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Science and Amersham Pharmacia Biotech Grand Prize:
"Jumping DNA" Discovery Explains Immune System Evolution

1 December 2000 -- By discovering jumping DNA's role in creating our modern-day immune system, a 31-year-old scientist in Stamford, Connecticut, earned this year's $25,000 Young Scientist Prize, awarded by *Science* and Amersham Pharmacia Biotech (APBiotech).

Alka Agrawal was working on her doctoral degree at Yale University when she proved that genes called *RAG1* and *RAG2* carry out genetic reshuffling or "transposition" reactions in a test tube.

In theory, if these genes trigger transposition in living cells, too, they may be involved in harmful DNA translocations associated with certain cancers, Agrawal explained in her winning essay, which appears in the 1 December 2000 issue of *Science*.

It is unclear whether *RAG1* and *RAG2* cause translocations in systems such as T-cells and B-cells within the human body's immune system. But, the possibility underscores the importance of better understanding the function of these genes.

APBiotech, a leading global provider of biotechnology systems, products and services, teamed up with *Science* to establish the Young Scientists Prize in 1995. Each year, the Prize supports molecular biologists in an early stage of their careers.

A judging panel selects the Young Scientists grand prize winner and may present regional awards in four geographic regions: North America, Europe, Japan and all other countries. These regional winners receive $5,000 awards.

The grand prize recognizes Agrawal's contribution to evolutionary biology, resulting from her discovery of mobile cut-and-paste artists within the immune system. "We observed an unexpected product in our tests, and oddly enough, it turned out to be really important," Agrawal said of her research experience. "It was one of those serendipitous moments in scientific investigation, when a big puzzle piece suddenly falls into place."

Found in all jawed vertebrates, from sharks to humans, the *RAG1* and *RAG2* genes explain why higher animals have complex immune systems, including a first and second line of defense against invading pathogens.

Some 450 million years ago, Agrawal's research suggested, a bit of jumping genetic material, containing the *RAG1* and *RAG2* genes, infected an early jawed vertebrate such as a primitive shark. The microbe jumped into this ancestor's genome, allowing it to crank out antibodies generated by transposition reactions.

Agrawal's discovery, shared with her Yale University adviser, David G. Schatz, and colleague Quinn M. Eastman, was made possible by a unique petri-dish system for studying the chemical steps involved in genetic reshuffling events that produce millions of different antibodies. Specifically, the system tracks the products of a phenomenon called V(D)J recombination.

During development of the immune system, Agrawal noted, the body produces many lymphoid cells, each expressing a receptor specially designed to grab an antigen, which marks invaders as foreign. Fighter cells called B-lymphocytes crank out immunoglobulin receptors, for example, and T-lymphocytes produce T-cell receptors. The immune system generates receptors capable of recognizing many different antigens by rearranging gene segments called V, J and D.

This cut-and-paste process depends on the *RAG1* and *RAG2* genes. Moreover, Agrawal found, the proteins encoded by the genes cause DNA to jump into other DNA molecules by attacking bonds in the DNA backbone. Millions of years ago, Agrawal has proposed, a "RAG transposon" or ancient jumping DNA, produced our current two-level immune system, including immunoglobulin and T-cell receptor gene segments, by splitting sequences, which then duplicated.

When jumping DNA malfunctions, Agrawal's essay pointed out, "continued transposition could be mutagenic and lead to leukemia by activating oncogenes, inactivating tumor suppressor genes, or creating chromosomal translations." Research has not yet demonstrated jumping-DNA transposition in living cells, Agrawal emphasized. But, she added: "It's somewhat logical that errors in V(D)J recombination could have undesirable results, and we therefore must continue to investigate whether this is happening."

Agrawal grew up in Farmington Hills, Michigan, not far from Detroit. Because her father is a mechanical engineer, she said, "Science and mathematics were always very important." A biochemistry course while she was an undergraduate confirmed her interest in research, and prompted her to pursue an undergraduate degree in chemical engineering from the University of Michigan. After earning her B.S. degree, Agrawal decided that she was more interested in pharmaceuticals development than chemical manufacturing, so she began working toward a doctoral degree in pharmacology at Yale.

Since then, she has studied science policy and completed a Mass Media Fellowship offered by the American Association for the Advancement of Science (AAAS), which publishes *Science.* As a result, Agrawal has launched a science journalism career.

Arne Forsell, Deputy CEO of APBiotech, commented: “Alka Agrawal’s research exemplifies the importance of and the need to encourage scientific pursuit. The achievements of Agrawal and the regional prize winners clearly demonstrate the reason APBiotech established with *Science* a program to encourage young scientists in their pursuit of breakthrough discoveries. We are proud to help these promising researchers continue their work.”

Applicants for the APBiotech and *Science* Young Scientists Prize earned their Ph.D.s in 1999 and submitted a 1,000-word essay based on their dissertations. Their essays were judged on the quality of research and the applicants’ ability to articulate how their work would contribute to the field of molecular biology, which investigates biological processes in terms of the physical and chemical properties of molecules in a cell.

“*Science* is proud to recognize Alka Agrawal’s outstanding contribution to molecular biology,” said Donald L. Kennedy, Editor-in-Chief of *Science.* “Her accomplishments will benefit a generation of scientists investigating the molecular mechanisms responsible for immune system responses, which may also be involved in some cancers.”

Science / APBiotech also named four $5,000 regional winners:

Yuki Yamaguchi, Japan (Tokyo): Yamaguchi’s research may provide insights into how human immunodeficiency virus (HIV) proliferates as viral genetic sequences elongate during transcription. To investigate the regulation of transcript elongation events, Yamaguchi studied the process in a model system: eukaryotic RNA polymerase II (pol II). The function of two elongation stoppers, which inhibit lengthening, is switched on and off by another complex, he found. Specifically, when the C-terminal domain (CTD) within pol II’s largest subunit combines with phosphorus, Yamaguchi learned, it prevents the inhibitors DSIF (DRB-sensitivity inducing factor) and NELF (negative elongation factor) from binding with pol II. In this way, Yamaguchi wrote, the phosphorylation of CTD functions as a molecular switch, regulating the activity of other players in transcript elongation. Because HIV’s chief activator, Tat, is also sensitive to DRB (5,6-dichloro-ß-D-ribofuranosylbenzimidazole), Yamaguchi’s research sets the stage for new disease-blocking strategies.

Rafal Ciosk, Europe (Vienna): When cells divide, chromosomes duplicate but stick together for a time, as so-called “sister chromatids.” Molecular glue keeps the sisters linked until opposing forces suddenly rend them apart. Researchers have long hoped to learn what binds and then frees sister chromatids, in part because these mirror-image blueprints may contribute to cancer or inherited genetic diseases when the duplication process occurs at abnormal levels. Ciosk invented a special assay to study cohesion proteins linking sisters in a budding yeast model. At least three classes of proteins participate in binding, Ciosk determined while working at the University of Vienna. A substance called APC (Anaphase Promoting Complex), or cyclosome, then liberates a “sister separating” protein, Esp1, which would otherwise be inhibited by Pds1p. The existence of similar proteins in vertebrates suggests that sister separations may be similarly regulated in humans, Ciosk concluded.

Douglas M. Heithoff, USA (California): While pursuing his Ph.D. at the University of California-Santa Barbara, Heithoff identified a “master switch” that allows bacteria to orchestrate the infection process. By removing the gene for the switch, disease-causing bacteria were rendered harmless in mice. The switch is found in pathogenic microbes responsible for many of the world's worst killers, including bubonic plague, cholera, dysentery, and typhoid fever. New vaccines and antibiotics may ultimately result from the research, completed at a time when drug-resistant bacteria are on the rise. Heithoff and colleagues Michael J. Mahan, Robert L. Sinsheimer and David A. Low demonstrated how Salmonella bacteria could be disabled by knocking out the switch, then exploited the system to develop a vaccine which generates protective immune responses in mice.

Avraham Yaron, Middle East (Israel): At the Hebrew University, Yaron helped explain a critical molecular mechanism at work in chronic inflammatory diseases and tumor-cell resistance to chemotherapy drugs. With Yinon Ben-Neriah, Ada Hatzubai and others, Yaron demonstrated how and when ubiquitin—a small molecule found in all cells—decides to plot the destruction of certain proteins, including regulatory proteins responsible for inflammatory responses or the survival of tumor cells. The research team discovered that a receptor “lock” recognizes a protein segment that combines with phosphorus, then helps ubiquitin attach to the regulatory protein. Methods for blocking this process, and perhaps improving treatments for cancer and asthma, may result from Yaron’s research.

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Science is a leading international journal covering all scientific disciplines. It is published by the American Association for the Advancement of Science (AAAS), the world’s largest general scientific organization. *Science* has the largest paid circulation of any peer-reviewed general science journal in the world.

APBiotech, the life sciences business of Nycomed Amersham plc (LSE: NAM; NYSE: NYE), is a leading global provider of biotechnology systems, products and services for research into genes and proteins, for the discovery and development of drugs and for the manufacture of biopharmaceuticals. The customers for APBiotech’s products and technology are pharmaceutical and biotechnology companies and research and academic institutions in North America, Europe, Latin America and Asia.

Information about the prize and copies of the winning essays will be posted on *Science* Online (http://www.sciencemag.org/feature/data/pharmacia/prize/apbprize.shl) and will be available on 30 November.