Understanding the Nucleolus and Ribosomes at the service of biomedical innovation

Interview with Pr Denis LAFONTAINE,
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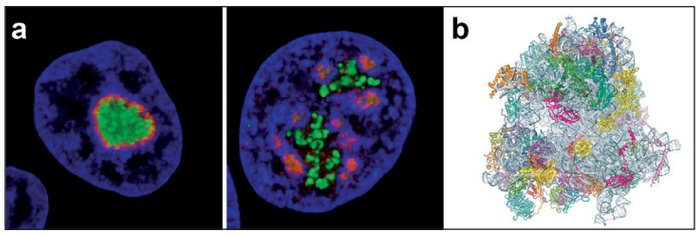
What are the key figures and area of expertise of your laboratory?
Created in 2001 at the ULB, my laboratory employs a dozen people and carries out several dozen research projects. It has to its credit >80 scientific publications in internationally peer-reviewed journals accounting for >7,500 citations (h-index 44) as well as the training of some forty researchers of 15 nationalities. The area of expertise of my laboratory is RNA biology. Ribonucleic acids (RNAs) play fundamental roles in our cells, being part of essential nanomachines, they are also among the most ancient molecules dating from the prebiotic world.

Could you tell us about your main areas of research and give us some examples of current research projects?
My team is interested to understand how ribosomes, the nanomachines inside our cells that produce all our proteins, are made and how the structure of the nucleolus (the cell's ribosome factory) is organized and maintained. We are studying the diseases associated with the poor assembly of ribosomes. If ribosomes are in excess, they cause cancers because the excess protein stimulates the proliferation of cancerous cells. If they are in deficit or defective, they induce ribosome-related pathologies, the so-called ribosomopathies, affecting primarily the blood (haematopoiesis) and the brain (brain malformation, neurodegenerative diseases).

As an example, we are studying Diamond-Blackfan anemia (DBA), a congenital disease that affects the production of red blood cells and makes patients dependent on weekly blood transfusions. In a collaborative effort, the study of the mutations underlying this pathology has enabled us to develop and test therapeutic vectors based on gene correction to restore normal ribosome production. We have also been involved in characterizing the impact of ribosome biogenesis dysfunction on leukoencephalopathy with calcification and cysts (LCC), a terrible brain disease and we hope our findings will soon translate into biomedical applications.



a, The nucleolus (the ribosome cell' factory) in a healthy (left) and diseased (right) cell (size range microns); b, The ribosome is the nanomachine inside our cells responsible for producing all our proteins (size range nanometers).

What research partnerships have you developed?
The laboratory is a member of several European academic consortia including RiboEurope and DBAGenCure, funded by the European Commission within the framework of the European Joint Programme on Rare Diseases (EJP-RD). It also offers its expertise in the form of services or scientific collaborations to Belgian companies (GSK, Progenus, OncoDNA…).

Could you tell us about your spin-off project?
Our spin-off project is based on the biosensor properties of the nucleolus whose morphology varies greatly in disease such as cancer, viral infection, neurodegeneration etc. We have developed a powerful patented algorithm to characterize nucleolar morphology with unprecedented statistical power. We plan to use nucleolar morphology as a *proxy* to screen novel molecules with anticancer properties. So far, we have benefited from two funds from the Walloon Region (FIRST Spin-off and PoC - proof of concept). We are currently organizing a first round of fund raising. The company RIBOGENESIS should be created during the winter of 2021.

What do you see as the main challenges ahead for molecular and cell biology research?
The main challenge for us will be to integrate the concepts of soft matter and biophysics in biology. There is an urgent need to decompartmentalize research. In the September 2020 issue of *Nature Reviews Molecular Cell Biology*, we have developed the view that the nucleolus is a multiphase liquid condensate. Put simply, the nucleolus behaves like a liquid droplet inside our cells sharing many of the biophysical properties of immiscible liquids like "when oil and vinegar are mixed". In fact, each cell comprises many such compartments or "droplets" that do not mix. The biophysics underlying the behavior of immiscible liquids will therefore be essential to understand how cells are organized and functionally compartmentalized.

For more information:
- Lab website www.LafontaineLab.Com
- Lab Twitter: @LafontaineLab
- Denis L.J. Lafontaine, Joshua A. Riback, Rumeyza Bascetin, Clifford P. Brangwynne (2020) "The nucleolus as a multiphase liquid condensate" **Nature Reviews Molecular Cell Biology** DOI: 10.1038/s41580-020-0272-6.