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Scientific Newsletter

SPRING 2022

"Imaging" molecules in a bio-inspired nanocomposite material for hydrogen fuel cells

The development of new energy technologies relies, among other things, on devices such as fuel cells that use catalysts to convert hydrogen into electricity. For this purpose, a family of nickel-based molecular catalysts offers a credible alternative to the use of noble metals in conventional hydrogen fuel cells. These molecular catalysts, inspired by the structure of the active sites of hydrogenases, outperform traditional catalysts both in terms of efficiency per metal atom and environmental impact. In order to efficiently collect the current produced during hydrogen oxidation, the catalyst must be anchored onto a conductive support. However, the way in which catalysts interact with their support is poorly understood.

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Chemistry and Biology of Metals Laboratory
Pascale Chenevier
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Molecular Systems and nanoMaterials for Energy and Health Laboratory

Researchers at IRIG have developed different grafting strategies to maximize the performance of the final device. In particular, the conductive support should maintain a high porosity to allow access to the hydrogen gas, as well as a conduction network to transport the ions. Because of these requirements, carbon nanotubes are among the most suitable supports for immobilizing new catalysts [1]. However, these catalysts, which are mostly organic in composition and have a mobile and flexible structure, cannot be modified without affecting their catalytic activity. Moreover, once integrated in the composite catalytic layer, they escape conventional detection or imaging techniques.

A ***consortium*** of three IRIG laboratories and one CEA-Liten laboratory has studied this elusive structure by combining advanced and highly complementary characterization techniques. All the results obtained converge towards a new image of the association of the molecular catalyst with its support: a homogeneous coverage of the whole available surface of the nanotube to which is added a regular and nanostructured distribution of small agglomerates of catalysts.

On the basis of these observations, IRIG researchers, in collaboration with the Joliot Institute, have set up a fine control of the catalyst surface concentration. They were also able to optimize the hydration level of the active layer, a critical characteristic that ensures both the diffusion of gaseous substrates and ionic products. Thanks to these improvements, they have just achieved current densities of 0.4 A/cm² approaching the industry standard [2] of 1 A/cm² achieved by conventional platinum-based electrodes.

The integration of this new electrode into compact hydrogen fuel cells will be the next challenge.

The laboratories involved are:

- the CBM laboratory at IRIG (***Vincent Artero***, ***Bertrand Reuillard***) with a team from CEA-Joliot for sample preparation and electrochemical studies,
- the Symmes laboratory at IRIG (***Pascale Chenevier***, ***Sandrine Lyonnard***) for its expertise in surface characterization and small-angle neutron scattering, which allowed the observation of catalyst/nanotube self-assembly at the nanoscale in the presence of solvent,
- the nanocaracterization platform, the MEM laboratory at IRIG (***Hanako Okuno***) with the LCEA of Liten-DTNM (***Laure Guetaz***) for the use of transmission electron microscopy to image the catalytic layer on individual carbon nanotubes

This work is part of the PTC Materials and Processes BioPAC project entitled "Multi-scale physical characterization for optimization of bio-inspired PEMFC anode materials", and the FCH-JU CRESCENDO project (GN 779366) "Critical Raw material ElectrocatalystS replaCement ENabling Designed pOst-2020 PEMFC".

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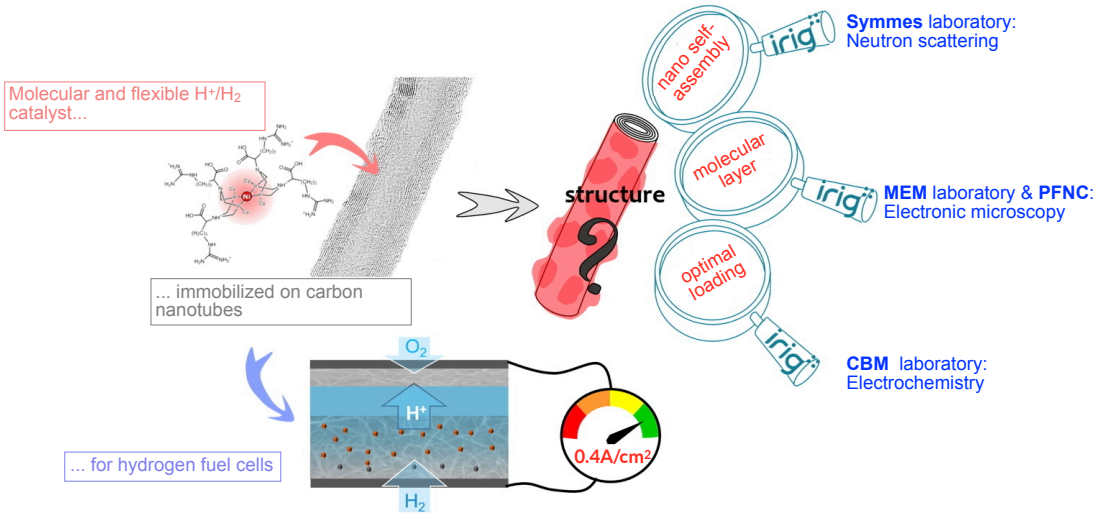

Vaccine candidate protects from SARS-CoV-2 infection

Antibodies targeting glycoprotein S (S) have been identified in SARS-CoV-2 ***seroconversion***. They mainly target an immunodominant region of S: the Receptor Binding Domain (***RBD***). Many of these antibodies confer protection *in vivo* but the magnitude of antibody responses to the S protein following natural infection varies considerably. For example, basal responses are generally maintained for months but may decline within weeks of infection, particularly in asymptomatic individuals. A vaccine approach that would induce sustained immunity capable of preventing infection and transmission of the virus would be a major asset in the fight against the pandemic.

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The stability of native S-glycoprotein is limited, yet its stability is essential for the presentation of relevant epitopes in a vaccine. Researchers at IRIG used chemical cross-linking with formaldehyde, widely used in clinically approved vaccine formulations, to increase the stability of glycoprotein S and thus preserve its native conformation for extended storage periods.
In collaboration with the François Jacob Institute of Biology, the University of Amsterdam and the Pasteur Institute, the IRIG researchers then presented these S antigens in the form of lipid nanoparticles *via* liposomes. These offer a controllable degree of multivalence and stability as well as a prolonged circulation half-life *in vivo*. Preclinical studies conducted with these protein S-loaded liposomes induced high antibody titers after two immunizations with potent neutralizing activity against the vaccine strain (alpha, beta and gamma variants). Although the predominant initial response was the production of antibodies directed against RBD, a third immunization significantly increased the production of antibodies directed against other regions of the S protein, encoded by sequences less prone to mutations. Immunization with the lipid nanoparticles led to complete protection against SARS-CoV-2 infection. In fact, the data indicate a sterilizing immunity. Indeed, no viral replication could be detected during the viral infection of the vaccinated group compared to the unvaccinated control group. This protection is most likely correlated with the presence of high antibody titers in the nasopharyngeal mucosa.

The creation of a vaccine candidate *via* lipid nanoparticles thus proves to be an effective approach, based on a classical and proven approach. In addition, the study provides a pathway to induce sterilizing immunity in correlation with a mucosal immune response that is desired to prevent the spread of the virus.

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The S protein is the main player in the infection of cells. It consists of two subunits: the S1 subunit allows the binding of the virus to the host cell receptor and the S2 subunit ensures the fusion of the viral envelope with the cell membrane. S1 contains two domains including ***RBD***, each recognizing different cellular receptors. The main domain used so far by SARS-CoV-2 is RBD, which allows binding to the ACE receptor, which is present on the surface of lung cells.

Seroconversion: phase during which the circulating antibodies are in sufficient quantity to be measured.

Identification of a new actor of light acclimation in marine microalgae

The process of photosynthesis used by diatoms, among others, is a real biochemical prowess because it allows the conversion of electromagnetic energy - carried by photons - into chemical energy that can be directly used by the cells. Although light is a free and abundant source of energy, it is nevertheless intrinsically variable in intensity and quality, and this characteristic can cause irreparable damage to the photosynthetic apparatus. Photosynthetic organisms have developed protective mechanisms to dissipate excess light energy, namely the Non-Photochemical Quenching (NPQ) process. Despite the ecological importance of diatoms, the determinants of NPQ regulation are still poorly understood.

Contacts: Giovanni Finazzi
Florence Courtois and Guillaume Allorent
LPCV
Plant & Cell Physiology Laboratory

Diatoms are a remarkably diverse family of marine microorganisms, capable of living in fresh and salt water as well as on ice. Their abundance in the oceans gives them an essential role in the functioning of marine ecosystems, notably as carbon sinks and oxygen producers. Their ecological success is due, among other factors, to the exceptional flexibility of their photosynthetic apparatus, which allows them to adapt to changing light conditions.

Using a spectroscopy approach, IRIG researchers demonstrated that in diatoms there is a direct coupling between NPQ and the ΔpH component of the ***proton-motive force*** (PMF) generated by photosynthetic activity. In the model alga *Phaeodactylum tricornutum*, they identified the existence of a proton/potassium ***antiport*** called KEA3. Being an important regulator of the PMF, this antiport is essential for NPQ to be established under normal conditions. By combining genetics and photophysiology, the researchers observed that the antiport KEA3 is responsible for adapting the NPQ response to environmental conditions. Because KEA3 is an ion exchanger, it is able to convert the ΔpH component of PMF to ΔΨ without energy loss. Thus, the PMF, and ATP production, is maintained while providing good protection to the photosynthetic apparatus through the establishment of NPQ.

Although evolutionarily related to the KEA1-3 family found in plants, the diatom KEA3 protein contains a motif capable of binding calcium. The researchers have shown that this domain controls KEA3 activity in diatoms, providing a possible link between intracellular Ca^{2+} concentration and responses to rapid (minutes-long) or slow (*e.g.* daily) changes in the light environment.

Overall, the elucidation of the NPQ regulatory circuitry in diatoms as well as the role of the KEA3 protein may help explain the prosperity of the diatom family in diverse environments, where light acclimation is often a major determinant of growth and survival.

The ***proton-motive force*** corresponds to a proton gradient across a biological membrane that is both electrical (ΔΨ) and osmotic (ΔpH) in nature. This gradient is used by the transmembrane complex ATP synthase in chloroplasts and mitochondria to produce ATP, an energy molecule that is essential for carrying out the rest of the biochemical processes in the cell.

An ***antiport*** protein is a protein that allows the exchange of two molecules across the cell membrane.

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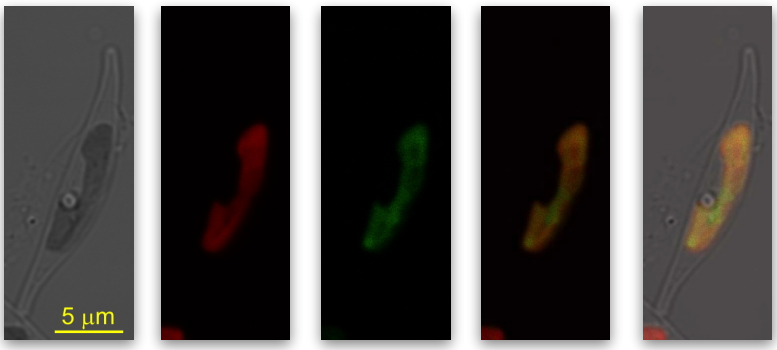

Localization of the fused KEA3 protein in *Phaeodactylum tricornutum*.
1 - light microscopy image of the diatom;
2 - auto-fluorescence of chlorophyll;
3 - fluorescence of the fused KEA3 protein;
4 - fusion of the images;
5 - fusion of the images on the light microscopy.

Measurement of insulin production in a single pancreatic islet using a microfluidic chip

Islets of Langerhans or pancreatic islets are clusters of cells specialized in the production of insulin and glucacon, two hormones regulating blood glucose levels. Type 1 diabetes is a chronic metabolic disease related to an active autoimmune destruction of insulin-secreting pancreatic cells, resulting in total insulinopenia responsible for chronic hyperglycemia. The transplantation of pancreatic islets from a deceased donor is now standard of care reimbursed by social security since 2021. However, these islets have extremely variable insulin production capacities. It would be very useful to be able to measure the insulin production of each islet in order to choose the most efficient ones before their transplantation.

Researchers at IRIG, in collaboration with Leti's Technologies for Biology and Health Department at CEA-Grenoble, have developed a microfluidic chip (*Figure*) that traps a single islet of Langerhans at a dedicated site on the chip. Once trapped, the composition of the medium can be changed at will using a set of highly elastic valves incorporated into the chip. Thus, by switching from a low concentration of glucose to a high concentration, the production of insulin by the entrapped islet can be stimulated. Thanks to a second network of hyper-elastic valves, the secretions from the islet can be collected and the quantity of insulin produced measured. At this stage of the project, this measurement has been performed outside the chip, but developments are underway to be able to dose insulin directly on the chip. Beyond the measurement of insulin from a tissue explant (here a pancreatic islet), the organ-on-chip that has been developed demonstrates the ability that researchers now have to measure secretions from a single ***spheroid***, ***organoid***, ***tumoroid***, automatically trapped in a chip, thus opening up a wide field of possible applications.

The next step will be to isolate, thanks to the chip, about ten islets producing very little insulin and about ten others producing a lot of insulin, in order to identify by multi-omics analysis the still unknown molecular mechanisms that are at the origin of this physiological difference. The researchers hope to be able to identify a biomarker, which will then allow us to sort out very quickly (5,000 islets/second thanks to a large particle FACS) the best performing islets before their transplantation into the patient.

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Contact: Xavier Gidrol
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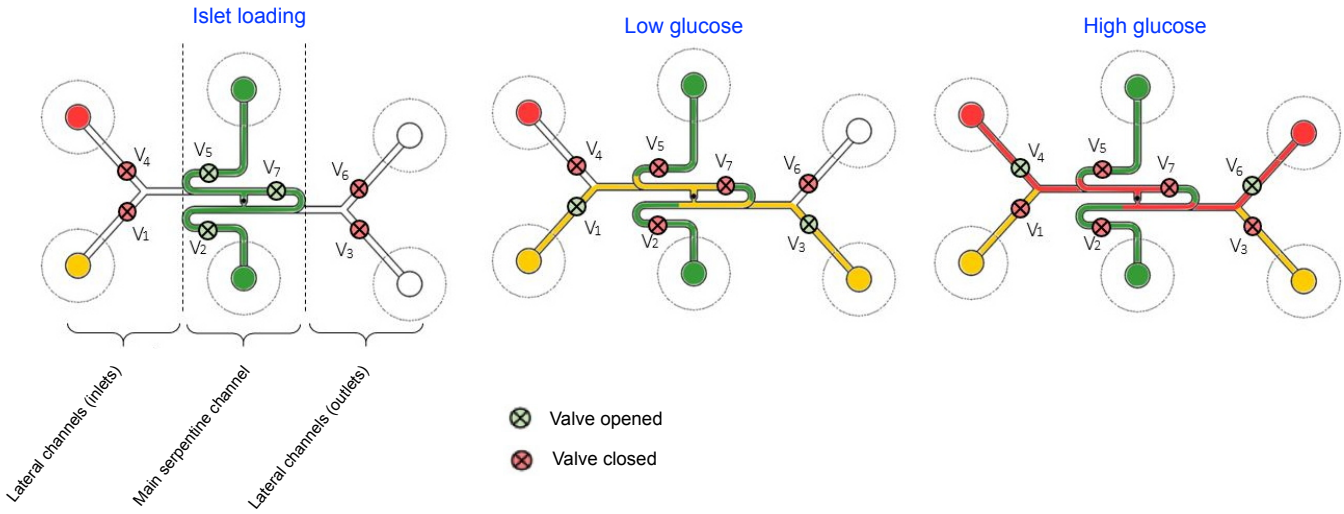
Biology and Biotechnology for Health Laboratory

In cell culture, ***spheroids*** are three-dimensional cellular aggregates.
An ***organoid*** is a three-dimensional multicellular structure that mimics the micro-anatomy of an organ and recapitulate at least one physiological function of the organ; it is therefore an *in vitro* model of the organ (or a mini-organ).
When the organoids are cancer cells, they are called tumoral organoids or ***tumoroids***.



Architecture of a microfluidic chip to measure glucose-stimulated insulin secretion (GSIS) from a single pancreatic islet. Scheme showing an overview of the GSIS assay protocol on a serpentine chip using a pneumatic valve array.

UTe_2 superconductor resists magnetic field

Superconductivity is characterized by the absence of electrical resistance and the expulsion of an external magnetic field. This spectacular manifestation of quantum mechanics down to macroscopic scales is well interpreted by the theory of superconductivity developed for simple metals more than 60 years ago. The recent discovery of new families of superconductors with unexpected properties has challenged this understanding.

Contact: Georg Knebel Pheliqs
Quantum Photonics, Electronics and Engineering

IRIG researchers are currently studying the compound UTe_2, a superconductor discovered in 2018 by researchers at the University of Maryland (USA). This metal has surprising properties. It becomes superconducting at temperatures below 1.6K. The magnetic field to suppress its superconductivity is anisotropic, which seems natural for a metal with an orthorhombic crystal structure like UTe_2. However, the required field strengths to suppress the superconductivity are much higher than those needed of a classical superconductor. These results show that UTe^2 is a rare "spin triplet" superconductor, where the electrons group together in pairs with their spin oriented in the same direction[1, 2].

The compound UTe_2 presents another remarkable property. As in a classical superconducting material, the critical temperature for the onset of superconductivity first decreases under the effect of the magnetic field. But, surprisingly, the behavior is reversed for stronger fields: the magnetic field strengthens the superconducting state when it exceeds the threshold of 15T. The critical temperature continues to increase up to exceptionally high field strengths of 35T, ten to one hundred times higher than for conventional materials.

Moreover, considering the discovery by American researchers of another superconducting phase of UTe_2 at even higher magnetic field strengths, IRIG researchers subjected UTe_2 to pulsed fields at the Laboratoire National des Champs Magnétiques Intenses (LNCMI National Laboratory of Intense Magnetic Fields) in Toulouse. A new superconducting state was then revealed above 45T. This state is maintained until at least 60T. Finally, under high pressure, the researchers also discovered transitions between different superconducting phases, at zero magnetic field and under field.

Until now, scientists believed that superconductivity was weakened to the point of being suppressed by the application of magnetic fields. The described results show that this property is not systematic. The characteristics uncovered by the IRIG researchers show how UTe_2 is a remarkable superconductor, with a "spin triplet" state that is extremely rare in nature and particularly interesting because of its intrinsic topological nature. Its totally unexpected properties are the source of a strong motivation to continue its experimental exploration. Their interpretation is also an exciting challenge for the theory.

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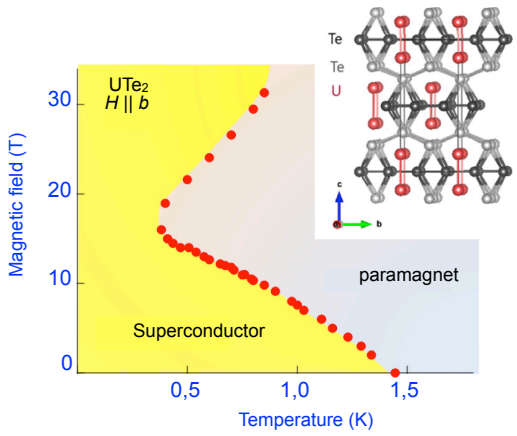

Figure: Temperature dependence of the critical magnetic field of UTe_2 applied along the crystal b-axis between a metallic and a superconducting phase. The magnetic field enhances the superconductivity from 15T to 35T. The insert shows the orthorhombic structure of UTe_2.

Bio-inspired superoxide dismutase complexes to fight the effects of oxidative stress

Superoxide $O_2^{\bullet-}$, a reactive oxygen species, is a free radical produced in living cells that use oxygen. This radical can be toxic to living organisms by reacting with DNA or disrupting protein production. Superoxide dismutases (SOD) are metalloenzymes that catalyze the dismutation of superoxide. This reaction takes place at their active site based on metal ions (Fe, Mn, Cu, Zn). Recent studies have focused on a bacterial SOD, NiSOD, whose active site has a nickel ion. The understanding of the catalytic mechanism of NiSOD and the optimization of bio-inspired complexes of this enzyme could lead to the design of new therapies against oxidative stress related diseases, such as chronic inflammatory bowel diseases

Contact: Pascale Delangle Symmes
Molecular Systems and nanoMaterials for Energy and Health laboratory

In some bacteria, the dismutation of superoxide $O_2^{\bullet-}$ is catalyzed by the enzyme NiSOD which active site is a square planar complex of the metal ion Ni^{II}. In order to elucidate the catalytic mechanism of this enzyme (*Figure 1*), researchers at IRIG and the Department of Molecular Chemistry DCM at UGA are developing complexes inspired by the active center of the NiSOD, by varying the coordination of the nitrogen and sulfur atoms around the Ni^{II} ion. A tripeptide derived from the ATCUN (Amino Terminal Cu^{II} and Ni^{II}) binding motif reproduces the N_3S_1 coordination of the metal ion in a square planar geometry (*Figure 2*). Under physiological conditions (water, pH 7), the results obtained with this complex show a SOD-like catalytic activity. Despite their short lifetime and low concentration, the researchers could identify, in organic solvent and at low temperature, two unstable reaction intermediates: the superoxo Ni^{II}, and hydroperoxo Ni^{III} complexes (*Figure 2*). The latter shows a direct interaction of the superoxide with the metal ion, indicating an inner sphere mechanism during catalysis. These two complexes characterized experimentally by Electronic Paramagnetic Resonance and by spectroelectrochemistry have signatures in agreement with the calculations obtained by DTF (Density Functional Theory).

These bio-inspired complexes constitute versatile structures that have the advantage of being stable in water and in organic solvents and provide insight into the mechanisms of superoxide dismutation by the NiSOD enzyme. In the future, researchers will optimize these bio-inspired complexes in the hope of developing new molecules to fight the harmful effects of oxidative stress.

Project supported by the EUR-CBH (Graduate School of Chemistry, Biology and Health).

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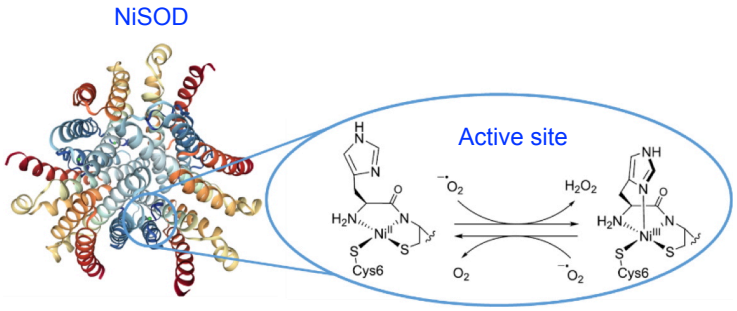

Figure 1: At the core of the NiSOD superoxide dismutase active site (pdb 1T6U), the square planar Ni^{II} center is coordinated to two cysteinate thiolate functions, the terminal amine of the peptide chain and an amidate function of a peptide bond. The Ni^{III} state formed during dismutation has a square-based pyramid-like geometry due to the additional bonding of the imidazole of the histidine in the axial position.

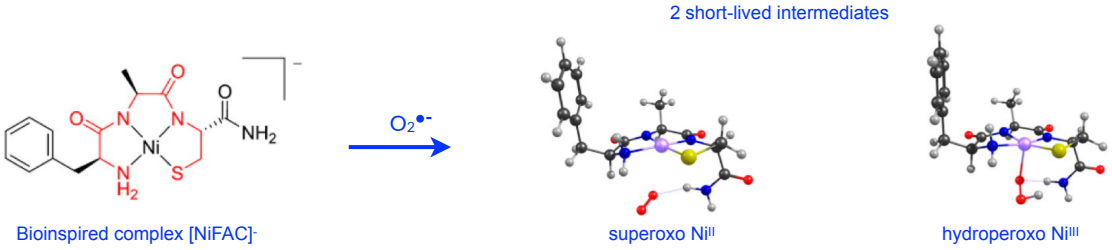

Figure 2: Upon reaction with superoxide, the bio-inspired NiSOD complex, $[NiFAC]^-$ reveals two short-lived reaction intermediates:
1) the superoxo Ni^{II} complex involves binding of $O_2^{\bullet-}$ *via* a terminal NH_2 group;
2) the hydroperoxo Ni^{III} complex shows the direct interaction of $O_2^{\bullet-}$ with the nickel ion.
The structures are optimized by DFT: C (black), H (grey), O (red), N (blue), S (yellow), Ni (pink).

Magnetic fluctuations in the UTe_2 superconductor

The superconductivity of materials, *i.e.* the ability to conduct electric current without loss of energy, is attracting the attention of fundamental and applied research. In a well-understood behavior, most metals become superconductors at very low temperatures, and this state is incompatible with magnetic properties. The discovery of new families of materials is challenging the understanding of the mechanisms of superconductivity. Indeed, researchers have discovered materials that can be both magnetic and superconducting, such as certain uranium-based alloys.

Contact: Stéphane Raymond
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Discovered in 2018, the superconductivity of the compound UTe_2 has the remarkable property of being robust to the magnetic field, because the electrons gather in pairs with their spin oriented in the same direction. This superconductivity is of the "spin triplet" type. IRIG researchers have performed neutron scattering experiments at the Institut Laue Langevin in Grenoble to measure the magnetic fluctuations of UTe_2 at the atomic level. A detailed analysis has allowed to highlight the local ferromagnetic coupling of Uranium atoms in the middle of dominant ***antiferromagnetic*** fluctuations. This coupling is located within the crystallographic structure of UTe_2, between the two closest uranium atoms forming a ladder composed of legs and rungs (*Figure*). The hypothesis is that this ***ferromagnetic*** coupling is very favorable to the realization of the "spin triplet" state of the electron pairs.

Later, the researchers will study precisely the link between the ferromagnetic ladder rungs and superconductivity. The characteristics obtained by neutron scattering are essential information, at the microscopic scale, to build a theoretical description of the superconducting behavior of UTe_2. This fundamental knowledge will allow a more general understanding of unconventional superconductivity.

Antiferromagnetism: the magnetic moments of neighboring atoms have opposite orientations.
Ferromagnetism: the magnetic moments have parallel orientations.

Collaboration: Laboratoire National des Champs Magnétiques Intenses de Toulouse (LNCMI), Institut Laue Langevin de Grenoble (ILL), Tohoku University and Japan Atomic Energy Agency (JAEA), Japan.

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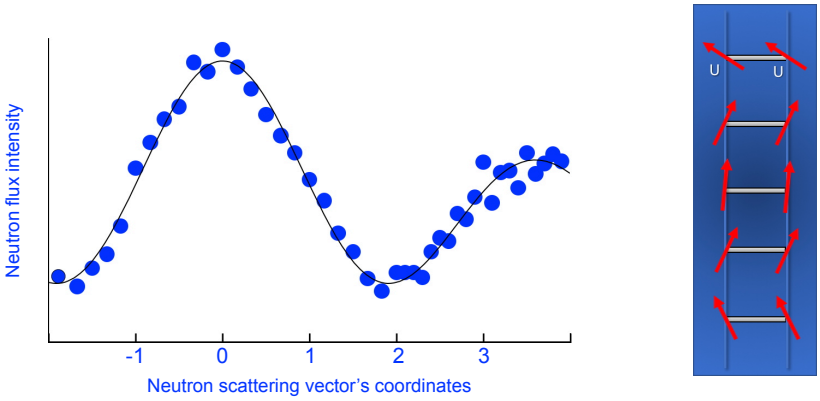

Figure: Spectrum of neutron scattering in UTe_2. The magnetic fluctuations describe a sinusoidal curve. The maximum of the curve is due to the ferromagnetic coupling of the uranium atoms (red arrows) which form the rungs of a ladder.
: Magnetic moment

Towards new anti-cancer treatments through the use of magnetic microparticles?

In the context of the fight against cancer, magnetic nanoparticles are used for several purposes: tissue labeling for imaging, targeting of drug delivery, destruction of cancer cells by magnetic heating, etc. A more general line of research focuses on the effect of local mechanical forces applied to the cell to modify its physiology or behavior. It has been shown, for example, that the vibration of micron-sized magnetic particles, by applying an external low-frequency magnetic field, leads to cell death in a few minutes.

Contact: Robert Morel
Spintec
Spintronics and Component Technology
Marie Carrière and Yanxia Hou-Broutin Symmes
Molecular Systems and nanoMaterials for Energy and Health laboratory

The most commonly used nanoparticles for biomedical applications are made of iron oxide, with a size of at most a few tens of nanometers. However, these are much too small to generate the magneto-mechanical forces likely to disrupt the cell, which requires micron-sized particles instead. Such magnetic particles (MP) have been developed at IRIG, for example in the form of permalloy disks ($Ni_{80}Fe_{20}$ alloy) a few tens of nanometers thick (*Figure left*). These particles are made by optical lithography in a clean room. They have the disadvantage of a high manufacturing cost and a low production yield. On the other hand, studies conducted *in vivo* where the particles were injected into a tumor have shown that they circulate very little at the tumor tissue level, thus preventing a global action on the whole tumor.

To overcome these drawbacks, researchers at IRIG [***collaboration***] have developed a new type of magnetic microparticles. These are magnetite particles, obtained by grinding a magnetite powder, which allows mass production at reduced cost. Their size, about one micron, is optimized so that their vibration induces the desired mechanical stress on the cells (*Figure right*). After obtaining the desired granulometry, the microparticles are covered with a silica envelope on which are grafted various types of PEG ligands (poly(ethylene glycol)). The choice of grafting PEG molecules, which form an envelope of flexible molecules of varying lengths on their surface, was to improve their dispersion within the cells.

The first step in validating these new microparticles was to verify their intrinsic toxicity on glioblastoma cells, an extremely aggressive form of brain cancer, through an *in vitro* study. The particles were found to be well tolerated up to the highest doses. These tests also showed that grafting with PEG considerably improves the dispersion of the particles in the middle of the cells, which was one of the desired effects.

The second validation step consists in observing the effect on the cells of the vibration of the particles under the action of an external magnetic field of frequency ranging from 2 to 20Hz. An interesting result emerges if we compare the effect of bare particles and the effect of particles coated with PEG (MP-PEG): while bare particles lead to the death of 90% of the cells, the vibration of MP-PEG leads to a lower mortality. Nevertheless, cells exposed to MP-PEGs showed a proportionally higher ratio in ***apoptotic*** death. Moreover, the increase in apoptosis is more pronounced at the lowest vibration frequency (2Hz).

These results highlight a difference in the mechanism of cell death depending on the type of particles (functionalized or not) and the conditions of the mechanical stimulation. One hypothesis would be that this difference could be attributed to the damping of vibrations by PEG chains: where more energetic vibrations would lead to cell ***necrosis*** by membrane rupture, the softer vibrations and damping induced by PEG would initiate a chain of cellular reactions leading to apoptosis.

These results open the door to further studies of the effect of magneto-mechanical vibrations on the cell, both in the context of research into new therapies and in the more fundamental context of research into cellular mechanosensitivity.

Collaboration: Molecular Systems and nanoMaterials for Energy and Health laboratory (SyMMES).

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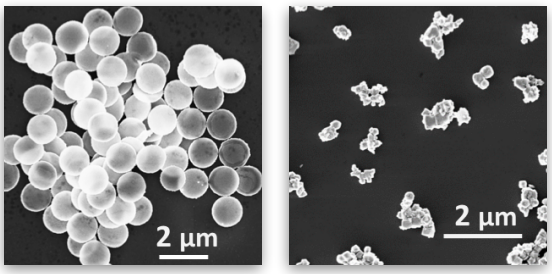
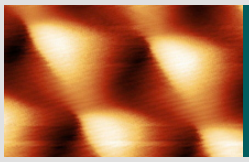
Apoptosis (or programmed cell death) is the process by which cells trigger their self-destruction in response to a signal. Death by ***necrosis*** results in the dispersal of the cancer cell's contents throughout the body, which can contribute to the spread of metastasis. Conversely, during the process of apoptosis, the cellular debris is evacuated without harmful consequences for the organism.



Left: Magnetic permalloy microparticles manufactured by optical lithography.
Right: Magnetite microparticles made by grinding powder.

Other scientific news of the IRIG laboratories



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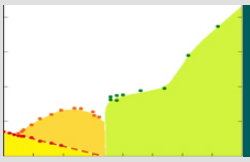

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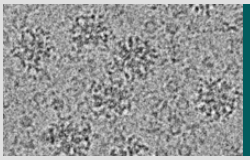

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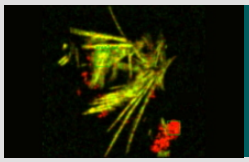

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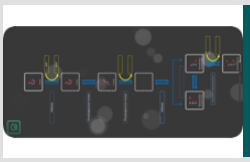

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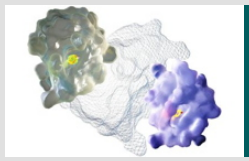

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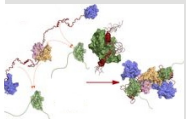

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