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BMP9 and pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure greater than 25 mmHg at rest. It is a rare disease (15 to 25 cases per one million adults), with a 5-year survival rate of 59% in absence of treatment. Since 2000, mutations in the BMPR2 (Bone Morphogenetic Protein Receptor type 2) gene have been identified as genetic factors predisposing to the development of PAH.

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In 2008, researchers at IRIG's Cancer Biology and Infection laboratory identified BMP9 as a high affinity ligand for the BMPR2 receptor [1] and very recently, mutations in the gene coding for BMP9 were identified in patients with PAH. The question arose as to what is the role of BMP9 in the development of PAH.

In ***collaboration*** with researchers from the "Hypertension, physiology and therapeutic innovation" laboratory at Plessis-Robinson, they show [2] that, contrary to what could be expected, blocking the BMP9 ***signaling pathway*** through ***three different approaches*** reduces the development of pulmonary hypertension in different preclinical models. The ***proposed mechanism*** is that BMP9 is a vasoconstrictor agent, the absence of which would therefore cause vasodilation, explaining the protection observed against PAH. In agreement with this hypothesis, the only current therapeutic treatments for this disease are vasodilators.
This discovery offers new insights into the complexity of the processes involved in PAH and shows that additional experiments are needed to understand the function of the BMP signaling pathway in the development of this pathology.

**Collaboration with the UMR_S 999, Marie Lannelongue Hospital, Le Plessis-Robinson*

** **Signaling pathway:** A sequence of steps involving multiple molecules in a cell or on its surface that work together to control certain cellular functions.*

** **The three approaches are:** inactivated mice for Bmp9, anti-BMP9 neutralizing antibody and injection of the extracellular domain of the ALK1 receptor, trapping BMP9.*

** In the **mechanism proposed** by the authors, BMP9 would regulate the expression of endothelin-1, apelin and adrenomedullin.*

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[2] **Tu L, Desroches-Castan A, Mallet C, Cumont A, Phan C, Robert F, Thuillet R, Bordenave J, Sekine A, Huertas A, Savale L, Feige JJ, Humbert M, Bailly S and Guignabert C.** Selective BMP-9 inhibition partially protects against experimental pulmonary hypertension. Circulation Research, 2019

In search of a drug in action by X imaging

Some types of cancer remain resistant to chemotherapy treatments. Researchers at Inserm, CNRS, Sorbonne University, PSL University, Univ. Grenoble Alpes, CEA and ESRF have studied the properties and mechanism of action of a new organometallic anti-tumoral molecule.

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When tested on a model of breast cancer, this compound was shown to penetrate the membranes and to accumulate intracellularly into the ***endoplasmic reticulum*** (ER in the Figure) where it is oxidized. The metabolites generated seem to attack simultaneously different parts of the cell, leading to anticancer activity.

These results are promising because this new family of organometallic compounds could become an alternative in the arsenal of conventional chemotherapy, particularly in order to overcome resistance to current drugs while having a low cost.

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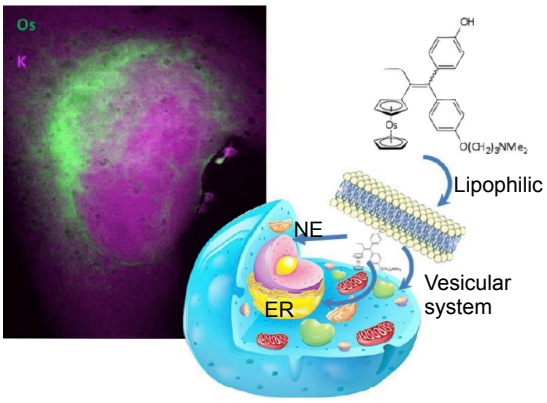

Synchrotron radiation-enhanced fluorescence mapping of the potassium distribution, an essential physiological element of the cell (K, pink) and osmium (Os, green), a constitutive element of the osmocenic derivative of hydroxytamoxifen, within cells type triple negative breast cancer.

ER = ***Endoplasmic reticulum:*** *network of membranous tubules dispersed throughout the cytoplasm of eukaryotic cells.*

Titanium dioxide effect in the diet

Titanium dioxide (TiO_2) is a food additive authorized since the 1960s. Used for its whitening properties, it is included in confectionery, pastries and other industrial preparations under code E171 in the European Union. Its initial authorization file states that it poses no health risk and that its intestinal absorption is minimal. Its re-evaluation by the European Health Authority (EFSA), published in 2016, led the experts to conclude that the available data indicated that dietary exposure to this substance was not a health problem for consumers. Nevertheless, they emphasized the lack of data on some organs, particularly reproductive organs, and recommended to conduct studies to fill these voids.

In 2017, a study was published by the French National Institute of Agronomic Research (INRA), highlighting its promoter effect in colorectal carcinogenesis on rats exposed by gastric gavage or drinking water at realistic doses of E171, as well as disturbances of the immune system of exposed animals [1].

Researchers at IRIG's Molecular Systems and nanoMaterials for Energy and Health laboratory (SyMMES) have been studying the effects of TiO_2 nanoparticles on *in vitro* models of intestinal ***epithelial cells*** for about ten years. These models combine ***enterocytes*** and cells secreting mucus, thus reconstituting the most superficial layer of the ***epithelium*** bordering the terminal part of the small intestine - the ileum. While prior results of the researchers have shown a transfer of TiO_2 nanoparticles from the intestinal lumen to the internal environment [2], their most recent data point out significant cellular effects, although of small magnitude. Thus, E171 does not result in a decrease in cell viability or chromosomal breaks or damage in the DNA of exposed cells, but disrupts the oxidative balance (homeostasis) of the cell, in particular by causing the accumulation of reactive oxygen species, toxic for the cell, coupled with the appearance of oxidized bases of DNA [3]. These disturbances do not cause endoplasmic reticulum stress but are associated with an inflammatory pattern, an increased expression of efflux pumps responsible for the release of xenobiotics out of intestinal epithelial cells, and with increased mucus production by Goblet cells [4].

On the basis of these results, E171 therefore appears to cause sub-lethal perturbations in intestinal epithelial cells, leading these cells to put in place defense mechanisms.

E171 seen in scanning electron microscopy.

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Collaboration: Institut de Recherche en Santé Digestive, Inserm, Toulouse; Toxalim, Inra, Toulouse; Laboratoire Chimie et Biologie des Métaux, CNRS-CEA-UGA, Grenoble.

Enterocytes are one of the four main types of cells in the intestinal epithelium, within the intestinal mucosa.

Epithelium: a fundamental tissue forming either an outer (on the surface of the skin) or an internal (on the surface of a mucous membrane) surface, or a gland composed of ***epithelial cells***.

The intimate secrets of photosymbiosis in marine plankton

Described a few years ago, the symbiosis between two marine planktonic organisms, the Acantharia (host) and a microalga called *Phaeocystis*, is ubiquitous in the oceans. Thanks to subcellular imaging technologies, partially developed in Grenoble, researchers from the Helmholtz Center for Environmental Research (UFZ), UGA, CNRS and CEA, in collaboration with the ESRF, have unveiled key mechanisms showing that this unique form of symbiosis is essentially beneficial for the host (Acantharia).

According to this interdisciplinary consortium, the cellular architecture and metabolism of the microalga *Phaeocystis* are greatly modified by the host toward high photosynthetic productivity. This new mode of symbiosis is very likely a strategy of "farming" algae by host cells rather than a win-win relationship between the two species over evolutionary terms.

An Acantharia (host) 100-200 µm long with its intracellular symbiotic microalgae (10 to 100 copies) of 5-10 µm (yellow cells). Credit: Johan Decelle

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New modeling of magnetic memory

Random Access Magnetic Memories (MRAMs) are spintronic devices combining non-volatility (keep the data without power supply), speed and robustness against radiation. They are intended to become one of the basic building blocks of future neuromorphic devices and / or architectures (e.g. neural network). At the heart of the component, there is a magnetic tunnel junction consisting of two ferromagnetic layers (reference and storage) separated by an insulating barrier (Figure 1). The most promising approaches are based on the configuration so-called perpendicular magnetic tunnel junctions for which the magnetizations of the two ferromagnetic layers are perpendicular to their plane.

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To increase the integration density of the memories, the lateral size of the magnetic junction (Figure 1) is constantly reduced, but this generates a sharp increase in the current required for writing. Naturally, as a consequence the Joule effect become important and lead to the heating of the storage layer whose magnetic properties are disturbed. The magnetic behavior thus deviates from the desired standard behavior. Therefore, the reversal of the magnetization is no longer precisely controlled and the operation of the memory point is challenged.

Researchers at IRIG's Spintronics and Component Technology Laboratory (Spintec) have adjusted the modelling approach, which is usually used to describe the magnetization reversal, taking into account the Joule effect. In this novel model, the magnetization of the storage layer is uniform and its orientation free to evolve with the field and / or the applied current (pulse). During the pulse, the temperature variation, due to the Joule effect, impacts several magnetic parameters of the system that are calculated. A calibration of this model (Figure 2) was carefully performed to accurately describe the behavior of the perpendicular junctions regardless of the applied voltage, and thus determine the stability points (field, voltage) of operation.

The interest of this new model lies in its generality being applicable to various kinds of magnetic tunnel junction of lateral nanometric size. In the close future, the model will be integrated into microelectronic design tools.

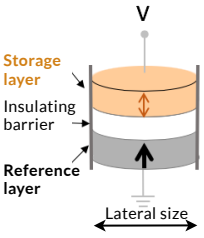

Figure 1: Diagram of a nano-pillar JTM. Depending on the parallel or antiparallel orientation of the magnetization between the two ferromagnetic layers (arrows), the electrical resistance of the junction will be low or high, thus encoding the binary information. One of these layers, called reference, has a fixed magnetization during operation of the memory point. The second, or storage layer, is used to record the information via its magnetization which, during writing, changes under the action of a voltage step of a few nanoseconds.

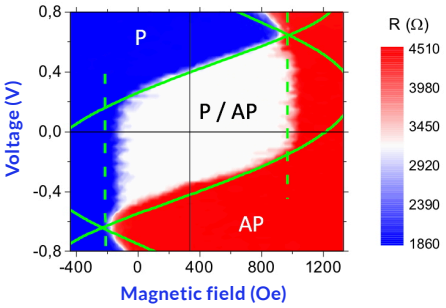

Figure 2: Field-voltage diagram measured experimentally. The blue color indicates the parallel state of the two ferromagnetic layers (P, low electrical resistance), the red indicates the anti-parallel state (AP, high electrical resistance). White is the bi-stability zone (P / AP). Green lines are the stability lines from modeling.

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