Frederic Bard: The sweet side of traffic

Bard's work focuses on how membrane trafficking regulates protein glycosylation and other cellular functions.

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Frederic Bard

At the age of seven, Frederic Bard's father taught him about the atomic composition of water molecules. Bard was flabbergasted to learn that water is not simply "made of water." He became fascinated by the idea that deeper truths about the world were waiting to be discovered, and in middle school he fell in love with biology. Noticing his interest in class, a teacher predicted that he would become a medical doctor. He rebuked and claimed that he wanted to become a researcher, though at the time he had very little idea what it meant.

Throughout his upbringing, Bard's parents moved every few years all over France. He found it an excitement to leave behind the past to discover a new place and new people, and as an adult, he has kept with this trend, always moving west until Singapore, which has been his home for the last 10 years. Bard now operates his lab out of the Institute of Molecular and Cell Biology at the Agency for Science, Technology and Research. His research investigates the regulation of glycosylation through membrane trafficking and the ways in which various toxins hijack the trafficking machinery. We contacted him to learn more.

Where did you study before starting your own lab?

In college, a professor arranged for me to spend a summer at Harvard in the lab of Bjørn Olsen, a great scientist and very sweet man. My English teacher at the time almost had a heart attack, thinking that I was not going to be able to survive or, worse, that I would dishonor our prestigious École Normale Supérieure. I managed in English, but I also messed up most of the experiments I performed. I must have asked at least a few relevant questions because Bjørn did not mind too much and actually supported my (unsuccessful) application to the Harvard PhD student program. On a dare from one of my best friends at the time, I then started an intense year of studying for the Biochemistry Agrégation. I had to absorb a great deal of knowledge and, to the great irritation of some of my teachers, was often more focused on what was still undiscovered. I then started a master's thesis working on the funkiest of human cells, the osteoclasts. I was in awe of these bone-dissolving, multinucleated monsters and was lucky to join the lab of osteoclast expert Roland Baron at Yale for my PhD thesis work and to study why the tyrosine kinase Src was essential for osteoclasts. There, my early research career took an unexpected turn when I observed that Src and its buddy Cbl were located on Golgi membranes. Since I could not make any sense of this observation at the time, I became a bit obsessed with it. I finished my PhD in France and followed up with a short postdoc at the ENS-Lyon, where I discovered that Src had a massive effect on one Golgi marker but not others. This marker recognized O-glycans in the Golgi; a long road into glycobiology had started. My friends kept reminding me how few publications I had produced during my PhD and that maybe I should move on from Src and the Golgi question. Instead I decided to learn more about the Golgi and applied to Vivek Malhotra's lab in San Diego. I moved there in 2001 and learned much about the field over my five years there: how Vivek conducted his high-impact research, the power of RNAi screening, and that I was really not meant for surfing.

> "Biology is not always reducible to a sequence of letters."

What was it that first drew your interest to the regulation of membrane trafficking and secretion through the Golgi and ER?

My long-term interest revolves around cellular compartmentation and how signaling pathways regulate membrane trafficking to influence cell physiology. This interest has led us to study how signaling pathways regulate protein glycosylation through membrane trafficking events. By attending glycobiology meetings, I slowly realized how large and underappreciated this field of study is. While much is already known, the world of glycans remains perhaps the last and largest unexplored "continent" of biology. Its remoteness from the classical concepts of genetics and molecular biology is unnerving: glycans are not directly encoded in nucleic acids but are emerging features of the ER-Golgi-Glycosylation enzymatic machinery and regulation of their expression is largely mysterious. Today, when much faith is placed in exhaustive sequencing and quantification of DNA and RNA, glycans serve as healthy reminders that biology is not always reducible to a sequence of letters. Biological systems are many-layered, with each system emerging from the properties of the underlying system.

What is your lab actively working on?

Much of my lab is currently focused on the GALA pathway, the process of relocation

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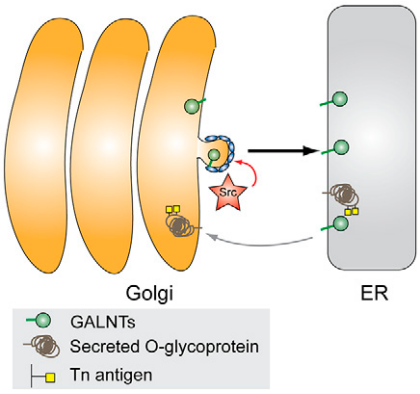

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Src induces the relocation of GALNTs enzymes from the Golgi to the ER and an increase in Tn intracellular levels.

of the O-glycosylation enzymes GALNTs from the Golgi to the ER that is activated by Src (1). Because the GALA pathway is strongly activated in many tumors and seems to drive tumor progression, we are now doing more mice work and diving into cancer biology. Our recent results indicate that relocation induces a strong increase in the glycosylation of many substrates. Our focus in coming years will be on these protein targets and how changes in their glycosylation pattern affects their function. We also aim to develop a translational program around this project.

I am also very excited by a relatively new direction in the lab: the nuclear associated endosomes. We chanced on them while studying protein toxin trafficking, which I thought would help us understand how GALNTs traffic from the Golgi to the ER. Instead, the toxins showed us an unexpected trafficking route whereby endosomes can dock and fuse with the nuclear envelope, their content finally ending up in the nucleoplasm (2). These observations are so counterintuitive for me that I feel completely humbled and excited at the same time.

What kind of approach do you bring to your work?

The major project of my postdoc was an RNAi screen in *Drosophila* cells, the first to interrogate the secretory pathway and leading to the identification of the TANGO genes (3). Starting my lab in Singapore, I decided to implement this technology, which opened genetic dissection to human cells. It has been a great tool, and I think it is still very relevant despite its much discussed drawbacks. The success of a screen is almost entirely in the design of the assay, so we invest heavily in it, especially focusing on image analysis.

What has been the biggest accomplishment in your career so far?

The discovery of the GALA pathway is without doubt my biggest accomplishment (4). Not only is it a new regulatory pathway, but I think it really opens up a more general idea: that glycan synthesis is regulated by when and where glycosylation enzymes interact with their substrate and that these parameters are controlled through membrane traffic. The fact that GALA seems to drive tumor invasiveness is obviously also very exciting.

What has been the biggest challenge in your career so far?

I think the challenges have been mostly self-imposed and internal. I used to oscillate between being stressed and depressed, neither of these states being very productive. The slow pace of scientific research and the feeling of being unable to think clearly and manage my time effectively felt like psychological torture. With time, I have learned to better accept myself and my limitations, to take the time to breathe on weekends, and to take care of my kids. My productivity has significantly improved since I have better learned to relax.

What hobbies do you have?

Hiking and various sports are essential for my sanity. I also enjoy reading science books. The feeling of belonging to the greater community of scientists is exhilarating, though I am often amazed by the difficulty of science to percolate into society. Anti-science in the US political arena is scary and heartbreaking. Europe is somewhat in a better place but the strong and unconditional anti-GMO movement is a stark reminder that gut feelings can easily overpower rational thinking anywhere in the world. Recently, I started to paint my cell biology projects and try using the paintings to try to better communicate with the public at large.

What has been your biggest accomplishment outside of the lab?

Raising two kids within reasonable levels of brattishness, at least by my own standards.

Any tips for a successful research career?

I think every scientist approaches research somewhat differently, and all advice should be taken with a pinch of salt. But I would suggest taking up a mental machete and going out of the well-mapped and groomed forest. Venture into the jungle. You'll probably sweat a lot but there is a good chance it will be worth it.

"[Take] up a mental machete and [go] out of the well-mapped and groomed forest."

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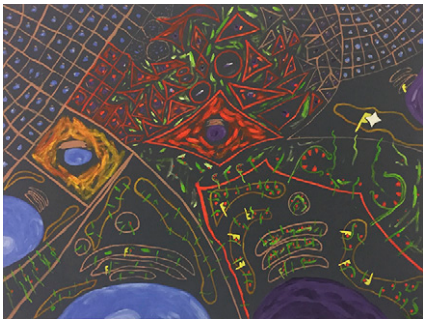

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Bard enjoys painting, inspired by his cell biology.