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PEOPLE & IDEAS

Johan Auwerx: Sowing the seeds of translational research

Nicole Infarinato

Auwerx studies the signaling networks that underlie mitochondrial function and metabolism.

Right from the start, Johan Auwerx was captivated by the natural world and eager to understand its complexities. It was this deep, innate curiosity that propelled him toward a lifelong career in science, medicine, and eventually entrepreneurship. Auwerx grew up in eastern Belgium and earned his MD and PhD in molecular endocrinology at the nearby Katholieke Universiteit. For his post-doctoral work, he made an intrepid leap and moved 5,000 miles away to the United States for a position at the University of Washington in Seattle. There, he performed research in genetics and metabolism, which sparked his intense interest in mitochondria. Auwerx now heads the Laboratory of Integrative Systems Physiology at École Polytechnique Fédérale in Lausanne, Switzerland. His laboratory uses systems biology and diverse model organisms to investigate mitochondrial signaling, dynamics, and metabolism.

Since its inception, the Auwerx laboratory has made numerous seminal discoveries in the field of nuclear-mitochondrial communication, elucidating both anterograde (nucleus to mitochondria) and retrograde (mitochondria to nucleus) signaling mechanisms. Although he is focused on tackling basic biological questions, Auwerx poses these questions with forethought of their potential clinical applications for human health, aging, and diseases such as diabetes. As a result, his studies often generate excitement far beyond the scientific community. Notably, this recently included a highly publicized study published in *Nature Medicine*, demonstrating that urolithin A, a compound found in pomegranate fruit, has anti-aging effects such as preventing the accumulation of defective mitochondria over an organism's lifetime (1). In anticipation that such findings could be recapitulated in humans, enthusiasm for Auwerx's science has permeated the business world and spurred the foundation of several biotech companies.

We reached out to Auwerx to learn more about his scientific journey and his mission to translate his discoveries to the clinic.

When did your interest in science begin?
I have always been curious and interested in finding out new things related to nature, and this drove me to study medicine and thereafter to obtain a PhD.

Where and with whom have you studied?
I graduated with MD and PhD degrees from the Katholieke Universiteit Leuven in Belgium. I performed post-doctoral work at the University of Washington, Seattle, where I worked in the Division of Medical Genetics with Samir Deeb and the Division of Endocrinology and Metabolism with John Brunzell and Alan Chait.

What sustains your interest in studying mitochondria?
Mitochondria have their own genomes and can be considered as separate organisms or bacteria within our own cells, yet most mitochondrial proteins are encoded in the nuclear genome. I am fascinated by the bidirectional relationship that exists between the nucleus and mitochondria as the synergy between mitochondrial and nuclear signaling mechanisms controls many different cellular processes and is essential in regulating stress responses. I am trying to understand nuclear-mitochondrial communication in all its facets. This is a rather new and emerging field and remains a huge challenge, which I am sure will keep me busy for some time.

What kind of approach do you bring to your work?
I use a variety of tools, ranging from genetics, omics, and cellular and molecular biology, and apply them to studies of mitochondrial function in *Caenorhabditis elegans*, mice, and humans. Our work using mouse genetic reference populations has been especially useful for dissecting the lines of communication—anterograde and retrograde—that exist between the nucleus and mitochondria, as we can keep potentially confounding environmental variables to a strict minimum, allowing us to dissect the underlying nuclear and mitochondrial genetic mechanisms.

Johan Auwerx. IMAGE COURTESY OF JOHAN AUWERX.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?
I received good training in endocrinology, molecular biology, and genetics, which were all essential for my future work. The most challenging aspect for me was to become an efficient group leader and transfer my interest and enthusiasm to the trainees in my group.

What has been the biggest accomplishment in your career so far?
We made significant contributions in establishing the mechanism of anterograde

Nicole Infarinato: ninfarinat@rockefeller.edu.

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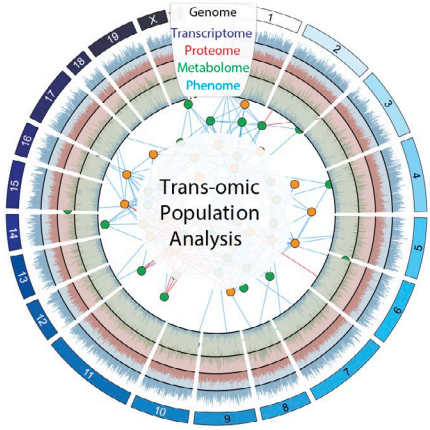

Different but overlapping systems biology approaches are used by the Auwerx group to map the signaling networks that govern mitochondrial function and determine organismal metabolism in health, aging, and disease. IMAGE COURTESY OF JOHAN AUWERX.

signaling (i.e., communications going from the nucleus to the mitochondria) through our work on nuclear receptors and their cofactors. One of our most important discoveries was the association between the PPARγ2 Pro12Ala gene variant with type 2 diabetes and obesity. We made this finding long before the era of genome-wide association studies and it was the first identification of a gene tied with metabolic control and a common complex disease (2). Furthermore, we contributed to the understanding of how transcription factors (in particular nuclear receptors such as the PPARs) and their cofactors (e.g., SIRT1) influence mitochondria and metabolism (3). Our studies about how cellular NAD^+ levels control the activity of the sirtuin cofactors actually paved the way for the clinical use of various NAD boosters and have quickly become classics in the field (4, 5). At present, we are focusing more on the reverse signaling mechanisms, that is, how mitochondria activate retrograde signaling pathways to control cellular homeostasis in general, and in particular how mitochondria control nuclear function (6).

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

The greatest challenge for me has been adapting to the ever-expanding areas that biologists have to cover, from classical cell biology to computational biology. In particular, the conversion into a fully-fledged systems biologist took some time and required me to sharpen my skills in math, stats, and computational approaches.

What is the best advice you have been given?

Always focus on delivering the best science, never compromise on quality.

What has been your biggest accomplishment outside of the laboratory?

I am proud to have raised a family and balanced family and work. The fact that my kids have also chosen biomedical careers indicates that I may have transmitted my curiosity and an interest in science to them.

Any tips for a successful research career?

Never give up, work hard, and, above all, be fast.

In addition to his success in academic research, Auwerx is committed to realizing the translational possibilities of his discoveries. To bridge the gap between basic science and human health, he has cofounded biotech companies such as Mitobridge, a pharmaceutical company pursuing novel compounds that can boost mitochondrial function. He also serves on the scientific advisory boards of companies including Amazentis, which develops therapeutic nutrition to combat the effects of aging, and collaborates with TES Pharma in small molecule discovery for the treatment of metabolic diseases and cancer. Intrigued by this slant to his career trajectory, we asked Auwerx to describe his experiences transitioning into the biotech sector.

What motivates you to realize the translational potential of basic research?

I am medically trained so translating basic science is kind of natural. I try to focus many of the basic questions we ask in the laboratory so that they are also likely to be relevant in an applied medical setting.

What key events were necessary for establishing your first biotech company?

I needed to have the following: (a) A good observation or finding from the laboratory that had the potential to translate into new treatments in patients, (b) a set of investors that believed in our idea and that we could convince to support further research and development, and (c) above all, to establish a good team dynamic within the company that could deliver. Such a team has to have a shared focus, from the scientists to management—all have to think in terms of the critical path toward the clinic.

Are there unique challenges in communicating science to the business world?

You need to be able to convince venture capitalists that your idea can be translated into a valuable product in a reasonable time. It is similar to how you convince a granting body to sponsor your research, as you have to try to understand how venture capitalists are thinking about a problem and formulate your ideas so they can embrace them. It is a very similar process to writing a grant application for a particular study section—you frame your question for that specific study section and their goals, and likewise when pitching your business proposal to venture capitalists.

Does thinking about how basic science can be translated affect your group's research direction?

Yes, we try to ask questions with medical relevance. Learning how the biotech world works helps you to focus your research and take into consideration factors that are key to the go/no-go decision stages that drug development requires. For example, we may work on many aspects of mitochondrial biology, but only a few of the signaling processes or steps will be druggable. If you adopt this way of thinking, you will spontaneously see which projects can be of direct benefit to patients or human health and wellness in general. That does not mean scientists should only do translational work, but it is desirable to know when you enter into a project whether translation is likely to be possible.

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The Auwerx family. IMAGE COURTESY OF JOHAN AUWERX.