When Anders Björklund started medical school in the early 1960s, scientists still believed that the structure of the adult brain was fixed and immutable and that nerve cells could not be regenerated after damage or death. But that view changed when Björklund began using a powerful new fluorescence microscopic method to view subsets of neurons. He became convinced that given the right conditions, immature neurons could be inserted into the brain to help regenerate damaged areas. That leap of faith—and the groundbreaking revelations that followed—jumpstarted his pioneering career in neuroscience.

Björklund, a founder of the Wallenberg Neuroscience Center (Lund, Sweden) and recently elected member of the National Academy of Sciences, is currently a professor and head of the neurobiology unit at Lund University in Lund, Sweden. In 2011, he received the Robert A. Pritzker Prize for Leadership in Parkinson Research from the Michael J. Fox Foundation. His initial finding soon opened the door to an entirely new line of research. After revealing that dopamine neurons could be transplanted into rats to relieve Parkinson-like symptoms, Björklund and former student Olle Lindvall initiated the first clinical trials in Parkinson patients to confirm that dopamine neuroblasts, implanted into the striatum, can survive, integrate, and function for years in the diseased brain. Researchers at Lund are now exploring the possibility of identifying effective alternative treatments for the damaged system. The effect was long-lasting, with the cells seemingly in-connections and substitute to a certain extent for the damaged pathways. They might repair the damaged brain areas, where the new cells damaged brain areas, where the new cells neuroblasts from developing rat fetuses then implanting immature neurons or neuroblasts from developing rat fetuses at the site of injury. “We got striking results,” says Björklund, who used microscopy, electrophysiology, behavioral measures, and other methods to systematically study the ability for implanted neuroblasts to develop in the adult rat brain (4, 5).

“The idea was to replace the damaged neurons with new cells that would assume functions similar to the original system,” says Björklund. “We demonstrated that immature neuroblasts, once they were allowed to develop and integrate in the host brain, could reestablish lost connections and substitute to a certain extent for the damaged system. The effect was long-lasting, with the cells seemingly integrating permanently into the host.”

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Radical Idea
By the mid-1970s, Björklund had switched focus from mapping brain anatomy and function to studying brain regeneration. He became absorbed in the then-radical hypothesis that brain damage could be repaired given the appropriate conditions through the transplantation of immature neurons. “The general view at that time was that the brain was like a telephone switchboard, fixed and immutable,” says Björklund. “Regeneration in the central nervous system was described as abortive and nonexistent. So no one was interested in studying brain regeneration, because they thought it was hopeless.”

However, Björklund and his partner, Ulf Stenevi, had spent years using the Falck–Hillarp method to study neurons in their entirety, exploring their growth and connections. The pair thought it might be possible to implant immature cells into damaged brain areas, where the new cells might repair the damaged pathways. They began working on rats, damaging nerve cells in specific brain regions, such as the hippocampus and the basal ganglia, and then implanting immature neurons or neuroblasts from developing rat fetuses at the site of injury. “We got striking results,” says Björklund, who used microscopy, electrophysiology, behavioral measures, and other methods to systematically study the ability for implanted neuroblasts to develop in the adult rat brain (4, 5).

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plasticity—is commonplace. Those early findings inspired Björklund’s laboratory to pursue a therapeutic technique.

Transplanting Memories

Björklund is most noted for his work on Parkinson disease, but in the early 19080s, he spent some time exploring whether cell transplantation could correct memory deficits caused by damage to the hippocampus. The study was an offshoot of a collaboration with Susan Iversen’s laboratory at Cambridge University (Cambridge, England). Iversen’s laboratory had sophisticated behavioral tests for measuring cognitive function in rodents. Iversen’s graduate student at the time, Steve Dunnett, spent a year in Lund setting up behavioral tests that would allow Björklund’s group to measure rat behavior after brain damage and then again after transplantation to see if the rodents had recovered any function.

During this time, neuroscientist Fred “Rusty” Gage joined Björklund’s laboratory as a postdoctoral student. During Gage’s 4 years in the laboratory, Björklund estimates that they wrote as many as 50 papers together. “We had a great time, the most stimulating and enjoyable collaboration of my entire career, and made remarkable progress,” he says. In one series of studies, the pair impaired learning and memory by removing the cholinergic inputs from the rats’ hippocampi, and then, they reversed the impairments by implanting cholinergic neuroblasts into the damaged areas (6). The grafted neurons accurately reestablished the terminal innervation patterns of the lost cholinergic pathways, and grafted neuroblasts were accompanied by improvements in maze-learning behavior.

The collaboration lasted long after Gage left Lund, eventually exploring the restorative effects of the neurotrophic factor Nerve Growth Factor (NGF) (7). The group showed that NGF could protect cholinergic neurons in the hippocampus from damage and that administration of NGF into the brain could ameliorate cholinergic neuron atrophy and cognitive impairments in animal models of cognitive decline (8, 9). Björklund believes that the work has implications for treating memory-related brain damage in humans, but no one has followed it up in a clinical setting; perhaps, he says, because most problems with learning and memory in humans are more complex than just damage to the cholinergic system.

Focusing on Parkinson

By the mid-1980s, Björklund’s attention had returned to Parkinson disease. “The scientific challenges for me have clustered in that area,” says Björklund. “That’s been a strong incentive to focus there. There are lots of nuts to crack.” The work started in 1979, after Björklund’s group successfully transplanted fetal cells into rat brains. From there, he and his colleagues began working on rats with injuries to the nigrostriatal dopamine system, which results in motor impairments that mimic Parkinson disease in humans. In a series of studies, the researchers showed that transplants of fetal dopamine neurons into the damaged regions of the rats’ brains restored local dopamine concentrations and reestablished normal synaptic contacts with other neurons in the striatum (10, 11). They also revealed that the transplants restored some of the basic motor functions that had been lost because of brain damage (12).

This research eventually led to attempts to transplant human fetal cells into the rat brain. After treating the rats with immune-suppressing drugs to prevent rejection, the researchers followed the development and growth of the human cells in the rats’ brains (13). “This work formed the link between our experimental work and moving into human patients,” says Björklund. “It allowed us to define the age window during which neuroblasts will survive and grow. If they’re too young, they won’t form functional cells, and if they’re too old, they die.”

In 1985, Björklund and Lindvall organized a program of clinical trials, where aborted fetal nerve cells were implanted into the brains of patients with Parkinson disease. The studies proved that immature dopamine neurons could survive and mature in the striatum of patients with advanced Parkinson disease. Furthermore, the transplanted cells were shown to restore dopamine neurotransmission in the striatum and, in some patients, restore partial motor function (14, 15). However, the results varied greatly among patients. In fact, two National Institutes of Health-sponsored studies of cell transplantation as a treatment for Parkinson concluded that, although transplantation sometimes provided sustained benefits for up to 20 years in some patients, the results were predominantly insignificant (16, 17).

“Those findings made us go back to the drawing board,” admits Björklund, who believes that variability in fetal material used for transplantation may explain some of the inconsistency.

His focus is now on creating transplantable cells from embryonic stem cells, which may provide a much more predictable supply of cells. However, the process is slow. Success depends, in large part, on understanding how to control neurogenesis and regulate a cell’s neuronal phenotype. “Today, compared to 10 to 15 years ago, we have a much better understanding of how dopaminergic neurons are formed,” says Björklund.

Looking Beyond Transplantation

Although Björklund remains interested in finding successful techniques for transplanting dopaminergic cells into Parkinson patients, he believes that there is promise for finding completely new—and perhaps more successful—therapies by investigating the usefulness of neurotrophic factors and better understanding the underlying cause of Parkinson disease. On the neurotrophic front, his laboratory has led efforts to explore the neuroprotective and regenerative properties of glial cell line-derived neurotrophic factor (GDNF) in the nigrostriatal dopamine system (7). Additionally, his team has worked tirelessly to develop recombinant adeno-associated virus (AAV) and lentiviral vectors for neuroprotective and restorative therapy in animal models of Parkinson disease (18).

Björklund’s group has also studied ways to make current treatments more effective by better understanding how the Parkinson drug known as L-3,4-dihydroxyphenylalanine, or L-DOPA, causes dyskinesia, an unwanted side effect characterized by involuntary muscle movements. Recent research in Björklund’s laboratory showed that serotonin neurons drive dyskinesia by taking up t-DOPA in a manner similar to the manner used by dopamine neurons but with less control, leading to the unregulated production of dopamine (19). Björklund’s laboratory is currently conducting a clinical trial to see if a drug that controls the serotonin neurons can alleviate dyskinesia.

The Inaugural Article by Lundblad et al. (1) suggests that Parkinson disease begins at the axonal level rather than the level of the neuron itself, which early models of the disease seemed to suggest. In the study, Björklund and his colleagues overexpress human α-synuclein in the substantia nigra of the rat brain—an area associated with Parkinson disease. They then monitored changes in the release of synaptic dopamine by neurons in this brain area. After 10 days and before observing damage to the axons, the researchers noticed a 50% reduction in dopamine reuptake. After 3 weeks, the first signs of axonal damage were evident, along with a 70–80% decrease in dopamine release. Between 8 and 16 weeks, abundant signs of axonal damage were present, along with an 80–90% reduction in dopamine release and reuptake. The findings, Björklund argues, support the idea that changes in how neurons handle dopamine may initiate and drive a progressive degenerative process that hits the axons and terminals first. “This could open the disorder up for therapy in a new way,” says Björklund. “If we can catch the neurons when they are still alive and just
showing very early signs of dysfunction, there may be a way to bring them back to normal function.”

Björklund will use the $100,000 from the Pritzker Prize to continue his work on Parkinson disease. The Michael J. Fox Foundation chose Björklund as the first recipient of the award, citing his “profound contributions to Parkinson disease therapeutic development and his exceptional commitment to mentoring the next generation of Parkinson researchers” (20). Indeed, Björklund is quite proud of his role as a mentor to more than 35 doctoral students and numerous post-doctorate students, many of whom have gone on to become influential researchers in their own right. His success, Björklund says, was because of timing. He was fortunate to enter the field at a time when research on the brain and molecular biology was opening up new areas of research. “I got a unique opportunity here in Lund that allowed me to thrive by looking at the world with fresh eyes.”

With those eyes, Björklund saw the potential for cell transplantation, a concept that has revolutionized biology.

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