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The Rockefeller University

SCIENCE FOR THE BENEFIT OF HUMANITY

BENCHMARKS

THE COMMUNITY NEWSLETTER OF THE ROCKEFELLER UNIVERSITY

FRIDAY, MARCH 11, 2011

FROM MARC TESSIER-LAVIGNE

Making Rockefeller my new home

I am honored and delighted to be joining the university on March 16. The past six months have been a busy and exciting period of preparation — for my family and my lab as well as for me personally — as we planned our move to New York. Over these months I have had the opportunity to meet many of the faculty, students, administration and staff, and the excitement I felt on my appointment as president has only grown during that time.

On Monday, March 21, I will hold a town hall meeting for all members of the campus community at 3 p.m. in Caspary Auditorium to discuss my initial priorities, to answer any and all questions you might have, and to set the stage for the strategic planning we will be embarking on collectively in subsequent months.

I very much look forward to meeting many more of the community in the near future, and to becoming part of the university, making it my home both personally and professionally.

Guiding neurons, and guiding scientists

Marc Tessier-Lavigne's career has straddled academia and industry, and blurred traditional boundaries between basic and translational science

by ZACH VEILLEUX

Marc Tessier-Lavigne's journey into neuroscience began a few hundred miles off the coast of Newfoundland, aboard the Queen Elizabeth II. It was 1980, and Dr. Tessier-Lavigne, then 20 years old, was headed to Oxford University with plans to pursue a Ph.D. in physics.

Physics wasn't quite what he'd envisioned doing as a child, but it was close. Growing up, Dr. Tessier-Lavigne was certain he would become a mathematician, something he loved and excelled at in the French schools he attended while his father, a member of the Canadian Armed Forces, was posted to Europe. In college, at McGill University, he became focused on physics, and wrote his undergraduate thesis on the biophysics of blood flow.

But it was the five-day crossing to the U.K. — the Rhodes Scholarship he had secured to attend Oxford came with a free transatlantic cruise — that caused him to rethink those plans.

"During those restful days of contemplation on the ocean, I began to realize there was much I still wanted to explore before locking myself in to a specialty," Dr. Tessier-Lavigne recalls. "While leafing through the thick book of Oxford's courses of study, I decided to put my plans for an advanced degree on hold and instead pursue a second bachelor's." The Rhodes Scholarships do not put any restrictions on field of study, and so by the time the ship docked in Southampton, his new course was set.

The program he chose to pursue was called Philosophy, Psychology and Physiology. Normally, students study all three in their first year, then select two to specialize in for their final two years. Dr. Tessier-Lavigne, whose previous undergrad credits allowed him to skip the first year, immediately chose philosophy and physiology — by far the least popular of the permutations.

"It was an odd combination, but it turned out to be the perfect course of study for me," he says. "It taught me logic and constructive skepticism and gave me my first exposure to neuroscience, which I immediately fell in love with. The brain is the most complex and fascinating organ in the body, and the thought that one could deconstruct and resolve that complexity was thrilling. My career was set."

In 1983, Dr. Tessier-Lavigne moved down the road to London, where he would spend the next four years, his Ph.D. training, at a University College London lab bench performing electrical recordings from neural cells in slices of retinal tissue from the back of the eye. His training in physics proved useful in his work to understand how neural circuits processed information, but his curiosity soon led him to wonder how such circuits develop and form connections and, ultimately, how they alter those connections throughout life as a result of experience.

It was these fundamental questions of neuroscience that would drive Dr. Tessier-Lavigne's work for the next three decades. Moving to the States for postdoctoral work at Columbia University, he sought to understand the molecular cues that are involved in guiding a developing neuron's tendril-like axons through the body to connect with an appropriate target cell. He and his colleagues developed simple models of specific path-finding events in a Petri dish, and used the preparations to demonstrate the existence of chemoattractive activity for axon tips in the spinal cord.

A few years later, as a junior faculty member at the University of California at San Francisco, he made a name for himself by discovering the molecular identity of this chemoattractive factor, now called netrin. It was a high-risk project involving brute-force biochemistry and the brains of more than 25,000 chicken embryos, but it answered a question that had stumped neurobiologists for over a century, and it launched a new era of discovery in the neurosciences. Techniques and knowledge developed during the search for netrin have since been used — by Dr. Tessier-Lavigne and other labs around the world — to determine the identities of other guidance factors and better understand the neural wiring code that underlies the structure of the human brain and nervous system. The work also had potentially ground-breaking medical applications.

"Insights into axon growth and guidance during development have important implications for attempts to stimulate axon regeneration following injury in the adult nervous system," Dr. Tessier-Lavigne says. "The development of drugs based on guidance factors like netrin has the potential to stimulate regeneration of nerve fibers following paralyzing spinal cord injuries."

The possibility of creating such drugs was tantalizing, and so starting in the late '90s, while still at UCSF, Dr. Tessier-Lavigne also became involved in a number of biotech ventures focused on bringing neurologic therapeutics to market. He served on several scientific advisory boards and cofounded a company, Renovis, Inc., devoted to treatments for neuroprotection, pain and neurodegenerative diseases. Moonlighting in the private sector turned out to suit him well.

"I was quite excited about what could be accomplished in industry, which has different strengths than academia," he

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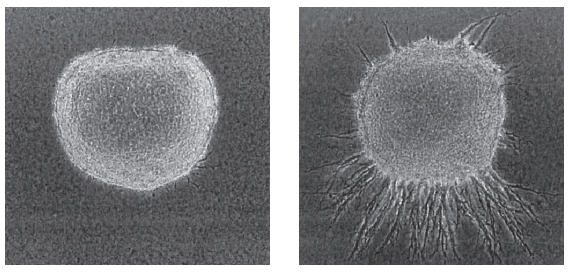
To understand the brain, Tessier-Lavigne studies its wiring

It takes several hundred billion nerve cells to put together the human brain, and they must be connected in an intricate and precise pattern in order to function properly. The formation of these connections — the brain's neural circuits — during an organism's embryonic development is what ultimately allows the brain to perceive, remember and issue commands to the rest of the body.

Since he first encountered neuroscience as a student at Oxford University, Marc Tessier-Lavigne has been fascinated with the formation of these neural circuits, and he has devoted his scientific career to understanding how nerve cells figure out where to go.

The key to this process of "neuronal guidance" is the axon, a slender extension to the neuron that seeks out and connects to the appropriate set of target cells. The tip of each developing axon contains a specialized sensory structure called the growth cone, which senses chemical guidance cues that instruct it to migrate in a particular direction. Until the early '90s, that was all anyone knew. But Dr. Tessier-Lavigne's key discovery — made when he was an assistant professor at the University of California at San Francisco — was that of netrins, a small family of proteins present in the axon's environment that interact with receptors on the growth cone in order to steer the developing brain cells. The discovery of netrins was published in two *Cell* papers in August 1994.



Neurons and netrin. Results from an early neuronal guidance experiment show the growth of long finger-like bundles of axons from neural tissue cultured with netrin (right) compared to tissue grown without. Dr. Tessier-Lavigne published these images in *Cell* in 1994.

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BENCHMARKS

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FROM RUSS CARSON

Welcoming the Tessier-Lavignes

As chairman of the Board of Trustees it is my great honor and pleasure to welcome Marc Tessier-Lavigne as our 10th president.

Through my role as chairman of the search committee that hired Marc, and through my frequent interactions with him since then, I can assure you that he is the right choice at the right time. Of the candidates we interviewed for the job, Marc had the best balance of being both a highly accomplished scientist and a proven administrator.

His prior experiences at UCSF, Stanford and Genentech have prepared him well for taking on the responsibilities of leading our university. Many of you have had the opportunity to witness Marc's energy and interpersonal skills; those who have not are in for a treat.

My fellow trustees and I are delighted that he chose to accept our offer and we look forward to a long and fruitful relationship with both Marc and his wife Mary.

Neuroscientist Mary Hynes named research associate professor

Marc Tessier-Lavigne's arrival at Rockefeller means the addition of not one, but two active neuroscience research programs to campus. This summer, Mary Hynes — Dr. Tessier-Lavigne's wife and a well regarded neuroscientist in her own right — will relocate from Stanford. As research associate professor, she will investigate the development of the key cells targeted by Parkinson's disease: dopaminergic neurons.

Dr. Hynes and colleagues were the first to show that dopaminergic neurons are induced by a molecule called Sonic hedgehog. Her work led to a widely used method involving a combination of this and other molecules to derive dopaminergic neurons from embryonic stem cells. Her research at Rockefeller will focus on identifying molecular markers that distinguish the two types of dopaminergic nerve cells, substantia nigra neurons, which are involved in motor control and die in Parkinson's disease, and ventral tegmental area neurons, which are part of a reward pathway and are not as affected by the disease. She wants to learn how to tease substantia nigra neurons from embryonic stem cells, and in better understanding their development, inform possible treatments for Parkinson's.

Substantia nigra and ventral tegmental neurons are closely related and very difficult to parse, especially in early stages of development. Her recent work has found that certain axon guidance cues, molecules that direct the growth of neurons, are expressed in striking patterns around the developing dopaminergic neurons. Using axon guidance receptor expression, guidance cue responsiveness, in utero tract-tracing, laser capture microdissection and microchip array analysis, she hopes to identify markers that distinguish the two key populations of dopaminergic neurons.

The work could lead to methods for specifically inducing and dissecting the development of substantia nigra neurons, and a better understanding of guidance cue responsiveness could be used to improve the targeting of transplanted neurons meant to replace those killed off by Parkinson's.

"Effective cell replacement therapy will be assisted by the ability to generate exactly the right kinds of dopaminergic neurons. We hope that our work will help accelerate this approach," says Dr. Hynes.

At Stanford, Dr. Hynes leads a research group in the department of biology. Like her husband, she has experience both in academia and industry. She graduated from the University of Vermont in 1980 with a degree in psychology before taking a fellowship to study electrophysiology at Kyushu National University in Japan. Then she joined an undergraduate mentor who had moved to University of North Carolina at one of the first major interdisciplinary neurobiology doctoral programs in the U.S. She earned her Ph.D. there in 1987 and took a postdoctoral position at Columbia University's Center for Neurobiology and Behavior, where she and Dr. Tessier-Lavigne first met. In 1991, she joined biotechnology giant Genentech, initially as a postdoc, and then on the scientific staff, eventually becoming head of lab. In the late '90s, she moved to a biotech startup, where she was associate director of neurobiology through 2002. She joined Stanford in 2003.

"I feel that my science has benefited tremendously from working in both industry and academia," Dr. Hynes says. "It is the basic science that drives my research program, but my time in industry has helped me understand how to move basic scientific discoveries towards applications that might benefit patients."

"Scientists from all over the city packed a lecture room here last month to hear Mary Hynes discuss her newest work on cues that guide dopaminergic axons to appropriate targets in the brain," says Mike Young, vice president for academic affairs. "She also spoke about her stem cell work, which has significant implications for cell replacement therapies. Mary is a great addition to the university's neuroscience research program and will have a valuable place in the growth of stem cell science on campus."

Dr. Hynes was born in New York City and grew up in Connecticut, and many of her relatives still live in the region. In the city, her great grandfather, Henry Heide, founded Heide Candy Company, the maker of Jujubes, Jujyfruits and Red Hot Dollars.

The Tessier-Lavigne-Hynes family

Marc Tessier-Lavigne and his wife, Mary Hynes, have three children. Christian (far right), 19, is currently a sophomore at Princeton University; Kyle, 18, is a senior in high school and will attend Dartmouth beginning this fall; and Ella, 12, is currently in seventh grade and will enroll in the Dalton School on East 89th Street in September. Dr. Tessier-Lavigne, Dr. Hynes and Ella Tessier-Lavigne will live in the President's House beginning this summer with their two dogs, labradoodles named Cameo and Cinnamon, and two American Shorthair cats, a brother and sister named Tom and Lily. This photo is from a 2009 vacation to Greece.

Understanding the brain (continued from page 1)

Discoveries of other chemoattractive factors involved in neuronal guidance soon followed, and over the years Dr. Tessier-Lavigne's lab has sought to identify the full complement of cues guiding particular sets of axons, as well as the intracellular pathways they trigger to signal directed motion.

Of course, the story gets more complicated. As an axon progresses along its trajectory, its growth cone exhibits a remarkable plasticity, changing its response to guidance cues — losing responsiveness to those that directed it over the previous leg of its trajectory and acquiring responsiveness to those that will guide it over the next leg. A major focus of Dr. Tessier-Lavigne's lab in recent years has been on understanding the mechanisms that control this plasticity and switching of growth cone responses, and their relation to other plastic changes, such as those occurring after injury and in learning and memory.

The mechanisms that direct the formation of connections in the embryo also regulate neuronal responses to injury in the adult. While damaged axons in the peripheral nervous system can regrow and regenerate connections, in the central nervous system — the brain and spinal cord — they usually cannot, and paralysis after spinal cord injury is often permanent. Dr. Tessier-Lavigne's lab has recently found that some of the cues that guide axons in the embryo contribute to blocking regeneration, and that inhibiting their actions can help stimulate repair.

The mechanisms regulating the development of circuits are also relevant to neurodegenerative disease. In the embryo, too many connections are initially formed and many axons have to be eliminated through a process of pruning or developmental degeneration. Dr. Tessier-Lavigne's lab has shown that several of the cues that initially guide axons are later responsible for triggering axon degeneration in the embryo, and that there are important mechanistic similarities between developmental degeneration and the degeneration that occurs in diseases like Alzheimer's, providing potential therapeutic entry points for these diseases.

Guiding neurons (continued from page 1)

says. "It's a team-oriented environment where people are working towards a defined goal — the development of medicines — and you can get to see the fruits of your work make their way through the clinic."

He maintained relationships with several biotech firms as he climbed the ranks in academia. He was promoted to associate professor with tenure in 1995 and to professor in 1997, and he became a Howard Hughes Medical Institute investigator beginning in 1994. In 2001 he moved down the road to Stanford University, where he was named Susan B. Ford Professor in the School of Humanities and Sciences. But two years later, the draw of helping manage the scientific portfolio of one of the biggest names in biotechnology — Genentech — proved too powerful to resist.

Genentech was the original biotechnology firm, a company established in 1976 to harness the power of recombinant DNA technology. Its founders, a venture capitalist and a biochemist, joined forces at a time when neither academia nor industry had much interest in one another. Structured much like an academic institution, with semi-independent labs run by investigators and staffed with postdocs and technicians, Genentech proved to be an enormous success. Its first product, synthetic insulin, was the first genetically engineered human medicine to be approved by the FDA. Today, Genentech is owned by Hoffmann-La Roche and employs more than 11,000 people.

In 2003, Dr. Tessier-Lavigne took a leave of absence from Stanford and set up shop at Genentech. The firm had just had a string of commercial successes, and Dr. Tessier-Lavigne's job was to help invest the new revenue into the next generation of therapeutics. Leading an enormous research organization — he started out directing about two-thirds of Genentech's scientific personnel and eventually ran all of it — gave Dr. Tessier-Lavigne the chance to impact not just the sliver of neuroscience he had staked out as an academic, but also to influence how resources are allocated across many areas of bioscience. What's more, although he could continue his basic research (Genentech, like Rockefeller, has a tradition of executives maintaining active labs), he could also be involved with translational work. He soon decided that biotech suited him well, and made a long-term commitment to Genentech.

"Over the course of my career, my initial interest in basic biological processes has grown into an equally strong interest in disease processes and in the medical applications of basic science," Dr. Tessier-Lavigne says. "Genentech was appealing because of its deep commitment to innovative research that has the potential to create breakthrough therapies for unmet medical needs. It also has a vibrant and exciting scientific culture that fosters intellectual freedom."

In fact, in many ways it's a lot like Rockefeller. And since Dr. Tessier-Lavigne has made a career out of straddling the fence between basic and translational science, and has moved easily between the lab bench and executive suite, coming to Rockefeller feels like a natural progression. Rockefeller, after all, was founded to focus on translational medicine, pioneered the concept of a clinical research hospital and has a long history of encouraging scientists to straddle as many fences as they can.

"Basic and translational research depend on one another, and in many areas I believe we still don't have the basic insights on which clinical work can build — that's why places like Rockefeller are so important to our ability to tackle disease," Dr. Tessier-Lavigne says.

Dr. Tessier-Lavigne's own field, neuroscience, is a fitting example. Although he has continued to chip away at the mysteries of neuronal guidance over the past decade, and has made several important discoveries about the processes of neuronal degeneration such as those that underlie Alzheimer's and Parkinson's diseases, there are still no cures or reliable treatments. "Even now our understanding of what goes wrong in the brain is limited, and it's holding up our ability to develop therapies," he explains.

"Beyond disease, I remain as fascinated as ever by what initially drew me to biology: the functioning of complex biological systems, from the operation of molecular machines, to the morphogenesis of tissues and organs, to the ability of the brain to perceive and store memories. Rockefeller scientists remain at the forefront of research into these fundamental processes — another reason I am so excited to join this community."

Dr. Tessier-Lavigne starts at Rockefeller on March 16. Several members of his existing Genentech research program will move with him over the next few months, and he plans to ultimately staff his lab with a total of a dozen or so members — postdocs, grad students and technical staff. It's a size he feels is both manageable and productive and will allow him to keep his feet firmly planted in the process of making discoveries, his greatest joy. His family will move to New York once the school year ends. In coming months, he plans to familiarize himself with the institution, tap into its diverse community for counsel, and ultimately work with them to craft a strategy for guiding Rockefeller through the coming years.

He sees his roles at Rockefeller, as at Genentech, as those of leader and supportive player. "In both jobs, my primary responsibility is to help recruit great people and enable them to do great science," says Dr. Tessier-Lavigne. "In that regard, the skills I have developed in eight years at Genentech are directly relevant to how I will operate as president of Rockefeller. Together we will chart the course for the university in the next five, ten, twenty years. Within that framework, my aim will be to enable the university's faculty, students and research staff to be all that they can be, to serve as mentor, colleague and problem-solver and to make sure people have the resources they need to focus on producing transformative science with a minimum of distractions. Just as important, I will focus on making the university a great place to work for all its members — scientists, administrators and support staff.

"That's the formula that has led to the university's sustained success over its long history, and it's what will allow it to remain an international pioneer in fundamental bioscience, in its application to human health and in training future scientific leaders."