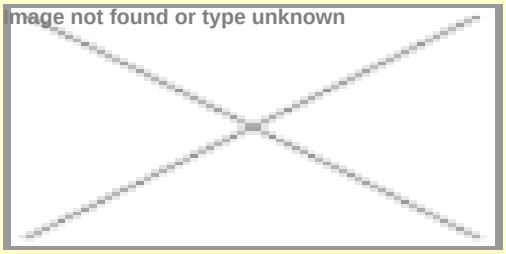
Apoptosis is regulated by the Bcl-2 family of proteins. These proteins contain regions of homologous sequences (BH1, BH2, BH3 and BH4 domains) that play an important role in their function. This family induces pro-apoptotic proteins Bax and Bak (contains BH1, BH2 and BH3) and Mcl-1S, Bad, Bid, Bik etc (these contain only BH3) and anti-apoptopic proteins (Bcl-2, Bcl-X, Mcl-1L, Bcl-w etc) that contain all the four BH domains.

In many types of cancers one or more of the anti-apoptotic proteins are elevated which help the cell to escape apoptosis. One such cancer is myeloma whose survival is completely dependent on Mcl-1L.

Anila's project targeted this type of cancer. Anila's project used RNAi to specifically alter the Mcl-1L and Mcl-1S levels in cancer cells and test their sensitivity to accept apoptosis. She showed that RNAi could be used to silence and inhibit Mcl-1L protein production which leads to the death of cancer cells. This technology could lead to the development of a therapy to cancer. The advantage of this method is that being target specific, it does not induce side effects observed in chemical compounds used to treat cancer.

N Suresh in Cleveland, Ohio

What next with RNAi



The search for an effective cure against cancer has been going on for decades. In December 2002, the Science magazine named RNAi as the most promising breakthrough of the year.

"RNAi is the most important and exciting breakthrough of the last decade, perhaps multiple decades," leading biotechnologist and Nobel-laureate Philip A Sharp told the magazine.

Thomas Tuschl, a top researcher at the Rockefeller University, is credited with the development of the RNAi technology. The power of the technology was demonstrated recently by Harvard geneticist Gary Ruvkun. His team identified some 300 genes that regulate the body fat in worms which could be turned off using the RNAi technology. This led to the reduction of body fat in these worms. The counterparts of many of these genes exist in humans and scientists believe that with more research it may be possible to target them for treatment using conventional drugs.

What is heartening is the fact that only a small amount of RNAi inducers are required to selectively turn off genes. However, a method to deliver the right amount of the siRNAs directly to the cells may prove to be tricky. Scientists may have to use aerosols to reach the target cells. Because in many experiments in test tubes, compounds that trigger RNAi break down within seconds when they enter the bloodstream.

Other experiments with RNAi technology show a lot of promise. Boulder-based Sirna Therapeutics (formerly Ribozyme pharmaceuticals) has shown that it was possible to slow down macular degeneration (a type of eye disease caused by abnormal growth of blood vessels) in rats with some synthesized RNAi compounds. These compounds block the growth of the genes that improve the development of abnormal blood vessels. Buoyed by the success of these studies, Sirna managed to get a $ 48 million venture fund from Oxford Bioscience Partners and Venrock Associates to carry the development further.

Though the RNAi phenomenon was first observed in 1830, it came into prominence only in 1998. This was when Andre Fire at the Carnegie Institution of Washington showed that gene-like fragments introduced in small worms called nematodes had formed 'double-stranded RNA''. These abnormal versions of RNA molecules resembled closed zippers and triggered RNAi in nematodes. Tuschl's team reported in April 2001 issue of Nature how to make siRNAs.