

### Fred H. Gage

Profiling a scientist from his or her curriculum vitae is not unlike reading a professional criminal's rap sheet—a few pages of hard facts speak volumes about what the person has been doing with his life basically since leaving the teen years.

Dr. Fred H. Gage is one of those rare scientists who has achieved significant success in his career but at the same time, can talk to the interested nonscientist and a room of specialists with equal ease. Known as “Rusty” in closer circles, Gage possesses the kind of professional ‘rap sheet’ that many a fellow scientist would envy.

Biographies of scientists often begin at the beginning—from place and time of bestowed degrees down a familiar path to the subject's current office and trophy case.

Gage's current situation so aptly reflects his career that much can be said about him by simply presenting his current professional status and activities. Gage is Professor of Genetics at The Salk Institute for Biological Studies and professor of neuroscience at the

University of California, La Jolla. Gage's “untitled” academic activities include memberships on the NIH National Advisory Council on Aging, Advisory Board of the American Society of Gene Therapy, Chair of the Scientific Advisory Board—Christopher Reeve Paralysis Foundation and American Foundation Prize Technical Advisory Committee. And he just completed service on the NIH Working Group on Guidelines for Use of Human Embryonic Stem Cells.

Gage is on the editorial boards of numerous scientific journals, 26 in fact. There are more than 20 honors to his credit, notably a Max Planck Research Award, Fellow of AAAS, Decade of the Brain Medallist (Congress of Neurosurgeons) as well as an NIH MERIT Award. And Gage's publications number just shy of 300.

We are pleased to present Fred “Rusty” Gage as the keynote speaker at the *Promega Neurosciences 2000 Symposium, Recent Advances in Neural Stem Cell Technologies*.

## Symposium Preview: Recent Advances in Neural Stem Cell Technologies

3:00–6:30pm  
Saturday, November 4, 2000  
New Orleans Marriott Hotel  
New Orleans, LA USA

*This preview presents brief biographies of the speakers for the Promega Neurosciences Fall Symposium as well as synopses of their current research. Register for this exciting symposium online at: [www.promega.com/neuro/](http://www.promega.com/neuro/).*

### Speakers

David Kaplan, Ph.D. (Moderator)  
Montreal Neurological Institute

Fred Gage, Ph.D. (Keynote Speaker)  
The Salk Institute

Derek van der Kooy, Ph.D.  
University of Toronto

Ron Mc Kay, Ph.D.  
National Institute of Neurological Disorders and Stroke

Clive Svendsen, Ph.D.  
University of Cambridge

Freda Miller, Ph.D.  
Montreal Neurological Institute

### Regulation of Cell Genesis in the Adult Nervous System

Fred Gage has devoted much of his latest work to exploring the factors and mechanisms regulating neurogenesis in the adult CNS in a variety of mammalian systems. Gage's group developed a method to enrich for progenitors in the adult CNS that allows these cells to be studied and characterized immediately after isolation. Using this technique to study cells isolated from rat CNS, Gage's group showed that progenitor cells derived from the hippocampus, as well as the cortex, spinal cord and optic nerve are capable of yielding populations of precursor cells with the ability to give rise to a variety of cell types including neurons and glia. Upon transplantation of these isolated and characterized cells to the adult brain, the cells differentiate into cell types that are specific for the transplanted region.

Dr. Gage and his colleagues have also demonstrated the dentate gyrus of adult mammals, including humans, con-

tains proliferating populations of cells that can give rise to neurons throughout life. He has also shown that the rate of cell division in the adult brain as well as the fate of the cells can be regulated by growth factors as well as changes in the environment. Specifically the behaviors of adult mammals can effect the rate of cell division and the fate of neurons in the adult brain, and that these changes in structure of the hippocampus are correlated with function.

### How To Make a Mammalian Brain

Derek van der Kooy's group has three major research interests: i) the neurobiology of motivation, ii) the genetic basis of learning and memory and iii) the establishment and regulation of lineage of the mammalian brain. van der Kooy's laboratory studies opiates and their characterized receptors to investigate motivation and reward in naive and addicted brains. Work on learning and memory in his lab uses mutational screens to identify genetic players required for associative and non associative learning in the nematode, *C. elegans*. His group investigates mammalian brain development at several levels beginning with the establishment of neural stem cells from totipotent embryonic stem cells, the development of neuronal progenitor cells and finally the differentiation of neurons and glia. In addition to studying early specification and development of the brain, van der Kooy is also characterizing populations of neural stem cells in adult mammals.

van der Kooy's work on stem cell populations in the adult brain generated headlines when he and collaborators published results showing that adult mammalian retinas contain true neural stem cells (1). Previously mammals were thought to have lost the ability to regenerate specialized cells of the retina. van der Kooy and colleagues identified a rare cell type derived from the pigmented cells of the ciliary margin of the retina in mice that can self renew and produce multiple retinal-specific cell types. Furthermore, similar cells were demonstrated in post-mortem bovine and human ciliary tissue, suggesting that these stem cells are conserved across mammalian species.

### From ES Cells to Synapses

Ronald Mc Kay's group has made several significant contributions to the understanding of the regulation of neural stem cell differentiation. In 1996, Mc Kay and colleagues published work that identified signals regulating embryonic stem cell differentiation and demonstrated that these signals regulated adult stem cell differentiation as well.

In July 1999, Mc Kay's laboratory, in collaboration with researchers at the University of Bonn and the University of Wisconsin, Madison, created headlines with their

After receiving his Ph.D. from the University of Toronto, **Derek van der Kooy** pursued studies on brain development and function while a postdoctoral fellow at Cambridge University and The Salk Institute. Since completing his postdoctoral studies, van der Kooy joined the faculty of the University of Toronto and is now a Professor in the Department of Anatomy.

As a result of his work in the field of neurobiology, van der Kooy has received awards as a Medical Research Council Senior and Distinguished Scientist. van der Kooy serves on the Board of Reviewing Editors for the journal *Science*, and is a member of the editorial board for *Pharmacology, Biochemistry and Behavior* and *Behavioral Brain Research*.

finding that oligodendrocytes and astrocytes, which differentiated from embryonic stem cells in culture, could be transplanted into myelin-deficient rats and that these transplanted cells were capable of myelinating rat axons in the CNS. This research has clear clinical implications for the treatment of demyelinating diseases such as multiple sclerosis.

Further studies into the ability of the adult brain to regenerate cells led Mc Kay's group to investigate the effects of corticosteroids on proliferation of cells in the

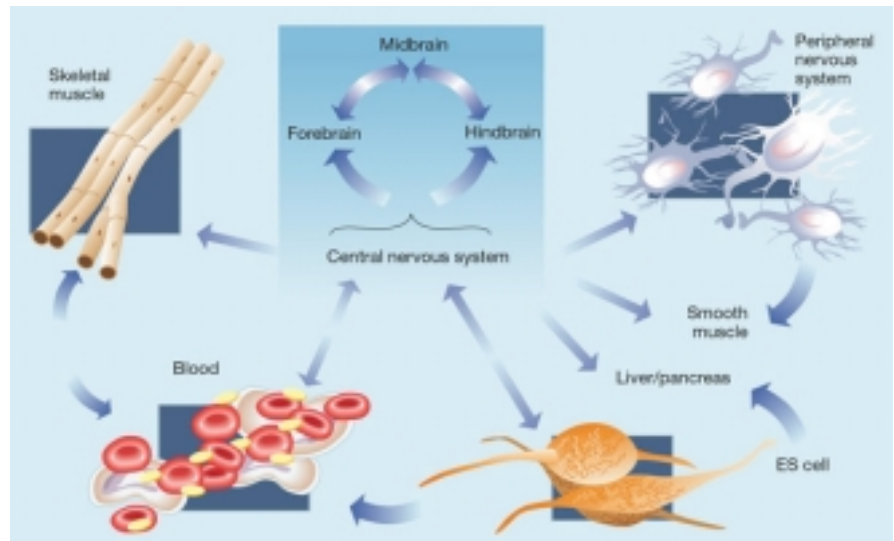
**Ron Mc Kay** received his B.Sc. and Ph.D. from the University of Edinburgh. His dissertation studies, in the lab of Edwin Southern, focused on DNA organization and chromosome structure. After receiving his Ph.D., Mc Kay next completed a postdoctoral fellowship with Walter Bodner at the University of Oxford where he examined RFLPs. As a senior staff investigator at Cold Spring Harbor Laboratory, Mc Kay researched the interaction of the SV40 T-antigen at the viral origin of replication, and he began studies on the molecular organization of the nervous system.

As a faculty member of the Massachusetts Institute of Technology, Mc Kay continued work investigating the cellular organization of the nervous system. Currently Mc Kay is the chief of the Laboratory of Molecular Biology at the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health. His current studies focus on stem cell differentiation.

hippocampus. Production of hippocampal granule neurons decreases with age. Mc Kay and colleagues removed the adrenal glands in young adult and aged rats and demonstrated that the rate of proliferation of these cells was restored. This research points to corticosteroid synthesis and corticosteroid receptors as potential therapeutic targets for neurodegenerative diseases.

**Figure 1.** ▶

**Stem cell transitions.** In vitro, stem cells are not always restricted to one particular pathway of differentiation. For example, CNS stem cells form the cell types of the CNS, but can also differentiate into haematopoietic stem cells. Haematopoietic stem cells can form blood cell types or differentiate into skeletal muscle stem cells. The figure indicates the plasticity of stem cell differentiation potentials. Image reprinted from Mc Kay, R. (2000) *Nature* 406:361, by kind permission of Macmillan Magazines, Ltd, and the author.



## Controlling the Growth and Differentiation of Human Neural Stem Cells

Currently, Clive Svendsen seeks to understand how human stem cells are instructed to become dopamine neurons. This work has the potential to influence clinical programs that have demonstrated the benefits of primary human fetal tissue transplants into the striatum of Parkinson disease patients. The generation of dopaminergic neurons from stem cells in culture could replace fetal tissue—difficult to obtain and highly controversial—allowing more widespread use of neural transplantation in clinical settings. Neurological disorders such as Huntington disease, multiple sclerosis and stroke stand to benefit from the expanded use of neural transplantation therapy, and some of Svendsen's recent work involves the propagation of human neural precursor grafts in an animal model of Huntington disease.

Svendsen's interest in mechanisms of neuronal cell death and growth factors also contributes to his work on the propagation of dopaminergic neurons in culture. Work in his laboratory has identified many factors that prevent death of dopaminergic neurons in culture. His group has also developed an assay to determine the response of individual cells to growth factors, a valuable tool for understanding the requirements of neuronal growth and differentiation. Svendsen will discuss some of these requirements in his talk.

**Clive Svendsen** received his Ph.D. from the University of Cambridge under the direction of M.V. Sofroniew, studying cell death regulation in basal forebrain cholinergic neurons. This work grew from a long-standing interest in the problem of the specification, differentiation and design of the nervous system. Even prior to attending King's College, London University, Svendsen completed a research assistantship at Marine Biology Laboratory, Woods Hole, MA, where he studied tissue organization in the neuronal gland of the solitary sea squirt, *Ciona intestinalis*.

Svendsen has published extensively on his research in neuroscience, and he has been an invited speaker at over 30 scientific meetings in the last 5 years. Not only does Svendsen work to communicate with the scientific community, but he is also committed to increasing public awareness and understanding of science. To that end he is involved in two BBC documentaries and a segment on stem cell biology to air on the Discovery Channel this fall.

## Isolation and Transplantation of Neural Precursors From Mammalian Skin

During development, limiting concentrations of NGF create an environment in which sympathetic neurons compete for signals that support cell growth. In addition to NGF, neuronal activity is also important for survival of sympathetic neurons. Much of Freda Miller's recent work has focused on identifying the molecular players involved in maintaining the balance between signals for neuronal survival and cell death. Miller and collaborators identified the downstream effectors of the Ras pathway that are involved in sympathetic neuron survival during development. They showed that Ras, activated through NGF/TrkA signaling, works primarily through phosphatidylinositol 3 kinase (PI3-K), secondarily through Raf and that it inhibits the JNK/p53/Bax apoptotic pathway. Additional work in the labs of Miller and Kaplan described an anti-apoptotic role for p73, the p53 family member which is expressed as a truncated protein lacking a transactivation domain in developing sympathetic neurons. Similar collaborative research led to the elucidation of the mechanism by which depolarization and NGF pathways act synergistically to regulate neuronal survival in sympathetic neurons. This research showed that depolarization affects L-type calcium channels, and the Ca<sup>2+</sup> in turn activates Ras. The NGF and depolarization signals for cell survival converge into the PI3-K-Akt pathway.

Understanding the signaling pathways that coordinate to regulate neuronal growth and survival is a natural prerequisite for developing the technologies to replace neurons damaged by disease. In this symposium, Miller will discuss unpublished work concerning the isolation and transplantation of neural precursor cells from skin.

**Freda Miller** currently serves as Professor and MRC Senior Scientist at the Center for Neuronal Survival, Montreal Neurological Institute and the Department of Neurology and Neurosurgery, McGill University. She began her scientific career as a graduate student in the laboratory of J.H. van de Sande at the University of Calgary where she obtained a Ph.D. studying DNA conformation in chromatin. She next completed a postdoctoral fellowship at the Scripps Research Foundation.


Miller brought her molecular biology background to the field of neurobiology, where she has studied neurotrophic factors and their receptors. Miller's work in neurobiology has led to nearly a dozen patents, and she and colleagues founded Aegera Therapeutics, formerly Exogen Neurosciences, a company whose goal is the development of therapies for neurological diseases based on neurotrophin targets.

## Neurotrophin Signal Transduction

Work in David Kaplan's laboratory centers on neurotrophin signaling pathways that regulate neuronal growth and death. Recent work published in the *Journal of Neuroscience* from his laboratory describes the role of BDNF in the regeneration of serotonergic neurons after insult by the amphetamine neurotoxin, PCA (2). This research shows that BDNF promotes regeneration of the serotonergic neurons but does not protect them from PCA damage. Also, this research describes local activation of TrkB in response to BDNF, suggesting a link between TrkB signaling and serotonergic neuron regeneration.

Additionally, Kaplan's group has collaborated extensively with Freda Miller and colleagues to describe the role of Ras in the signaling pathways that mediate neuronal survival and to identify downstream players in the Ras pathway.

Kaplan's group is also exploring the role of other molecules, such as the Gab-1 docking protein, in the survival and growth of neurons. They have shown that Gab-1 is capable of mediating the events of differentiation and survival of PC12 cells through the phosphatidylinositol kinase and MEK signaling pathways.

Kaplan has moderated past *Promega Neurosciences* symposia, and we look forward to his keen insight as moderator at this fall's "Recent Advances in Neural Stem Cell Technologies." 

## References

1. Tropepe, V., et al. (2000) *Science* **287**:2032
2. Mamounas, L.A., et al. (2000) *J. Neuroscience* **20**:771.

**David Kaplan** received his B.A. from Clark University in Worcester, MA, and his Ph.D. from Harvard University. Working under the direction of Thomas Roberts at the Dana-Farber Cancer Institute, he identified the PI-3 kinase regulatory subunit, a protein now known to be a key regulator of cell proliferation, survival and tumor formation. Kaplan advanced his studies in cell signaling and regulation through a postdoctoral fellowship in the laboratory of Harold Varmus at the University of California, San Francisco.

While a staff scientist at the National Cancer Institute in Frederick, MD, Kaplan focused on discerning the processes that regulate death and survival in neurons. He collaborated with Luis Parada to identify the receptor tyrosine kinase, Trk, as the receptor for nerve growth factor (NGF).

Currently Kaplan is Professor at the Montreal Neurological Institute, Department of Neurology and Neurosurgery, at McGill University and Head of the Brain Tumor Research Center. Kaplan holds several patents as a result of his research and has published extensively. The 1997 *Science* paper that described PI-3 kinase activation of Akt from his laboratory was recently selected a "Hot Paper" by *The Scientist* (1999, **13**:15). Kaplan is also a cofounder of Aegera Therapeutics (formerly Exogen Neurosciences), a company whose goal is the development of treatments for disorders of the nervous system focusing on neurotrophins as primary targets. Kaplan has moderated the *Promega Neurosciences Symposium* previously, in 1996 and 1997.

## Molecular Players in Neuronal Survival and Differentiation.

BDNF: Brain Derived Neurotrophic Factor

NGF: Nerve Growth Factor

Trks: A family of receptor tyrosine kinases that bind and are activated by neurotrophins.

TrkA: Receptor for NGF

TrkB: Receptor for BDNF and NT-4

TrkC: Receptor for NT-3

PI-3K: Phosphatidylinositol kinase, a downstream target of NGF signaling

Ras: A monomeric GTP-binding protein. It is activated through tyrosine kinase signaling pathways (such as the NGF/TrkA pathway).

Akt: A serine/threonine kinase that is a target of NGF-induced PI-3K activity. (Also known as Protein Kinase B).

JNK-p53-Bax: Proteins involved in major apoptotic pathway in neurons.