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Cédric Blanpain: ISSCR's Outstanding Young Investigator for 2012

Cédric Blanpain from the Interdisciplinary Research Institute, Université libre de Bruxelles earned the 2012 ISSCR-University of Pittsburgh Outstanding Young Investigator Award for his exceptional achievements as an early-career stem cell researcher.

The International Society for Stem Cell Research (ISSCR) was delighted to highlight the remarkable caliber of an early-career stem cell biologist with the fourth annual ISSCR-University of Pittsburgh Outstanding Young Investigator Award. This year's award went to Cédric Blanpain, M.D., Ph.D., a tenured Assistant Professor of the Belgian Research National Scientific Fund (FNRS) at the Interdisciplinary Research Institute (IRIBHM), Université libre de Bruxelles (ULB) in Belgium. Since starting his own laboratory at FNRS in 2006, Cédric has distinguished himself as a leader in stem cell research, defining stem cell contributions to development, tissue homeostasis, and cancer, focusing on the skin, the mammary gland, and the heart.

Cédric received his M.D. at the ULB, in June 1995, with summa cum laude and was board certified in internal medicine in 2002. He demonstrated his talent as a researcher from the start, excelling in his Ph.D. studies. In the laboratory of Marc Parmentier, M.D., Ph.D., at the ULB, Cédric studied how CCR5, a receptor critical for HIV infection, interacts with its natural ligands and the viral envelope, and how CCR5 trafficking influences this critical step of viral infection. This research resulted in a number of highly cited publications and was recognized by several awards, including the Galien Award of Pharmacology in 2002, a prestigious award for young scientists in Belgium.

After graduation, Cédric moved to the Rockefeller University in New York City, where he launched his career in stem cell biology as a postdoctoral fellow in my laboratory. In my group, Cédric began a longstanding and remarkably fruitful collaboration with another of my postdoctoral fellows, William (Bill) Lowry (now at University of California, Los Angeles), publishing three important co-first-authored papers during their postdoctoral studies at Rockefeller.

When the first and most important of these studies was launched, Doina Tumbar in my group had just developed a novel method to isolate and purify hair follicle bulge stem cells by using transgenic mice that fluorescently marked infrequently cycling, label-retaining cells of the skin epidermis. Exploiting our stem cell gene expression profile, Cédric and Bill devised a new purification scheme to isolate follicle stem cells by fluorescence-activated cell sorting for surface markers. By optimizing conditions that permit clonal analyses in vitro and engraftments in vivo, they showed that the progenies of a single bulge stem cell were able to differentiate into all lineages of the epidermis, including hair follicles and sebaceous glands, when transplanted into recipient hairless mice. This landmark work provided the first demonstration that the infrequently cycling hair follicle bulge cells can function as multipotent stem cells in tissue regeneration (Blanpain et al., 2004).

In the second major study, the two pursued another of our prior observations, namely that excessive β-catenin stabilization in the developing epidermis resulted in de novo hair follicle morphogenesis. Using a regulateable gain-of-function strategy, Cédric and Bill demonstrated that in the adult follicle, β-catenin stabilization results in precocious activation of the stem cells (Lowry et al., 2005). Finally, the two used a loss-of-function approach to show that Notch signaling functions in the skin epidermis in vivo by promoting the transition of proliferative basal epidermal cells to differentiating suprabasal (spinous) cells (Blanpain et al., 2006).

All three of these papers were highlighted by other journals and have received considerable attention in the field. When Cédric departed from my lab to begin his independent career, he did so leaving a legacy as a brilliant young scientist with an extraordinary capacity to ask interesting questions, collaborate, and—through his leadership—move science forward. What also makes Cédric special is his gift for delivering incisive, constructive, and fair criticism with a smile. Importantly, the high standards he applies to others are also the ones he applies to himself. Such people are both rare and exceptional in science, and they make the research of those around them better.

As an independent researcher in Brussels, Cédric has continued to shine in pursuing his interests in epithelial stem cell biology. His research group now studies the role of stem cells during homeostasis and in disease, particularly cancer. He has applied his knowledge and skills beyond the skin, and has made groundbreaking contributions to the field of stem cell research. Here, I highlight only some of the seminal work that Cédric's group has accomplished in the short time since he left my laboratory.

For the vast majority of cancers, the origins of the tumor-initiating cell are still unknown. To address this problem, Cédric's lab focused on basal cell and squamous cell carcinomas of the skin, providing key insights into which cells within the skin give rise to these two common epithelial cancers. His team first reported that basal cell carcinomas arise from long-lived stem cells of the interfollicular epidermis (Youssef et al., 2010). He

then showed that, in contrast, squamous cell carcinomas can derive from hair follicle stem cells and possibly other cell types within the skin, a finding supported by similar findings from his former collaborator, Bill Lowry (Lapouge et al., 2011; White et al., 2011). These results were quite unexpected, since basal cell carcinomas more closely resemble hair follicle cell differentiation whereas squamous cell carcinomas show a differentiation program more closely parallel with the epidermis.

Another key question in the cancer field is how adult stem cells maintain their genomic integrity, and sense and respond to DNA damage within their natural niche. Cédric's group was one of two that showed that hair follicle stem cells do not protect their genome by asymmetrical chromosome segregation (Sotiropoulou et al., 2008; Waghmare et al., 2008). His group also demonstrated that adult bulge stem cells are resistant to DNA-damage-induced cell death due to an elevated expression of *Bcl2* and an accelerated DNA repair activity (Sotiropoulou et al., 2010). This work has important implications for our understanding of how skin stem cells protect themselves against sun damage and how these cells may get transformed.

Cancer stem cells (CSCs) have been described in many different mouse and human cancers, including squamous tumors of the skin (Schober and Fuchs, 2011). Cédric's group showed that one of these CSC factors, VEGF, plays a critical dual role in regulating skin tumor "stemness" (Beck et al., 2011). The secretion of VEGF by tumor cells stimulates neoangiogenesis, which creates a vascular niche. Intriguingly, VEGF also acts directly on tumor cells in an autocrine loop through an Nrp1-dependent mechanism to promote CSC renewal and tumor growth. These elegant studies give new insights and add a concrete mechanism to our understanding of the intricate crosstalk happening between CSCs and their microenvironment.

Illustrating his versatility and ability to address important questions in the field, Cédric used novel lineage tracing and clonal analysis in mice to decipher the cellular hierarchy of the mammary epithelium during development, homeostasis, and lactation. His group discovered that under physiological conditions, mammary epithelial lineages originate from multipotent embryonic progenitors that are replaced soon after birth by distinct, lineage-restricted unipotent stem cells (Van Keymeulen et al., 2011). This work has been widely discussed and highlighted and is likely to be a paradigm-shifting landmark in the field.

In a final example of Cédric's ability to transition from one stem cell type to another, he identified the earliest cardiovascular progenitor cell and described stem cell hierarchy and functionality in the mammary gland. He used mouse embryonic stem cells (ESCs) in which gene expression can be temporally regulated, demonstrating that Mesp1 acts as a key regulatory switch during cardiovascular specification (Bondue et al., 2008). Since then he has engineered a Mesp1-GFP reporter in ESCs and shown that Mesp1-GFP cells are strongly enriched for multipotent cardiovascular progenitors, which at the clonal level can differentiate into all cardiovascular cell types (Bondue et al., 2011; van den Ameele et al., 2012).

Cédric's broad expertise and diversity of accomplishments in stem cell biology has earned him wide respect, and his work has been praised for its thoroughness and conceptual depth. He is widely commended for his active participation in the stem cell community, his contributions to editorial boards, and the authoritative reviews that he has continued to write on his own as an established independent investigator. His recognition by the field is illustrated by the numerous talks he has been invited to give and by grant support and awards. It is only fitting that he is now the recipient of the 2012 ISSCR-University of Pittsburgh Outstanding Young Investigator Award. Within the international community of stem cell biologists, Cédric has emerged as a collegial, versatile, and thoughtful young scientist with a spectacular ability to conduct stem cell science at the highest level. Those of us who have had the pleasure of interacting with Cédric have witnessed his scholarship and productivity first-hand. In awarding Cédric this honor, the stem cell community applauds his shining trajectory and eagerly anticipates his next discovery.

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Elaine Fuchs[1,*]
[1]Laboratory of Mammalian Cell Biology and Development, Howard Hughes Medical Institute, The Rockefeller University, New York, NY 10065, USA
*Correspondence: fuchslb@rockefeller.edu
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