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INTERDISCIPLINARY CHARACTERIZATION OF BIOLOGICAL SYSTEMS THAT CONTROL CELL PROLIFERATION, DIFFERENTIATION, MIGRATION AND APOPTOSIS (PDMA) IN HEALTH AND DISEASE

KERLOUAN
BRITTANY FRANCE
OCTOBER 9TH - 13TH

Contrôler le cancer et les maladies dégénératives

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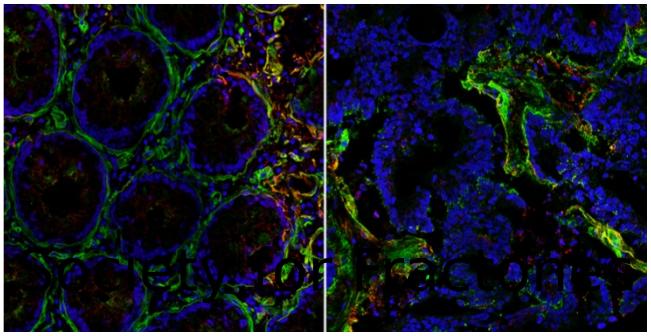

Controlling cancer and neurodegenerative diseases
First workshop of the Society for Fractones
October 9-13 2023 in Kerlouan

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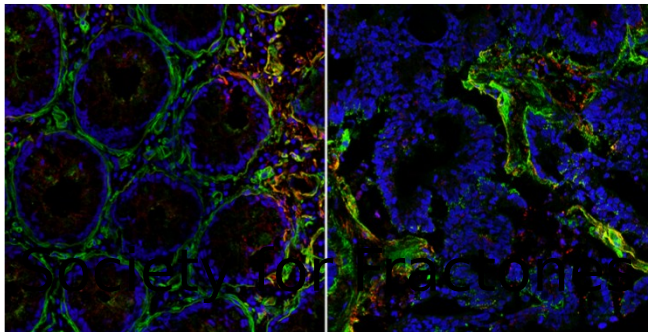

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Interdisciplinary Characterization of Biological Systems that Control Cell Proliferation, Differentiation, Migration and Apoptosis (PDMA) in Health and Disease

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The construction of an organism (development) and its plasticity, i.e. its adaptability to changes in its environment throughout adulthood, can lead to both health and disease. Generation, Regeneration and Degeneration are based on a complex -hitherto unknown- interplay between cell proliferation, differentiation, migration and apoptosis (PDMA).

The outcome of PDMA regulation throughout life will be predominantly the body maintenance and evolution. However, a PDMA dysregulation may be associated with diseases as diverse as cancer, Alzheimer's disease, or multiple other diseases occurring in animals and humans. In response to challenges of the environment, the accurate response of an animal is usually adaptation. Otherwise, the disease installs, or the death occurs.

At this workshop in Kerlouan, biologists, mathematicians and philosophers embarked on a scientific excursion that brought us together to share our different fields of study. We immersed ourselves in a multidisciplinary approach aimed at answering the question of PDMA regulation.

This week has been a precious moment for us. The discussions were rich and stimulating and have fostered interdisciplinary collaborations on the control of PDMA. We are confident that this workshop will have a significant impact on the development of PDMA research in the years to come. Our work will contribute to the advance of science.

THE EXTRACELLULAR MATRIX AS THE INTERNAL COGNITIVE ORGAN OF THE MULTICELLULAR ORGANISM

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The animal autopoiesis for a standard viability tube of its species is characterised by

- A growing and then homeostatic cell renewal of almost all its tissues, with a speed varying from some days for the stomach cells to some months for the bones and even many years for the neurons and glial cells, that constitute the 'external sensorimotor recurrent network' of the whole organism;
- A permanent circular homeostatic renewal through the blood capillaries of the extracellular matrix:
  - The nano-inputs and nano-outputs of the extracellular matrix and its homeostatic fractone storage of all proteoglycans (for the homeostatic renewal of a little number of cells);
  - The lymphocytes for the immunity against living nano-organisms;
  - The neutrophiles for repairing some internal or external injury of tissues.

All these homeostatic dynamics of the extracellular matrix are nothing else than the result of 'internal sensorimotor recurrent networks'. It is proved for a recurrent network that 1) its internal state plays the role of the hidden state in a hidden Markov chain and 2) each hidden state represents a set of equiprobable futures (as 'learned' from the whole past!), i.e. a deep cognitive coordination property. And each fractone with its homeostatic role for delivering their proteoglycans to a little number of cells plays a crucial role in the whole animal autopoiesis.

Such characteristic property of internal and external homeostatic sensorimotor recurrent networks is also present in plants, in eukaryotes, prokaryotes as well as in cyanobacterias. That involves the following thesis characterising

the living organisms with its internal and external sensorimotor recurrent network: a living organism is both autopoietic and cognitive at all its organisational levels.

Controls engineering applied to biology

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While the mathematics of controls engineering are more commonly associated with robots, rockets, and electronics, the mathematics apply equally well to biological processes. Regulation in a variety of biological systems might be better understood utilizing the insights and measurement techniques from controls engineering.

How come alternative splicing may be so decisive in the life of a cell?

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Alternative pre-mRNA splicing allows ensuring the establishment of an immense repertoire of proteins that will, collectively and in association with other macromolecules, such as nucleic acids, lipids and sugars, fulfill all functions a specialized cell requires for living, and dying.

With this in mind, we will discuss about what is presently known of the mechanism of splicing, how it can get alternative and how it is linked to gene transcription. Put in context, we will show how it is modified or even disrupted in cancer, and what tools are available to try to predict the outcome of splicing decisions.

Finally, we will propose a fictive scenario showing how enzymes that participate in sugar presentation and hence, in fractone assembly, may depend on alternative splicing switches that take place in a timely manner.

The oyster crassostrea gigas as a new model for research in cancer biology

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The Warburg effect is one of the hallmarks of cancer cells in humans. It is a true metabolic reprogramming to aerobic glycolysis, allowing cancer cells to meet their particular energy needs for growth, proliferation, and resistance to apoptosis, depending on the microenvironment they encounter within the tumor. We have recently discovered that the Crassostrea gigas oyster can naturally reprogram its metabolism to the Warburg effect. Thus, the oyster becomes a new invertebrate model useful for cancer research. Due to its lifestyle, the oyster C. gigas has special abilities to adapt its metabolism to the extreme changes in the environment in which it is located. The oyster C. gigas is therefore a model of interest to study how the environment can control the Warburg effect under conditions that could not be explored in vertebrate model species.

Shape as a result of the viable control of proliferation, differentiation, migration and apoptosis

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Morphogenesis is the process by which a single cell develops into a multicellular organism. It is a complex and dynamic process that is controlled by cell proliferation, differentiation, migration and apoptosis (PDMA). Precise control of PDMA in time and space is essential for normal morphogenesis. Perturbations in this control can lead to malformations or disease.

Over a thousand growth factors, cytokines, and chemokines influence cell fate. These diffusible molecules act on receptors on the stem cell surface to control their PDMA. The binding of growth factors to fractones is required to activate on stem cell borne receptors. Fractones consist of glycoproteins that are involved in a variety of cellular processes, including signal transduction and cell adhesion.

Morphogenesis can be mathematically modeled as a multivalued dynamical system. A dynamical system is a set of objects that evolve over time according to predefined rules. Constraints are restrictions that limit the system's evolution. The viability kernel is the set of initial states from which the system can evolve in a way that always respects constraints. In other words, the viability kernel is the set of initial states leading to a viable evolution of the system. We hypothesize that regulations laws are the means by which the organism maintain a viable form. Cellular regulations are the mechanisms that control PDMA. They ensure that cells divide, differentiate, migrate, and die at the right time and place to construct and maintain the organism's form.

We study the dynamical systems of organisms that integrate environmental signals to control their morphogenesis. We believe that fractones and the

associated fibroblast/macrophage network play an important role in these systems. We anticipate that the latter create non-linear regulatory laws enabling the organism to remain within its viability domain. Fractone-borne glycoproteins are likely produced by macrophages, which are associated with a network of fibroblasts, are thought to play a key role in this process. That fractones associated with the fibroblast/macrophage network regulate PDMA, ensures that the organism develops in a healthy and coordinated manner.

Ruyer in the land of fractones; a revival of the arguments against Darwin's theory?

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What use can philosophy have in this conference focused on a scientific revolution which should allow us to better understand the genesis of living forms? It is above all because Raymond Ruyer, in the middle of the 20th century, was first of all a philosopher of life who developed his work from the scientific revolutions of his time: quantum physics, genetics, embryology, cybernetics. Many scientists contemporary to Ruyer probably knew his work better than contemporary philosophers who only had considerations for Sartre or Heidegger. Unlike philosophers who wanted to emancipate themselves from science to describe the mode of existence of beings, Ruyer tried to highlight, by studying sciences what they are missing that is essential to understanding living forms. That is to say : the difference between a true form and a structure. A philosophical conception of form makes it possible to understand that the living cannot be reduced to a scientific study of physico-chemical structures or biological processes. It is still necessary to define what a true form is. This is what we will clarify in Ruyer's perspective. This perspective makes finalism a means of completing the scientific explanation of life. And it leads to a questioning of Darwinism. Some arguments that Ruyer uses to show the weakness of scientific descriptions of the genesis of living forms have a family resemblance to those of Frédéric Mercier. Mainly when he tries to show the advantage that we can have by using fractones and not only the code genetics to conceive the emergence and evolution of living forms. We will try to highlight this air of resemblance in order to compare Ruyer's neo-finalism to the "micro-finalism" of Frédéric Mercier and his desire to do justice to Lamarck. As we believe that the importance of a discovery is not measured only by its explanatory power, we will also attempt to compare the paradigm shift accompanying Ruyer's work and that which seems to emerge from Frédéric's work: in both cases, the adaptive possibilities are not explained in the first place by the existence of the most recent structures on an evolutionary level but on the contrary the oldest.

Pourquoi parler de philosophie dans ce colloque essentiellement tourné vers une révolution scientifique qui doit nous permettre de mieux concevoir la genèse des formes vivantes ? Cette question n'aurait pas poser problème aux scientifiques contemporains du philosophe car ceci connaissait sans doute mieux ses travaux que les philosophes de l'époque qui n'avait de considérations que pour Sartre ou Heidegger. En 1954, il participa notamment à un très grand colloque sur l'instinct dans le comportement des animaux et de l'homme auquel participent une vingtaine de scientifiques de nombreux pays C'est avant tout parce que Raymond Ruyer, au milieu de XXème siècle, a été d'abord un philosophe du vivant qui a développé ses travaux à partir des révolutions scientifiques de son époque : physique quantique, génétique, embryologie, cybernétique. A l'opposé de philosophes qui voulaient s'émanciper de la science pour décrire le mode d'existence des êtres, Ruyer tenta de mettre en évidence, en étudiant les sciences, ce qu'elles ratent d'essentiel pour comprendre le vivant : la différence entre une vraie forme et une structure. Une conception philosophique de la forme permet de comprendre que le vivant ne peut être réduit à une étude scientifique des structures physico-chimiques ou des processus biologiques. Encore fait-il définir ce qu'est une forme vraie. C'est ce que nous détaillerons dans la perspective de Ruyer. Cette perspective fait du finalisme un moyen de compléter l'explication scientifique du vivant et aboutit à une remise en question du darwinisme. Certains arguments que Ruyer utilisent pour montrer la faiblesse des descriptions scientifiques de la genèse des formes vivantes ont un air de famille avec ceux de Frédéric Mercier. Principalement lorsqu'il tente de montrer l'avantage que nous pouvons avoir en utilisant les fractones et pas seulement le code génétique pour concevoir l'émergence et l'évolution des formes vivantes. Nous tenterons de mettre en lumière cet air de ressemblance afin de pouvoir juger si le néo-finalisme de Ruyer peut être lié au « micro-finalisme » de Frédéric Mercier et à sa volonté de rendre justice à Lamarck. Comme nous pensons que l'importance d'une découverte ne se mesure pas seulement à son pouvoir explicatif, nous tenterons également de comparer le changement de paradigme accompagnant les travaux de Ruyer et celui qui nous semble émerger des travaux de Frédéric : dans les deux cas, les possibilités adaptatives ne sont pas expliquées en premier lieu par l'existence de strcutures les plus récentes sur un plan évolutif mais au contraire les plus anciennes.

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Fractones are specialized extracellular matrix structures that regulate the fate of stem cell progeny. Abundant extracellular matrices (ECM) exist in the eye and play crucial roles in homeostatic and pathologic signaling pathways. Among other components, ocular ECM include laminin and heparan sulfate proteoglycan (HSPG). Fractones have been identified in the brain by immunolabeling each [1], however, little if any data, identifying and characterizing analogous structures in the eye exists. Furthermore, defective vascular and neural stem cell maturation play critical roles in the pathogenesis of ocular neovascular and neurodegenerative conditions, respectively. Given the capacity of fractones to regulate stem cell fate, their identification and characterization in the eye, may provide a better understanding of these blinding conditions, allowing the development of rational therapeutic strategies.

References

[1] F. Mercier, "Fractones: extracellular matrix niche controlling stem cell fate and growth factor activity in the brain in health and disease," *Cell. Mol. Life Sci.*, vol. 73, pp. 4661–4674, Dec. 2016.

Role of the Exracellular Matrix Structures Fractones in Development, Cancer and Adult Neurogenesis

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We have found a common feature between development, cancer and adult neurogenesis (the production of new neurons in adulthood): the systematic presence of glycoproteic extracellular structures, which we named fractones. Fractones are not present in tissues that are not engaged in an active process of construction. Construction involves cell Proliferation, Differentiation, Migration and Apoptosis (PDMA). In the neurogenic zone of the adult mammalian brain, we have demonstrated that the binding of growth factors to the glycosylated motives of fractones is required for the activation of growth factors at the surface of stem cells and for the consequent production of new neurons. We anticipate that cancer-fractones work similarly to stimulate the production of new cancer cells and the migration of the newborn cancer cells to develop the disease outside of the original tumoral mass. We also find a faultless correlation between the distribution of fractones and the morphogenic process throughout the development of embryos. Therefore, we further anticipate that fractones might be responsible for the production and guidage of new cells to ultimately construct the embryo. In an attempt to determine whether fractones are present in all animals including the most primitive ones, we characterized fractones fractones in cyanobacteria, sponges, and diverse arthropods (insects and copepods). Together, these results strongly suggest that fractones are structures that control cell PDMA throughout life, and that for more than three billion years. Therefore, it is worth to further investigate the function of fractones, and characterize fractone inhibitors and stimulators. Beyond the basic knowledge of mechanisms that control the emergence of life and its maintenance throughout adulthood, this will provide insights into potential innovative treatments against cancer, developmental disorders, and neurodegenerative diseases.

Fractones are associated with a fibroblast/macrophage network through the meninges/choroid plexus to drive adult neurogenesis

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The current view is that our genes are the principal means by which our body constructs during development and rules our functions and disfunctions throughout life. However, more and more data point out that that the extracellular matrix (ECM), ECM-borne glycoproteins that locally change their motives according to the local extracellular environment, and fibroblasts and macrophages, intervene in morphogenesis, new cell generation throughout life, response to injury and disease.

Therefore, the question arises as to whether a physiological system, based on ECM and connective tissue performs physiological functions, but also intervene in pathological conditions. Here, I will introduce the fibroblast/macrophage (FM) network and its association with the ECM network of fractones for transducing information and communication throughout the brain, with a focus on the generation of new neurons in adulthood.

While fractone-borne glycoproteins bind and activate growth factors to locally regulate proliferation/differentiation of adjacent neural stem cells and the generation of new neurons, the question arises as how multiple fractones work together to regulate the entire brain neurogenic zone.

We characterized macrophages, perivascular fibroblasts and choroid plexus-originating Kolmer cells next to fractones. Using transgenic green-fluorescent mice as a source for choroid plexus cells to xenograft through the brain of host regular mice, we show that fluorescent grafted choroid plexus cells behave as neural stem cells after they traverse the brain ventricle walls and dock to fractones.

The fluorescent chroroid plexus cells, originally unable to behave as neural stem cells, are now able to produce neurospheres in culture. This strongly suggests that fractones turn choroid plexus cells into neural stem cells. More-

over, we have evidence that a network of choroid plexus fibroblasts, connected through gap junctions, prolongates in the superficial meninges. Killing the fibroblasts in the superficial meninges with 6-hydroxydopamine resulted in raising neurogenesis.

Taken together, these results indicate that the meninges/choroid plexus regulate new neuron production in the adult brain via fractones. We anticipate that meninges orchestrate growth factors/cytokines and guides cell proliferation/differentiation via fractones through the ventricle walls. Further understanding of this system will provide insights into innovative therapies for neurodegenerative disorders such as Alzheimer, Parkinson and Lateral Sclerosis.

A datamodel for structuring and scaling an organic knowledge network

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Intricate objects of scientific interest may involve multiple fundamental mechanisms.

- They may operate at a range of different scales of time and spacial dimensions.
- They may be understood and modelled through a variety of different notions of causality.
- They may raise a wealth of questions that need to be met with a diversity of scientific approaches.

To be efficient, collective scientific efforts and findings must coordinate dynamically. To this end, the MMM project proposes a datamodel/format supporting an organically networked approach to documentation, honouring the dynamic and collective nature of science-making, simultaneously relaxing and constraining aspects of both the traditional, linear, text based apporach to documentation, and the Semantic Web's modelling approach. Knowledge stored in MMM format is to coordinate in a global knowledge network comprised of epistemically interacting pieces of information, whose global and local properties, I expect, will be worth investigating to gain foresight on the interplay between our scientific ventures and paradigms.

From statistical signal processing to models in biology: the GENSA approach

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Our research concerns mathematical models to help understand and characterize the system that controls the proliferation, differentiation, migration and apoptosis (PDMA) of cells. This work is in the continuation of and actually extends [1], initially motivated by fundamental properties of the immune system, and especially, its degeneracy.

Our basic paradigm is that any living organism interacts with its environment through several steps: 1) the living system permanently senses its environment to perceive a multiplicity of events and changes in its surrounding; 2) it changes state depending on its perception of the environment and 3) it has a feedback effect on its environment according to its new state. Typically, PDMA reflects the interaction via fractones between stem cells and the extracellular matrix. We postpone to further work the introduction of network models to account for networks formed by living systems to share information through a common interior.

In this paper, we introduce the GENeric Sensor Actuator (GENSA) as a first step to a general theory for modelling the interactions involved in the creation and variations of the PDMA. The GENSA is fundamentally based on the Random Distortion testing (RDT) theory [2]. The RDT theory was introduced for statistical signal processing applications where the lack of prior knowledge and the degree of incertitude are such that standard solutions can become inefficient to detect signals in noise. The GENSA approach allows to model the living system ability to cope with uncertainty and changes in its environment and the "balanced sensitivity and specificity" of the signal detection it performs" [1].

References

[1] D. Pastor, E. Beurier, and V. Thomas-Vaslin, "A multiplicity of statistical models for modeling the degeneracy of living communicating holons," *EPJ Web Conf.*, vol. 263, 2022.

[2] D. Pastor and Q.-T. Nguyen, "Random Distortion Testing and Optimality of Thresholding Tests," *IEEE Transactions on Signal Processing*, vol. 61, pp. 4161 – 4171, Aug. 2013.

Microglia lining the lateral ventricles contribute to a unique neuroinflammatory niche

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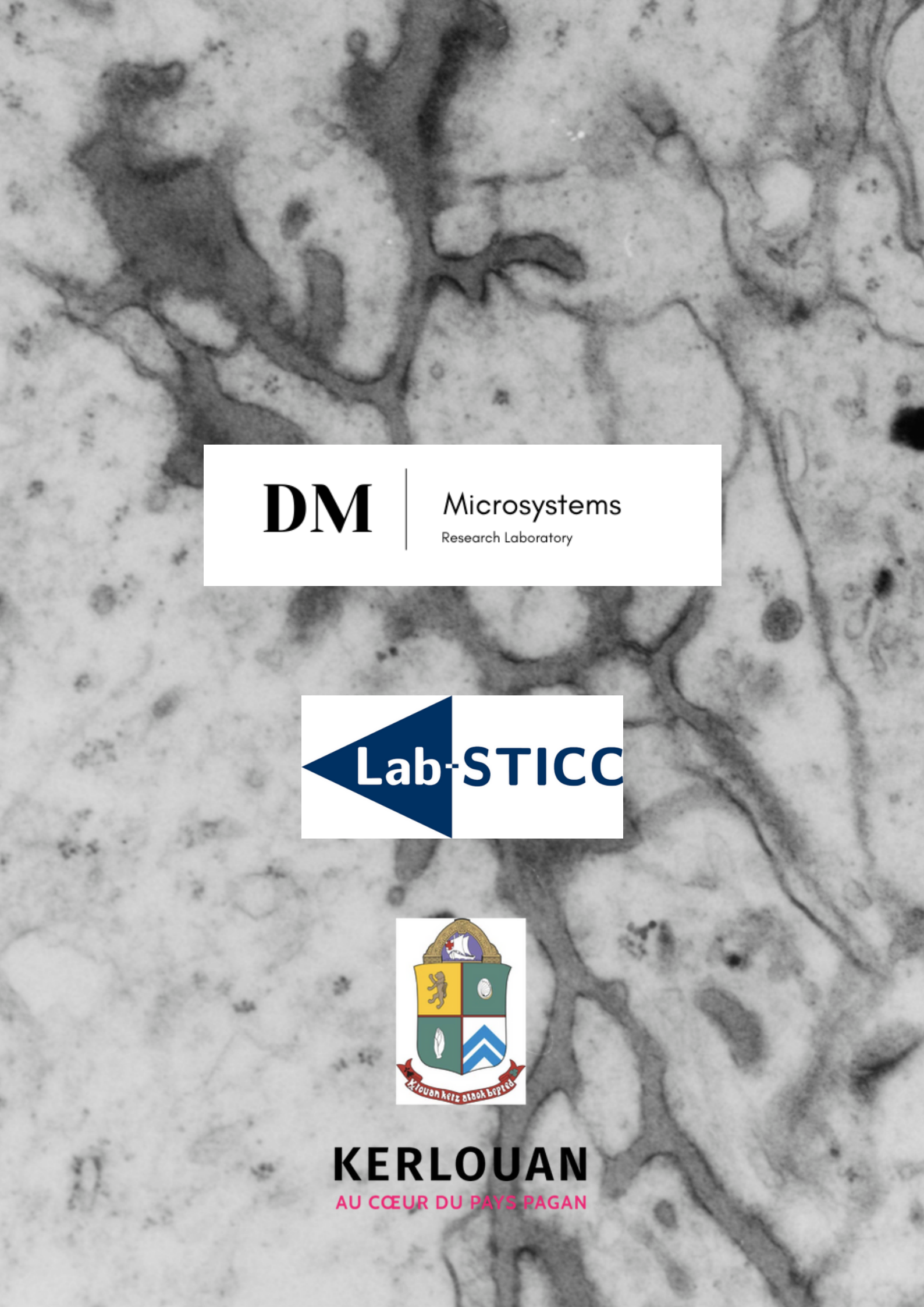
Microglia are becoming better and better understood in terms of transcriptomics, morphological variations, developmental functions and subtypes of responses to disease. Neverthess their phenotypic variations and full functional repertoire is still poorly understood. Although traditionally thought to respond to disease by clearing debris they are now known to progress through many phenotypic phases in disease and can be neuroprotective. There is also evidence that microglial activation can precede disease implicating them as potential causative agents and thus of interest for pharmacotherapeutic targeting. Microglia in the ventricular-subventricular zone (V-SVZ) are in contact with all cells in the neurogenic lineage as well as with ependymal and epithelial cells and are thus positioned to have broad functions in the niche. Even in the absence of disease, V-SVZ microglial cells have semi-activated morphology, marker expression and division rates - distinguishing them from microglia outside of the niche. The pro-inflammatory protein Galectin-3, which is normally expressed in microglia during pathological insults is constitutively expressed in the V-SVZ stem cell niche. These data suggest that cells lining the lateral ventricle have a specialise and poised neuroinflammatory phenotype during homeostasis. V-SVZ microglia become even more activated, less activated or remain stable in different models of disease. Surprisingly, they can respond to brain injury divergently compared to microglia in the non-neurogenic niche. These data together suggest that V-SVZ microglia exhibit unique phenotypes and functions.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