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MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

# Columbia Scientists Win International Award for Fundamental Research that Advances Understanding of Biology and Disease

*Prizes recognize their pioneering research illuminating how cells communicate with each other, a crucial factor to them developing properly.*

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*NEW YORK — Today, two scientists at Columbia University each received the Canada Gairdner International Award for research that helped yield critical insights on how cells communicate with their neighbors during animal development. Specifically, the awards celebrate their research on one of the fundamental pathways of developmental biology, known as Notch, which is found throughout the animal kingdom and plays a crucial role in the control of cell fate during development.*

*Columbia's recipients of the prestigious awards are developmental biologists Gary Struhl, PhD, a principal investigator at Columbia's Zuckerman Institute and a professor of genetics and development and neuroscience at Columbia's Vagelos College of Physicians and Surgeons, and Iva Greenwald, PhD, the Da Costa Professor of Biology in the Department of Biological Sciences and Professor of Biochemistry and Molecular Biophysics at Columbia University.*

*We talked with Drs. Greenwald and Struhl, who happen to be married, about the research recognized by these awards.*

**What is the focus of your research?**

**Gary Struhl**: All animals are composed of cells, often many millions if not billions of cells, which are organized into amazingly complex and remarkably reproducible patterns. Think of butterfly wings: all butterflies of the same species form wings of the same size, with beautifully complex patterns of colors, stripes and spots that are virtually identical.

The central problem of my research addresses how those cells communicate with each other to decide what to do during development.

**Iva Greenwald**: During development, initially "equivalent" cells often communicate with each other to choose distinct cell fates. My work focuses on how cells coordinate their

decisions with the choices made by their neighbors so that the correct numbers and patterns of different cell types are generated.

**Of the decades of research that you have conducted, what specific work of yours are these awards celebrating?**

**GS**: These awards recognize our contributions to the discovery of the Notch system, which is centered around the Notch superfamily of receptors, as well as the molecular logic by which this system operates. Resolving how the Notch system works is hugely important for us, medically speaking. The loss or inappropriate activity of this system can cause diverse cancers as well as catastrophic defects in virtually every organ system in our bodies.

**What did you discover?**

**GS**: Iva's pioneering work identified Notch as the central component of a system of intercellular signaling. It also identified its role as a receptor that coordinates the developmental fates of neighboring cells. Our experiments in fruit flies and worms confirmed that Notch acts as a cell surface receptor, but in the process yielded a surprising result. Notch is normally found predominantly at the cell surface, but when the part of Notch that extends into the cell is expressed on its own, it has constitutive signal transducing activity and localizes to the cell nucleus.

This unexpected result led us to propose a novel mechanism of signal transduction. When one cell sends a message, it triggers the cleavage of Notch on the receiving cell, releasing the intracellular part of the protein from the cell membrane. This piece then travels to the nucleus and changes gene expression, and hence the behavior of the cell. My subsequent work validated this hypothesis, establishing that Notch acts as a membrane-tethered transcription factor to transduce signals from neighboring cells. It also led to the discovery that signals from neighboring cells trigger Notch activity by force, by mechanically pulling on the receptor to initiate the proteolytic cascade that releases its cytosolic domain—the transcription factor—for import into the nucleus.

**IG:** While Gary was working out the mechanism using a chimeric protein approach in the fruit fly, *Drosophila*, genetic analysis in the roundworm *C. elegans* in my lab identified most of the evolutionarily conserved core components of this signaling pathway, including the protein presenilin, which is linked to Alzheimer's disease. We then combined forces to show that presenilin is required specifically for the cleavage of Notch within the cell membrane that releases the cytosolic domain for nuclear entry.

**What applications might this research have?**

**IG**: From a broader perspective, these discoveries provide valuable insights and potential therapeutic approaches to the many disease conditions caused by gain and loss of Notch signaling.

**GS**: In addition, the technologies used to investigate the Notch system, as well as the modular nature of Notch proteins, have allowed scientists to repurpose the basic mechanism of Notch to create new kinds of intercellular “synthetic Notch” communications systems, a now burgeoning field for cancer therapies and tissue engineering.

**What does winning the award mean to you?**

**GS**: I have a deep conviction in the values of basic research and the use of genetics in model organisms to discover fundamental properties of the natural world. For me, the award represents the recognition and justification of these values, and it is a great honor and privilege to represent the many other scientists who share these values and have contributed so much to society through their work.

**IG**: It's an incredible honor to have my life's work recognized by this award. Also, I appreciate that the Gairdner Foundation brings a celebration of basic, essential science to the public. This mission feels especially urgent now.

**What's next for you? Where do you see your field headed?**

**GS**: The general problem I am interested in continues to be the enduring mystery of how cells know where they are, and what they do as a consequence, the essential precondition for the control of growth and patterning in animal development.

**IG**: I always tell my students that progress is like moving upwards on a spiraling course. We keep coming back to the same issues at a higher point of understanding and then do another turn. I think we're poised to do another turn now, looking at cell-cell interactions and cell signaling with unprecedented rigor and resolution now thanks to the ever-increasing power of genome manipulation and microscopy methods.

Apart from the basic science, I look forward to seeing how others repurpose the basic mechanism of signal transduction that Gary and I elucidated to pay off in the clinic.

*The Canada Gairdner International Award bestows $250,000 Canadian to each recipient. More information can be found on the Gairdner Foundation's site.*