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The discovery of the first cadherin, a calcium-driven cell adhesion protein, came about by chance, says Masatoshi Takeichi. If so, it is a textbook illustration of Louis Pasteur's dictum that, "Chance favors the prepared."

Cell Adhesion Pioneer

Takeichi's chance discovery and three years of determined follow up led him to the first molecular description in 1977 of a cell surface protein that switched on cell-cell adhesion in the presence of calcium divalent cations. More definitive characterization of this protein in 1982 led Takeichi and graduate student Chikako Yoshida in 1984 to coin the name "cadherin" for what became a multiplying class of "calcium adhering" proteins. Today the class includes not only a string of "classic" cadherins but also desmogleins, desmocollins, protocadherins, and other cadherin-like proteins. The first cadherins were discovered in the context of developmental embryology, but the cadherin connection is one of the hottest topics today in cancer, aging, and neuroscience research.

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All this shows the power of chance or at least of reading bottle labels and questioning their contents. It started with a bottle of trypsin solution, a proteolytic enzyme long used in embryology labs to partially digest tissue and cause individual cells to disassociate. In 1974, Takeichi was issued a bottle of trypsin made in the usual way by technicians at the Carnegie Institution in Baltimore. On leave from his faculty position at Kyoto University, he had just arrived as a visiting scientist in Dick Pagano's lab. Repeating some earlier disassociation experiments with Chinese hamster V79 cells seemed a good way to adjust to lab life in a new country. So Takeichi ordered some trypsin and got to work. The experiments went well, but Takeichi noticed something odd. In his Kyoto lab, the trypsinized cells would reaggregate over time. At the Carnegie, the treated cells never reaggregated.

The difference in trypsin solutions turned out to be the addition of the chelate EDTA in the Carnegie recipe. EDTA effectively stripped the solution of all calcium ions. Takeichi theorized that the presence of small traces of Ca^{+2} in his Kyoto trypsin was protecting specific cell surface proteins involved in cell-cell adhesion. Returning to Japan in 1976, Takeichi explored both calcium-dependent and calcium-independent adhesion, using antibodies to identify and characterize what became cadherin. (Takeichi's future E-cadherin turned out to be identical to "uvomorulin," which was identified independently in François Jacob's lab.)

A Modest Revolutionary

Known internationally today as a pioneer of cell adhesion, Takeichi is a major player in Japanese bioscience as director of the government-supported but independent RIKEN Center for Developmental Biology in Kobe. Among his more recent honors, Takeichi was awarded, along with Erkki Ruosalhti, the 2005 Japan Prize for Cell Biology. When pressed for details, Takeichi mentions that the Japan Prize was presented in the presence of the Emperor and Empress. Then he adds that he met the Prime Minister, but he leaves out the Speakers of both houses of Parliament, the Justices of the Supreme Court, and the symphony orchestra performance. He also omits his 25 million yen award (roughly U.S. $237,000) and his selection of Mahler's Fifth Symphony for the musical program.

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Understatement is a Takeichi trademark, friends and colleagues say. Pressed on the impact of cadherins, Takeichi will only concede that the field of cell adhesion is a little larger than it was when he made his "chance" discovery in 1974. "Masatoshi is being his usual extremely modest self," says Ken Yamada of the National Institute of Dental and Craniofacial Research. "I expect that even though he realized that his findings were important at the time, the field has probably exploded much beyond what he imagined, and so many new cadherins have been discovered."

In the early 1990s, Yamada worked with Takeichi and Jean-Paul Theiry to organize an international cell adhesion research program funded by the multinational Human Frontiers Science Program. Says Yamada, "Masatoshi's studies were truly revolutionary in advancing our understanding of cell adhesion, with important implications for development, tissue repair, and cancer. Although it had been known for many years that calcium was important for cell adhesion, his brilliantly insightful studies provided the molecular basis, as well as antibody and cDNA probes to determine the functions of cadherins in innumerable biological events."

Kathleen Green of Northwestern University says that Takeichi was the first to delineate two separate mechanisms of cell adhesion, calcium-dependent and calcium-independent: "Takeichi followed up on the calcium-dependent mechanism, and he was the first to demonstrate the existence of an actual molecular entity as opposed to just showing that there was this adhesion phenomenon. Takeichi defined the first of a specific class of molecules that was responsible. In my mind, that really broke open this whole field."

Fundamental Problem-solving

The phenomenon of cell adhesion had been known since the late 19th century, when the first embryologists witnessed cells adhering to one another and then selectively changing their positions during development, according to Gerald Grunwald of the Jefferson Medical School in Philadelphia. "The difficulty was in getting behind the phenomenon [of cell adhesion] and identifying the molecules responsible. That's what Takeichi did. He was the first to get a biochemical handle on a key element of adhesion, the role of calcium in the process."

Grunwald emphasizes the contributions of others to cell adhesion, including Rolf Kemler, Malcolm Steinberg, Gerald Edelman, Jack Lilien, and François Jacob. But Grunwald suggests that if you want a snapshot assessment of Takeichi's impact, run a MedLine search for the term cadherin. (A recent search turned up 7,260 references.) "If and when there's an 'adhesion' Nobel Prize, I hope that Masatoshi will be there, maybe with others, but I imagine him standing there," says Grunwald.

Ironically, biology was considered an unlikely path to prominence in postwar Japan, Takeichi recalls. Even his beloved high school biology teacher, who honed Takeichi's interest in bird watching, advised him against pursuing a biology degree. His teacher advised Takeichi to join his father in the family business and make biology an outdoor hobby. Takeichi did become a happy amateur observer of insects, fish, and birds. "Bird watching is fun," he says, "but I didn't want to do it for a living."

The biology Takeichi learned at Nagoya University was analytical, experimental, and indoors. Working with Goro Eguichi at Nagoya as a graduate student, and then under Tokindo Okada at Kyoyo, Takeichi studied the development of the lens in chicken. Okada's innovations in culturing embryonic cells allowed Takeichi to study how signaling between retinal and lens cells affected differentiation. But Takeichi was increasingly drawn to the fundamental problem of cell adhesion. He wondered whether cations—not just those of calcium but perhaps magnesium or magnesium cations—could hold the molecular keys. That became the focus of his Kyoto lab in the early 1970s and for his fateful experiments with trypsin.

A Smaller Scientific World

Looking back on Japanese cell biology in the 1970s, Takeichi is struck by the isolation of Japanese labs from their American and European counterparts. "Now we have the Internet so we can get information very quickly. But 30 years ago, we only had contact through the journals, and they arrived several months later. At that time, journals came by sea because air mail was very expensive." The isolation was frustrating and worrisome, but Takeichi said it had its advantages. "If you know too much about what others are working on, it can make your thinking too similar to theirs," he says, undercutting your own ability to do truly original research. "Quiet environments are sometimes beneficial in cultivating uniqueness."

More worrisome today, says Takeichi, is the linguistic isolation that still plagues Japanese science students. They generally have a good command of written English but little experience in speaking it. Even at international meetings, Takeichi says that Japanese attendees tend to clump together because of their inexperience with spoken English. He urges his graduate students to travel and to seek out foreign lab placements. "Meeting people is very critical in science. At our institute, we have a training program for young scientists to improve their English communication abilities. I am happy to say that they now look more cosmopolitan than before."

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Change and Tradition

Being the director of RIKEN puts Takeichi in a unique position to affect the future of Japanese bioscience, says his former graduate student Naoshiga Uchida, a neurobiologist now on the faculty at Harvard. Being outside the Japanese university system and with independent funding, the RIKEN is able to sidestep the traditional scientific hierarchy, says Uchida. "He's trying to change things through his position at RIKEN. He's hiring younger people for independent positions, which is not common in the old Japanese universities. I think what he has done at RIKEN is a good model for the future of Japanese science," Uchida concludes.

When he took the RIKEN post in 2000, Takeichi and his wife, Miyuki, had to move from Kyoto to Kobe. "Kyoto is not so far but not so close," he says, for a daily commute. Next year, Takeichi will lose another tie to Kyoto, when he reaches the university's mandatory retirement age of 63 and gives up his Visiting Professorship there. RIKEN though will keep Takeichi busy for years to come.

The move to an apartment in Kobe forced another big change, a cut back in his legendary home greenhouse and tropical fish collections. Takeichi transferred his orchid collection along with a few of his prized fish to his RIKEN lab. Lately, Takeichi has noticed with some amusement the spread of a windowsill orchid-growing fad through the laboratory. "This is my influence," he says, "because these are very unusual plants here, and they are not very popular. Still, looking at these things every day makes me feel very comfortable."

If his scientific career has been firmly rooted in analytical and experimental biology, Takeichi still brings something of the traditional naturalist's approach to his bench science. Says Uchida, "He's very good at observing. Even after taking on this new position [at RIKEN], he still spends a lot of time looking at samples by himself. He's in the lab every day to see what's new."

Observing is part of the preparation for chance discoveries, says Gerald Grunwald. He remembers standing with Takeichi outside a Gordon Conference session during a break. "He's had this lifelong fondness for insects. So we were off to one side chatting when I suddenly noticed that Masatoshi's attention was elsewhere. Some exotic insect had just flitted by and caught his eye." ■