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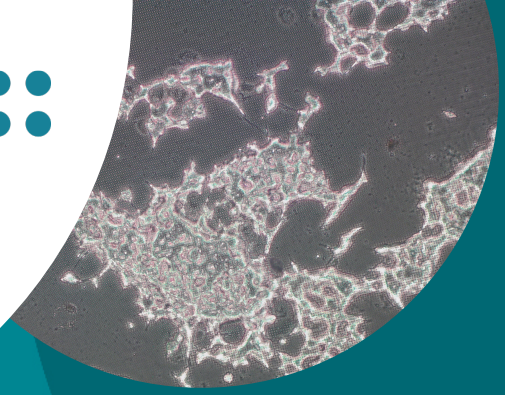

Scientific Newsletter

WINTER 2022

Editorial

The beginning of 2023 is the occasion for us to publish the first IRIG scientific newsletter during the winter season. It is a good time to take stock of what has been accomplished before looking ahead to the New Year.

Once again, the year 2022 has been marked by many successes and scientific results all across the 9 UMRs. The diversity of scientific topics our laboratories focus on, and the quality of your research work, make our institute a major player in the scientific and social fields. Like the previous scientific newsletter, the few highlights selected among many illustrate the wide range of scientific topics covered by the Institute. The year 2022 has been packed, first thanks to the numerous publications and awards recognizing both our doctoral students, post-doctoral students, as well as our senior researchers. Further, the sustained development of institutional and industrial partnerships (regional, national and European), as well as the launch of several start-up projects have also greatly contributed to the visibility of the Institute.

The year 2022 was also marked by the many participants invested to benefit from the new national REPP programs (Research and Equipment Priority Programs) within the framework of the France 2030 Plan and the PIA4, in order to consolidate French leadership in scientific fields that are a priority or likely to be linked to major transformations. IRIG is involved in nearly 20 highly supported or exploratory REPPs in the fields of digital technology, health, energy and the environment, etc. This great collective success demonstrates the strong position of our research teams at the national level and the recognition of our scientific skills.

In parallel with the scientific dynamic, we are also striving to improve our work together with the continuous help of the support teams from the UMRs and the central level of the Institute. We will pay particular attention to the quality of life at work by continuing the actions begun in 2022.

For the year 2023, I hope that the whole IRIG will develop further in order to better support the Institute's scientific projects and its involvement in major issues. Actions to promote our quality of life at work, an essential element to support our activities, will be pursued for the benefit of each of us.

I look forward to seeing you on February 3 for our IRIG annual meeting, which will give us a chance to discuss our successes and projects.

I wish you all, IRIG staff but also all our partners, the readers of this newsletter, my best wishes for this New Year 2023. May it be rich in success in your personal and professional endeavors, may it bring you joy and serenity.

Happy New Year to all of you!

Pascale Bayle-Guillemaud, Head of the
Interdisciplinary Research Institute of Grenoble

Magnetic microparticles to stimulate insulin secretion

In 2021, diabetes is a disease that affects approximately 537 million adults, according to the International Diabetes Federation. There are two types of diabetes that lead to hyperglycemia, i.e. too much glucose in the blood. The amount of blood glucose is regulated by the hormone insulin which is secreted by the pancreas. Type 1 diabetes results from a lack of insulin secretion while type 2 diabetes is due to a misuse of insulin by the body's cells. Patients with diabetes, typically monitor their blood glucose levels several times a day and then inject appropriate doses of insulin subcutaneously. This blood glucose control is for most patients, done manually.

More integrated solutions exist, but several technical problems persist and the technology is still invasive. The optimal medical device will include a blood sugar sensor able to monitor continuously, an algorithm to calculate the appropriate insulin dose, and an insulin pump. Regarding diabetes treatment, other lines of research can be considered, such as the development of artificial pancreas or the stimulation of the deficient pancreas in diabetic patients.

In this context, researchers at IRIG are studying how to stimulate insulin secretion by a failing pancreas. They use the vibration of magnetic microparticles deposited on the surface of pancreatic beta cells. Researchers had already used these particles to induce the death of cancer cells by apoptosis. These are microdisks (figure A) composed of iron and nickel, and which can be coated on both sides with a layer of gold.

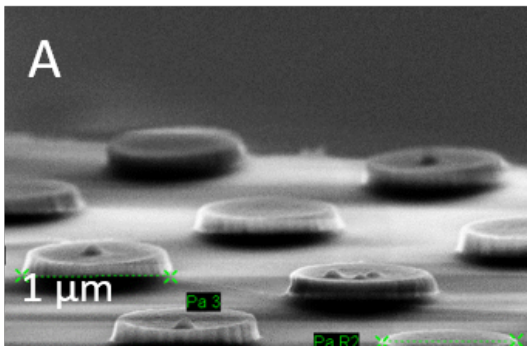

Figure A: SEM image of the $Fe_{20}Ni_{80}$ magnetic particles on silicon substrate used for magneto-elastic membrane fabrication (diameter: 1.3 µm; thickness: 60 nm).

When they are deposited on INS-1E (figure B) pancreatic beta cells and when the whole assembly is subjected to a low frequency magnetic field, the vibration of the particles stimulates the cell surface, which results in insulin secretion.

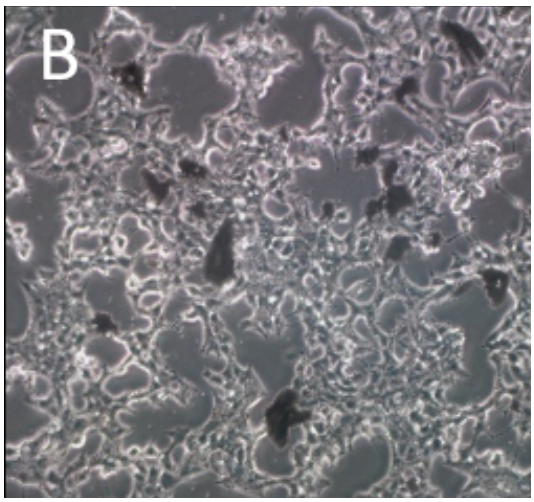

Figure B: INS-1E pancreatic cells exposed to agglomerated microparticles (magnification ×200).

The amount of insulin produced depends on the concentration of particles applied to the cell surface (10 to 50 µg/mL), the frequency of the magnetic field (10 to 40 Hz) and the duration of the stimulation (5 to 30 minutes).

Under optimal conditions, the amount of insulin secreted is close to that observed when the cells are stimulated via an effective concentration of glucose. This mechano-stimulation is not deleterious to the cells and does not lead to apoptosis.

However, these magnetic microparticles are internalized by the cells. To overcome this effect and to guarantee the safety of the device, the researchers incorporated the magnetic microparticles into a polydimethylsiloxane PDMS polymer film (figure C).

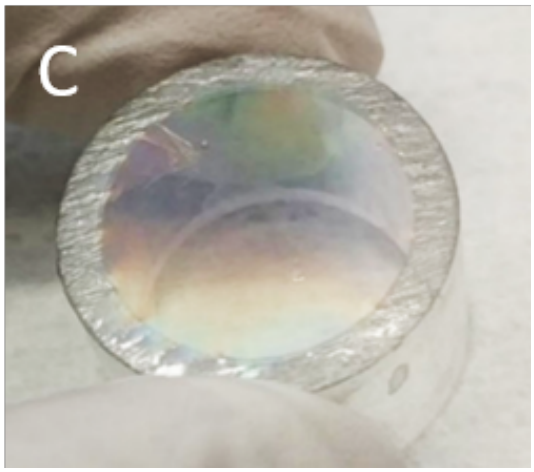

Figure C: fabrication of $Fe_{20}Ni_{80}$ magnetic particle-doped PDMS membranes, forming a well in which cells can be grown.

The new device avoids internalization of the particles and leads to insulin secretion by the cells (Figure D).

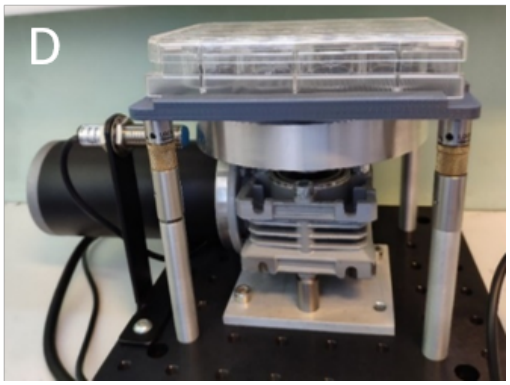

Figure D : dispositif magnétique pour stimuler la sécrétion d'insuline.

Thus, the mechano-stimulation of the surface of pancreatic beta cells, via the vibration of magnetic particles isolated or included in a polymer film, leads to insulin secretion and could eventually become one of the components of an artificial pancreas. It is also possible to imagine the implantation of magnetic particles in the deficient pancreas of diabetic patients.

Contact : Marie CARRIERE
SyMMES
Molecular Systems and nanoMaterials for Energy and Health

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Nanoscale, 2022

Towards the control of the polarity of an artificial cell

Cells are constantly sensing and adapting to their environment. In response to an external signal, they have the ability to "polarize" themselves by reorganizing their internal skeleton, the cytoskeleton, and repositioning their organelles along an axis defined by the position of the signal. The design of an artificial cell able to polarize itself from elementary components represents an interesting strategy to improve our understanding of the principles of self-organization of living organisms and could open the way to the elaboration of materials with capacities of adaptation to a stimulus.

Polarity acquisition is a primitive function that allows unicellular cells to move towards a nutrient source or to escape from a predator. Within a tissue, it allows cells to orient their secretory, absorptive, or signaling activities according to the position and shape of neighboring cells. Although the molecular actors vary from one organism to another, the mechanisms involved in polarization seem to be conserved in living organisms. They are based on the reorganization of the cytoskeleton.

In animal cells, the highly dynamic actin cytoskeleton is the first to react by locally adjusting its organization to the signal.

The microtubule network then adapts to the multiple local structures of the actin network. The radial organization of the microtubules around the organizing center, the centrosome, allows it to integrate its information at the scale of the whole cell and to define a single global response. The mechanism of information integration is still unknown. It involves a repositioning of the centrosome towards the signal in response to a reorganization of forces in the microtubule network.

Where and how are the forces generated on the microtubules? How are they integrated at the centrosome? How does the actin network influence these forces? These are all questions that need to be addressed to understand the mechanisms involved in cell polarity.

Researchers at IRIG used purified proteins to reconstruct in vitro in cell-sized microwells (Image above), the interaction of a microtubule aster with actin networks of various architectures. In the absence of actin filaments, the positioning of the aster is very sensitive to variations in MT length. Actin networks limit the sensitivity of MTOC positioning to MT length and reinforce the centering or decentering of MTOCs according to the isotropy of their architecture.

In the absence of actin filament, aster positioning is very sensitive to variations in microtubule length. Actin networks limit the sensitivity of centrosome positioning to microtubule length and reinforce their centering (or decentering), depending on the isotropy (or anisotropy) of their geometry.

These results are an important step towards reconstituting polarity in an artificial cell. They were the subject of a cover article in “The EMBO Journal”.

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Actin network architecture can ensure robust centering or sensitive decentering of the centrosome.
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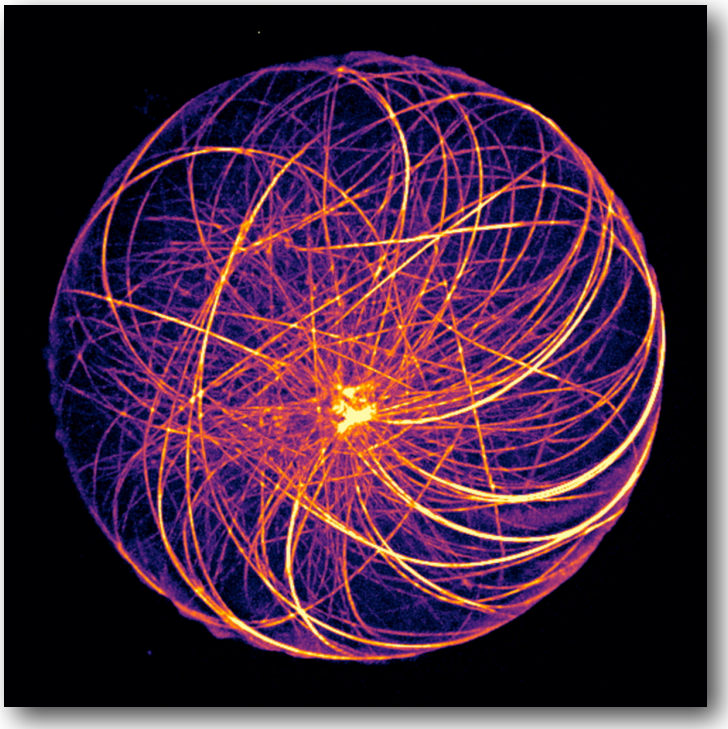
Contacts : Laurent BLANCHOIN
Manuel THERY
LPCV
Cell & Plant Physiology Laboratory



Organization of microtubules in a cell-sized compartment (diameter 60 µm)
© Jérémie Gaillard, Alfredo Sciortino, Benoit Vianay/Cytomorpholab

First manipulation of the chirality of magnetic skyrmions by a gate voltage

Skyrmions are magnetic quasi-particles, of nanometric to micrometric lateral size, composed of spins that roll up in a given direction, this rolling Skyrmions are magnetic quasi-particles, of nanometric to micrometric lateral size, composed of spins that wind up in a given direction, this winding direction being called chirality.
In magnetic films of nanometric thickness, if one passes radially through these skyrmions, the spins rotate 360° in a cycloid. The skyrmions can be moved in the direction of the electric current or in the opposite direction depending on their chirality. Until now, their chirality was fixed "by construction" according to the nature of the multilayer materials in which they were observed.

Researchers from our institute [***collaboration***] have succeeded in controlling in situ and locally the direction of motion of skyrmions by modifying their chirality using an applied gate voltage.

From a fundamental point of view, these results are interpreted as the change of sign of an interfacial interaction at the origin of the chirality of skyrmions (the so-called Dzyaloshinskii-Moriya interaction, much studied in the framework of the physics of thin-film materials). From an application point of view, it is a first step towards the possibility of controlling the displacement of individual skyrmions with a low energy consumption method, which is essential to be able to use them as coding units (memory) or in logic gates.

The skyrmions have been studied in a nanometer thick multilayer system (Ta/FeCoB/TaOx), typical of spintronic devices. The thickness of the ferromagnetic layer in which the skyrmions appear and the degree of oxidation of the adjacent oxide are parameters to be refined very precisely. The researchers fabricated a sample with a gradient of ferromagnetic layer thickness along one dimension and of oxidation along the other in order to determine the best combination, this know-how being available only in a few spintronics centers in the world, including the Spintec laboratory of our institute. A systematic study was then carried out to find the electrical parameters leading to the inversion of the motion. Figure 2 shows a magneto-optical microscopy image in which we observe the skyrmions (white dots) and their direction of motion in the initial material. Under the application of a gate voltage, the multilayer material is modified; in particular the displacement of some oxygen ions modifies the oxidation state of the interface with the ferromagnetic layer, and the new skyrmions obtained move in the opposite direction with respect to the first ones, due to an inversion of their chirality.
These experiments are accompanied by simulations to predict the magnetic configuration at the nanoscale: they explain the results in relation to more fundamental physics concepts such as interfacial magnetic interactions.

For future applications in spintronics, the next step is a fine control of the propagation of smaller (nanoscale) skyrmions, with the objective of being able to direct, in a reversible way, a chosen skyrmion in a desired direction. The researchers are starting to work on the integration of skyrmions in a patterned device (magnetic track) and to develop in parallel a model to deeply understand the physics mechanisms that control the movement of skyrmions under current.

Contact : Hélène BEA
Spintec
Spintronique et Technologie des Composants

Collaboration This work was carried out in collaboration with the Institut Néel (CNRS) in Grenoble and the Laboratoire des Sciences des Procédés et des Matériaux in Villetaneuse (CNRS)

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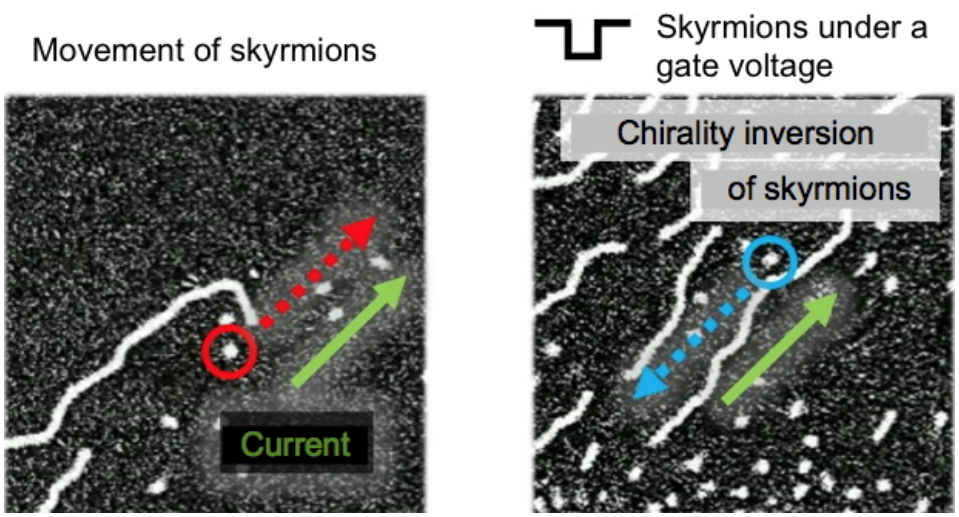
Gate-controlled skyrmion and domain wall chirality.
Nature Communications, 2022



Magneto-optical microscopy images illustrating, by the dotted arrows, the change in the direction of motion of the skyrmions (white dots) under the same current (continuous **green** arrow). (a) skyrmions in the initial material, (b) skyrmions under a gate voltage. The size of the images is about 50 µm.
Credit: Spintec (CNRS - CEA - Université Grenoble Alpes)

Membrane protein platforms for metal efflux in certain bacteria.

Metals are essential for cell function. In order to make them cross the cell membrane, specialized membrane proteins will either import them, in case of deficiency for example, or export them when they are at concentrations potentially toxic for the cell.

Present in all living organisms, P_{1B}-ATPases constitute one of the membrane proteins families specialized in the transport of metals, whether they are toxic, such as cadmium and lead, or essential at low concentrations and toxic at high concentrations, such as zinc and copper. The P_{1B}-ATPases share the same enzymatic mechanism and in part, the same structural organization as other well-known P-ATPases such as calcium-transporting ATPases or sodium/potassium exchangers.

In 2011, the team led by Olivier Neyrolles at the Institut de Pharmacologie et de Biologie Structurale (Toulouse) highlighted a previously unknown role for P_{1B}-ATPases. Firstly, this team showed that during infection by *Mycobacterium tuberculosis*, the pathogenic bacterium captured and stored in the phagosomes of the macrophage was subjected to toxic concentrations of zinc (Fig. A).

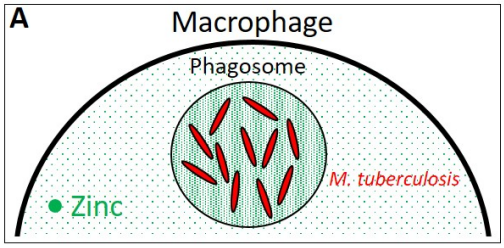


Figure A: *M. tuberculosis* inside the phagosome of a macrophage where zinc has accumulated.

The team also showed that in order to survive this metal poisoning, the bacterium overproduced a P_{1B}-ATPase, CtpC, whose role is to export excess zinc from the cytoplasm.

In the present study, researchers at IRIG [***collaboration***], experts in P_{1B}-ATPases, show that CtpC cannot function without the presence of a small membrane protein of previously unknown function: ***PacL1***. This protein colocalizes with CtpC at microdomains in the bacterial membrane (Fig. B) and has a zinc binding motif at its C-terminus.

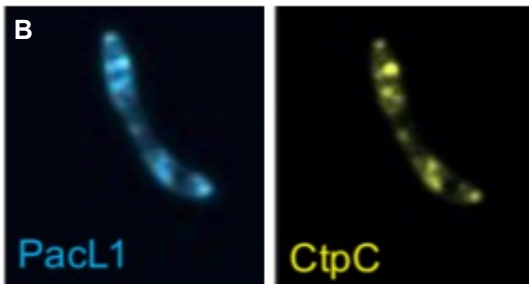


Figure B: Epifluorescence image of $PacL1_{mTurquoise}$ and $CtpC_{mVenus}$ colocalisation in *M. tuberculosis*.

Without PacL1, CtpC is no longer localized at the membrane and *M. tuberculosis* becomes highly sensitive to zinc. In this study, the researchers identified two other P_{1B}-ATPases/PacL pairs in *M. tuberculosis* involved in metal transport: CtpG/PacL2 and CtpV/PacL3. In addition, other P_{1B}-ATPases/PacL pairs are also found in different types of bacteria.

This work suggests that metal resistance in some bacteria may use membrane platforms combining P_{1B}-ATPases and small PacL-type chaperones, a new concept in the metallobiology of prokaryotes (Fig. C).

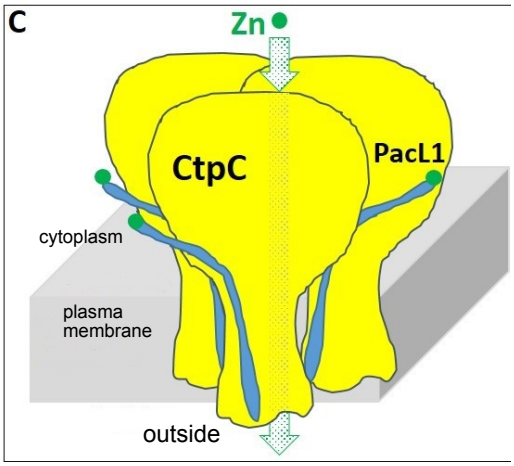


Figure C: Schematic representation of a membrane platform for zinc efflux by CtpC/PacL1

These results also open new perspectives for combating pathogenic bacteria by targeting their resistance mechanisms to metal stresses.

Collaboration: O. Neyrolles, Institute of Pharmacology and Structural Biology, Toulouse (France).

PacL1 *(**P**-ATPase-**a**ssociated **c**haperone- **L**ike protein **1**)*

is a membrane protein required to the correct targeting and transport function of CtpC, hence the name "chaperone".

Contact : Patrice CATTY
CBM
Chemistry and Biology of Metals laboratory

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Mycobacterial resistance to zinc poisoning requires assembly of P-ATPase-containing membrane metal efflux platforms.
Nature Communications, 2022

Proton wires play key role in the mechanism of proton transporters

Hydrogen bonds are fundamental to the structure and function of biological macromolecules. The chains of hydrogen bonds (***CHBs***) and low-barrier hydrogen bonds (***LBHBs***) were proposed to play essential roles in enzyme catalysis and proton transport.

Different research groups have determined bacteriorhodopsin structures at the ground and at functionally important intermediate states. Although this improved the understanding of ***bacteriorhodopsin***, a light-driven proton pump, and provided some insight into proton transport, the resolution of these structures (at best 2 Å) did not allow to decipher the detailed molecular mechanism of proton transport.

For more than 20 years, solving crystallographic problems step by step, researchers at IRIG revealed the true-atomic-resolution structure of bacteriorhodopsin (about 1 Å). An amazing picture of the proton storage and release mechanism presented experimentally shows for the first time that linear chains of hydrogen bonds (often called proton wires) and low barrier hydrogen bonds described in terms of quantum mechanics and symmetry considerations are at the core of the mechanisms.
The complete picture of hydrogen bonds, CHBs and LBHBs, discloses their multifunctional roles in proton transport. The discoveries demonstrated how hydrogen bonds, CHBs and LBHBs, not only serve as proton pathways, but are also indispensable for long-range communication, signaling and proton storage in proteins. This consistent picture of proton transport and storage is finally resolving long-standing debates and controversies.

This work does not only relate to a great problem of the mechanisms of proton transfer but also to a significant biological role of one-dimensional chains of hydrogen bonds and their symmetry described in terms of physics. The corresponding current studies aim to clarify the universality of the discovered mechanism (proton transfer reactions comprise more than 50% of all biochemical reactions) and their possible applications in nanomaterials.

History
It was 1971 when Dieter Oesterhelt and Walther Stoeckenius discovered bacteriorhodopsin, the first microbial rhodopsin. In 2021, Dieter Oesterhelt receiving the Lasker Prize mentioned: “I was met with everything from disinterest to complete disbelief from colleagues. The situation changed rapidly after 1972, when I collected the first data on the function of this molecule and showed that it was a pump that converts light energy into chemical energy for the cell – essentially a new form of photosynthesis.”

One of the reasons for high scientific interest was that the results obtained by D. Oesterhelt and W. Stockenius indicated that the proton gradient created by bacteriorhodopsin in H. salinarum plays the central role in energy coupling attributed to such electrochemical gradients by Mitchell's chemiosmotic theory, published in 1966 was first received with skepticism. The eventual acceptance by scientific community came with the demonstration of coupled ATP synthesis in the bacteriorhodopsin-ATPsynthase lipid vesicles (Nobel prize, 1978).

However, elucidation of the molecular mechanism requires knowledge of high-resolution structures of bacteriorhodopsin. It turned out to be a great challenge. Moreover, at that time it was considered to be impossible to crystallize a membrane protein. Hartmut Michel, wrote in his Nobel Prize (1988) autobiography: “Frustrated from the lack of the final success with bacteriorhodopsin, I tried to crystallize several other membrane proteins, mainly photosynthetic ones.”
Richard Henderson initially developed cryoEM crystallography working with bacteriorhodopsin and in 1990 obtained an unprecedented for that time 3 Å resolution (Nobel Prize, 2017).
One more breakthrough happened in 1996-97 when E. Landau and J. Rosenbush crystallized bacteriorhodopsin in an “exotic” lipidic cubic phase and Eva Pebay-Peyroula from IBS Grenoble solved bacteriorhodopsin structure at 2.7 Å (Science, 1997).

Interestingly, developing cubic phase crystallization with bacteriorhodopsin was instrumental for the downstream development of the structural studies of ***GPCR receptors***, the largest family of human receptors which are also critical for the development of 30-40% of the existing drugs (Nobel Prize, 2012).

Bactériorhodopsine is a protein used by Archaea, most notably by haloarchaea, a class of the Euryarchaeota. It acts as a proton pump; that is, it captures light energy and uses it to move protons across the membrane out of the cell. The resulting proton gradient is subsequently converted into chemical energy.

G protein-coupled receptors (GPCRs) also known as seven-(pass)-transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptors, and G protein-linked receptors (GPLR), form a large group of evolutionarily-related proteins that are cell surface receptors that detect molecules outside the cell and activate cellular responses. Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times..

Contact : Valentin GORDELIY
IBS
Institut de Biologie Structurale

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True-atomic-resolution insights into the structure and functional role of linear chains and low-barrier hydrogen bonds in proteins.
Nature Structural & Molecuklar Bilogy, 2022

Top coherence time for a hole spin in natural silicon

In the race to the quantum computer, different physical media are competing to encode quantum information. What do they have in common? They form systems with two energy levels - the quantum bits or qubits - which must be able to be initialized, read and manipulated.
Electron spins or electron gaps (holes) are promising candidates because they can now be isolated in silicon using technology compatible with industrial microelectronics processes.
However, electron spins can only be manipulated by locally applying a magnetic field oscillating at a microwave frequency. However, this constraint dissipates locally a lot of heat that reduces the performance of qubits. An alternative is to insert micro-magnets to couple the spins to an electric field, but this increases the footprint of the qubits and makes their large-scale integration more complex.

In 2016, researchers at CEA-Irig and CEA-Leti showed that the same is not true with holes. Their spin can be controlled "naturally" via an electric field, thanks to "spin-orbit coupling". These qubits therefore materialize in the form of transistors cooled to very low temperatures, for which coherent spin manipulation only requires sending a microwave signal to the transistor gate.

Recently, researchers at the Delft University of Technology (Netherlands) have developed a 4-hole qubit processor in germanium, a feat hailed by the whole spin qubit community. However, in their experiment (as in the first CEA experiments), the electrical control of the qubits exposes them to the surrounding electrical noise, thus limiting their coherence times to much lower values than those of electron qubits.
By deeply controlling a single hole spin in silicon, Irig researchers have just demonstrated that there is a sweet spot where the hole qubit becomes almost insensitive to electrical noise, while remaining tunable. This ideal configuration, which corresponds to a particular orientation of the magnetic field, is in agreement with theoretical models and should be achievable in other materials such as germanium.

The coherence times obtained in this sweet spot are close to 100 μs, surpassing by more than an order of magnitude the previous reported values. They are now very close to the values for electron qubits electrically controlled by micro-magnets, obtained in isotopically purified silicon - an option that reduces the perturbations brought by the nuclear spins of silicon 29Si present up to 5% in natural silicon and optimizes the coherence time of electron spins.

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Nature Nanotechnlogy, 2022

Contacts: Romain MAURAND
Pheliqs
Quantum Photonics, Electronics and Engineering Laboratory

Yann-Michel NIQUET
MEM
Modeling and Exploration of Materials

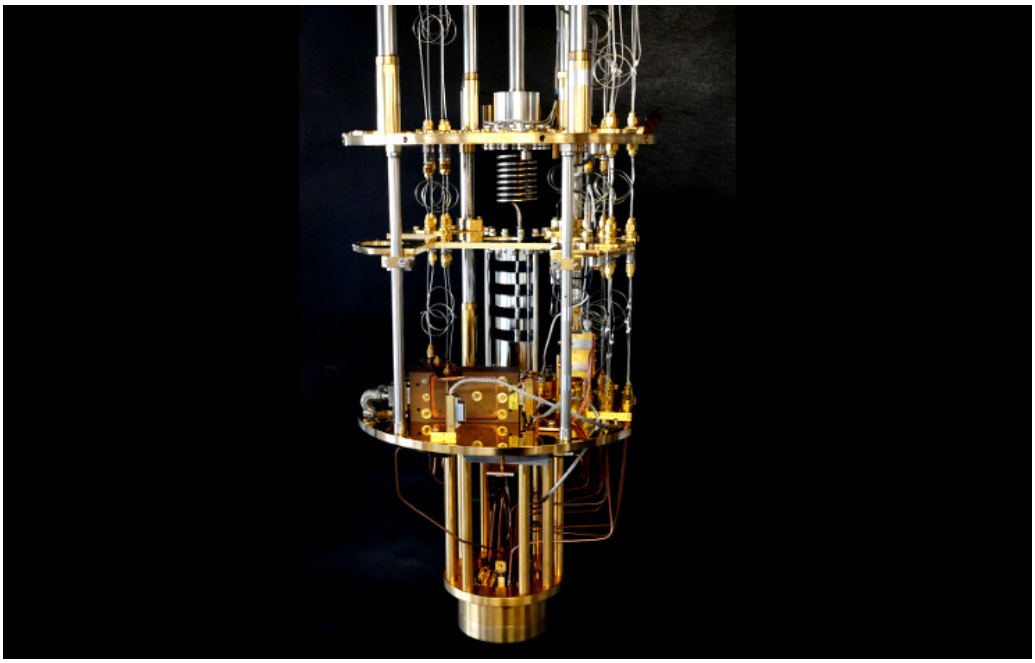

Image: cryostat © CEA / Estelle VINCENT

Spatial organization of growth factor receptors in anchoring zones of a cell

The organization of cell-surface receptors is fundamental to coordinate the biological responses of cells in response to physical and biochemical signals from the extracellular matrix. Indeed, proteins in the extracellular matrix transmit multiple signals to cells in a time-regulated and spatially structured manner.
For example, fibronectin, one of the main proteins of the matrix, has binding sites close enough to establish interactions with ***integrin*** adhesive receptors and with growth factors. This property allows a functional juxtaposition between integrins and growth factor receptors.

Contacts: Catherine PICART
Biosanté
Laboratoire Biologie et Biotechnologie pour la Santé

Corinne ALBIGES-RIZO
IAB
Institut pour l'Avancée des Biosciences

Previous work showed that the growth factor Bone Morphogenetic Protein 2 (BMP2), presented by a soft matrix, induces cell spreading. This spreading is associated with the formation of adhesive structures that depend on integrin receptors. However, the mechanisms and temporal events that enable concerted responses between integrin receptors and growth factor receptors remained poorly explored.

Researchers at Irig and IAB have been studying for 15 years how BMP-2 growth factor receptors cooperate with integrins, under the effect of BMP2, to drive cell adhesion and migration.
Their recent work has highlighted the cooperation between integrins, which are receptors involved in tissue mechanics, and growth factor receptors, which are of the tyrosine kinase type (named ALK3 and BMPR2) involved in cell differentiation. ALK3/BMPR2 receptors are described to form complexes on the cell surface when they bind to the growth factor BMP2 (see figure).
This finding shows that the ALK3 receptor exists as two populations distributed inside and outside the adhesion sites in response to BMP2 growth factor. Thus, a first population is associated with integrin and a second forms a complex with BMPR2 receptor. The spatial and temporal recruitment of ALK3 in integrin-based adhesion sites is a key aspect of the control of BMP-2 receptor-induced signaling. The partitioning of ALK3 outside and within adhesion sites provides a new mechanism to control the diversity of BMP signaling and couple cell functions.

For this study, biologists modified growth factor receptors to control their localization by light (***optogenetics***) and to monitor their diffusion and confinement properties at the nanoscale.
The combination of biomaterials with the optogenetic approach allowed to highlight that the proximity between integrins and growth factor receptors was sufficient to trigger cell spreading and to optimize cell differentiation. Biomaterial-mediated presentation of BMP2 allows spatial proximity between integrins and growth factor receptors, thereby promoting their cooperation.

Understanding the organization and spatial segregation of growth receptors is of pathophysiological interest as these receptors are described as tumor promoters or suppressors.

Integrin is a transmembrane receptor involved in cell adhesion and mechanics.
The structure comprises (1) an extracellular part recognizing proteins of the extracellular matrix and (2) an intracellular part connected to the cytoskeleton of the cell.

Optogenetics is a combination of optical and genetic techniques. Cells are genetically modified to express a photosensitive protein that activates at a specific location in the cell when illuminated with light.

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Integrin-based adhesion compartmentalizes ALK3 of the BMPRII to control cell adhesion and migration.
Journal of Cell Biology, 2022

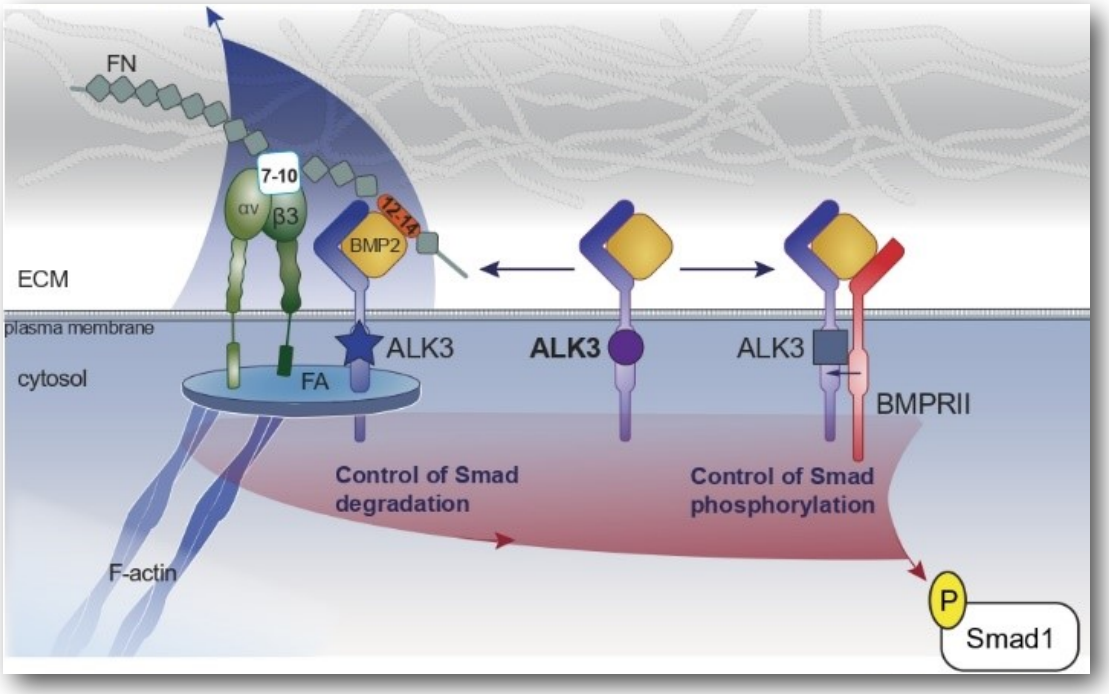

Figure: cell adhesive function
BMP2 induces redistribution of ALK3 receptor at the cell surface as two populations: one is sequestered in the integrin-mediated adhesion site (αvβ3); the other is immobilized in the plasma membrane outside the anchoring zones (FA), likely through its association with the BMPRII receptor.
The fibronectin matrix provides a binding site for integrin (domain 7-10) and a binding site for BMP2 (domain 12-14) promoting proximity between ALK3 and β3 integrin in adhesion sites. BMP2-induced Smad signaling requires ALK3, BMPRII, and β3 integrins, whereas cell adhesion processes (spreading and migration) rely solely on ALK3 and β3 integrins. The biomaterials developed at IRIG have the characteristic of presenting BMP2 which promotes the cooperation between integrins and growth factor receptors.

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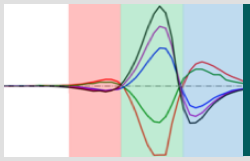

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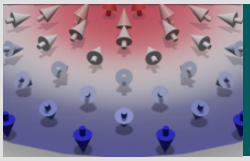

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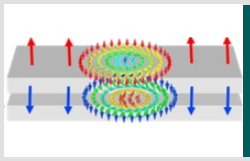

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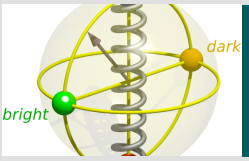

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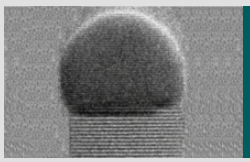

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Interdisciplinary Research Institute of Grenoble

CEA-Grenoble
17 avenue des Martyrs
38054 Grenoble cedex 9

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