FALL 2020

GIANT REVIEW

— Exploring Science in Grenoble —

CEA: PepS, automatic sample preparation for MS analysis

GEM: Trust, the difficulty of trusting in times of crisis

EMBL: Research, preparation for the next pandemic(s)

Grenoble-INP: 3D Printing, superhero hands made in Grenoble

A GIANT response to a global pandemic

Grenoble Alpes

GIANT (Grenoble Innovation for Advanced New Technologies) unites research, higher education and industry on a unique campus to overcome the major challenges of tomorrow.

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AWARDS & HONORS

Mihai Miron (CEA-IRIG)
ERC Proof of Concept 2020

Bernard Dieny (CEA-IRIG)
ERC Proof of Concept 2020

Eva Kowalinski (EMBL)
ANR JCJC Grant 2020

Victor Veille (Grenoble INP alumni and CNRS - Institut Néel post-doc)
Université Grenoble Alpes Innovation Thesis Prize 2020

Grenoble Ecole de Management (GEM)
The GEM MSc Management in International Business (MSc MIB) climbs +1 position in 2020 Financial Time ranking to reach 46th position

Alexandra Pacureanu (ESRF)
Alan Agar medal for Electron Microscopy by the Royal Microscopical Society

Wojciech Galej (EMBL)
ERC Starting Grant 2020

Université Grenoble Alpes
Top 100 world's best universities by Shanghai Ranking 2020

Joanna Wandzik (EMBL, EDCSV, UGA)
L'Oréal-UNESCO For Women in Science, French Young Talents Fellowship 2020

Luca Rizzi (CNRS)
ERC Starting Grant Geometric analysis of sub-Riemannian spaces through interpolation inequalities (GEOSUB)

Commissariat à l'énergie atomique et aux énergies alternatives (CEA) - Institut de recherche interdisciplinaire de Grenoble (IRIG) • Centre National de la Recherche Scientifique (CNRS) • European Molecular Biology Laboratory (EMBL) • European Synchrotron Radiation Facility (ESRF) • Grenoble Ecole de Management (GEM) • Grenoble Institut National Polytechnique (Grenoble INP) • Université Grenoble Alpes (UGA)

Welcome to the fall 2020 GIANT Review

The COVID-19 pandemic highlights, more than ever, the importance of state-of-the-art research infrastructure to rapidly enable the international scientific community to address global complex challenges facing our society.

The ESRF has joined forces with the partner institutes of the EPN Science campus (EMBL, IBS and ILL) and of the GIANT campus to actively contribute to the global effort to study the novel virus and to gain new scientific knowledge of key aspects of the virus, such as the interaction of the virus with human cells, the progression of the infection process at sub-cellular levels and the corresponding immune system response, and the function and efficacy of newly-designed antiviral drugs and treatments. In this context, since early June 2020, the ESRF's Extremely Brilliant Source (ESRF-EBS), the world's first fourth-generation high-energy synchrotron light source, has been put to the service of the international biomedical COVID-19 research effort. Its unparalleled performances have immediately provided new vistas in the 3D imaging of COVID-19-damaged human organs, insight into infected tissue networks, and understanding of the SARS-CoV-2 structure down to the atomic level.

The EBS-based COVID-19 research effort, with its increasing international impact, illustrates once more the 'GIANT effect': bringing together GIANT expertise and state-of-the-art facilities to keep science and innovation at the forefront and provide a collective response to the vital challenges facing humanity, in the key areas of health, environment and sustainable energy.

In this issue, you will discover some highlights of the research carried out by the partners of the GIANT campus and our efforts to jointly contribute to address the COVID-19 pandemic. I hope that you will appreciate the impact of the GIANT campus on science and society, taking pride from already being one of the many GIANT colleagues, or from knowing that you will always be very welcome to visit us and maybe start new mutually beneficial research and innovation collaborations!

Francesco Sette
Director General at the European Synchrotron (ESRF), Grenoble

UGA AWARDED THE 'WELCOME TO FRANCE' LABEL

The Université Grenoble Alpes has been awarded the two-star 'Welcome to France' label for the quality of its international student support services. With 9,000 international students, including 180 different nationalities, the UGA has developed numerous different initiatives to welcome international students. The International Students & Scholars Office (ISSO) informs, welcomes and accompanies international students, PhD students and researchers on various aspects that include accommodation, administrative procedures and residence rights. Other actions put in place include the availability of French classes at the University Center of French Studies (CUEF) and the reservation of housing for international students in partnership with the regional student welfare office (CROUS Grenoble Alpes). The 'Welcome to France' label is part of a national policy to develop the attractiveness of higher education institutions for international students and is awarded to French institutions that demonstrate the highest standards in the development of reception facilities to meet the needs of international students.

MOOVLAB: ENABLER OF INTERACTIVE VIRTUAL FITNESS

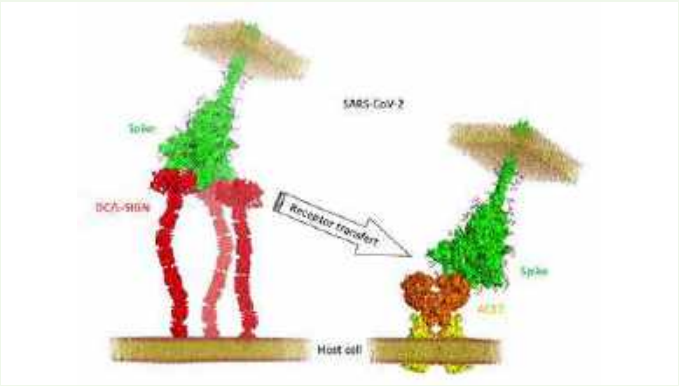
The lockdown certainly changed the sporting habits of a lot of people, sending many to search for online coaching and creating a desire for connected sport. Moovlab, a spin-off from CEA-Leti, is perfectly placed to help fitness studios respond to this new demand. The all-included system enables the creation of fun and interactive virtual fitness work-outs that can be adapted to the individual objectives of each person. With performance measuring technology and the capability to recognize different fitness exercises by the use of smart sensors worn on the wrists, the device enables an evaluation both in real-time and over an extended period allowing the person to track their progress. Under development since 2016, the product has now been launched and is currently under test in the gym chains Keep Cool and Unik.

AN IMMERSIVE, VIRTUAL WELCOME FOR GEM STUDENTS

Grenoble Ecole de Management (GEM) has pushed the boundaries of technology to provide the most immersive, interactive and human experience possible for its students. The start of the school year began with a virtual Welcome Forum, held live in the main auditorium of the VirBELA Open Campus - a virtual world created by Laval Virtual – for the 8000 GEM students from around the world. Immersive virtual technology has also been used to recreate the different GEM campuses online, enabling new students to visit and discover the different sites through virtual tours from wherever they are located. Each student can create their personally customized avatar and meet with program directors and department members in individual or group meetings. They can also get to know other students, take part in interactive activities and presentations and discover all the student services and associations that GEM has to offer.

SARS-CoV-2: discovery of a new mode of transmission at the IBS

Glycoprotein S, located on the SARS-CoV-2 virus membrane, is known to allow the entry of this virus into human cells via the ACE2 receptor, present on the surface of infected cells. Researchers at the Institute of Structural Biology (IBS, a joint CEA, CNRS and UGA research unit), in collaboration with groups from Spain and Italy, have discovered receptors different from ACE2, that are involved in the overall infection process. After attaching the virus to the cell, these lectin receptors are capable of transmitting the virus to permissive cells possessing ACE2. It is therefore a new mode of transmission in the infection process, detailed in an article posted on the BioRxiv preprint site (doi.org/10.1101/2020.08.09.242917) which is currently under evaluation by a peer-reviewed journal. They have also shown that it is possible to inhibit this new mode of virus transmission through the use of glycomimetics (sugar mimetics created by organic synthesis) previously developed at IBS.



The **ESRF EXTREMELY BRILLIANT SOURCE** (ESRF-EBS) is now open and running!

A new era for X-ray science has begun with the opening of the Extremely Brilliant Source at the European Synchrotron (ESRF-EBS). The first of its kind, this fourth-generation high-energy synchrotron is a world-unique research infrastructure and a landmark for the whole X-ray science community.
The ESRF-EBS generates X-ray beams that are 100 times brighter than its predecessor and 10 trillion times brighter than medical X-rays, enabling the 3D exploration of matter from meter to nanometer scales. Completed on time and within budget, scientific users are now back, albeit remotely, at the ESRF to carry out experiments with the new extremely brilliant source, that will contribute to tackling global challenges in key areas such as health, environment, energy and new industrial materials.

THREE, TWO, ONE… **LIFTOFF!**

AMICalSat, the first student nanosatellite from Grenoble, was successfully launched on the 2nd of September by the Arianespace Véga launcher from French Guiana. Developed by 40 students from the Grenoble Institute of Engineering and Management (Grenoble INP) and the Université Grenoble Alpes (UGA), AMICalSat is equipped for the acquisition of images of the northern (aurora borealis) and southern lights (aurora australis) from space. The aurora borealis occur at an altitude between 100 and 300 km, which is a very difficult zone to study as it's too high for stratospheric balloons and too low for satellites. The decomposition by spectrometry of the aurora borealis colors gives information on how the particles from the solar wind deposit in the atmosphere and about the disturbances they can cause.
The first data was received from the satellite during the morning of the 3rd of September showing that everything is working well.
More updates soon…

ALPX: the latest spin-off from EMBL in Grenoble

X-ray crystallography is widely used for drug design in the pharmaceutical and biotechnology industries. Researchers from the European Molecular Biology Laboratory (EMBL) in Grenoble have developed software and innovative technologies (CrystalDirect™) that offer remote-controlled and fully automated processes that form the technological core of ALPX. This spin-off, located at EMBL on the EPN campus, was created to respond to an increasing demand for these high-throughput services and to support the progress made in the pharmaceutical industry.
By allowing faster access to structural data, ALPX can particularly contribute to the acceleration of drug design. The newest EMBL spin-off already counts customers in both Europe and the United States.

Arrival of **the first InnovaXN students** at the **ILL** and the **ESRF**

The Institut Laue Langevin (ILL) and the European Synchrotron (ESRF) have welcomed their first InnovaXN students. The InnovaXN program is an exceptional opportunity for 40 industrial companies to work with 40 PhD students, performing advanced research and exploiting the unique characterization techniques of the two international large-scale research infrastructures in Grenoble: the ESRF and the ILL. Each student will work for 3 years on an innovative subject driven by industrial challenges, in collaboration with industrial and academic partners, while discovering and applying the advanced synchrotron and neutron techniques used by ESRF and ILL. In addition to working at the world's flagship synchrotron-based light source (ESRF) and the world's most intense continuous source of neutrons (ILL), students are also guaranteed direct exposure to an industry working environment and complementary technological training by a secondment period with the industrial partner.

Predicting the severity of **COVID-19**

COVID-19-infected patients have been treated at the Grenoble-Alpes University Hospital (CHU-GA) since the beginning of the pandemic. The collaboration between an infectious disease specialist attending to the patients and the biologist who analyses the prescribed blood samples has led to important insights into what was, just a few months ago, an unknown disease.

#Research — #Health — #Innovation

AUDREY LE GOUELLEC
Associate professor and hospital practitioner in medical biochemistry - CHU-GA and TIMC-IMAG laboratory (UGA, Grenoble INP, CNRS, VetAgro Sup).

"When the patients began arriving, we very quickly noticed that there was a high proportion of obesity amongst these patients," explains Audrey Le Gouellec, medical biologist at CHU-GA and researcher at the TIMC-IMAG laboratory of Université Grenoble Alpes (UGA).

> ***"We also realized that there was a link between obesity and both the level of inflammation and the severity of the infection,"***

adds Olivier Epaulard, head of the department of infectious diseases at CHU-GA and researcher at the Institute of Structural Biology (IBS).

With Geoffroy Méry, intern at the department of pulmonology at CHU-GA who is also studying infectious diseases under the supervision of Pr. Epaulard and carrying out a research internship with Dr. Le Gouellec, the group has worked together to formulate a medical hypothesis to explain their observations, which was recently published in the journal 'Frontiers in Immunology'.

"SARS-CoV-2, the novel virus which is responsible for the disease COVID-19, enters host cells by binding to the protein angiotensin-converting enzyme 2 (ACE2)," explains Dr. Le Gouellec. *"The binding prevents ACE2 from performing its normal function which is to convert angiotensin 2 (Ang2) into angiotensin 1-7 (Ang1-7). This leads to an accumulation of pro-inflammatory Ang2 and a decrease of anti-inflammatory Ang1-7, creating a pro-inflammatory environment in COVID-19 patients."*

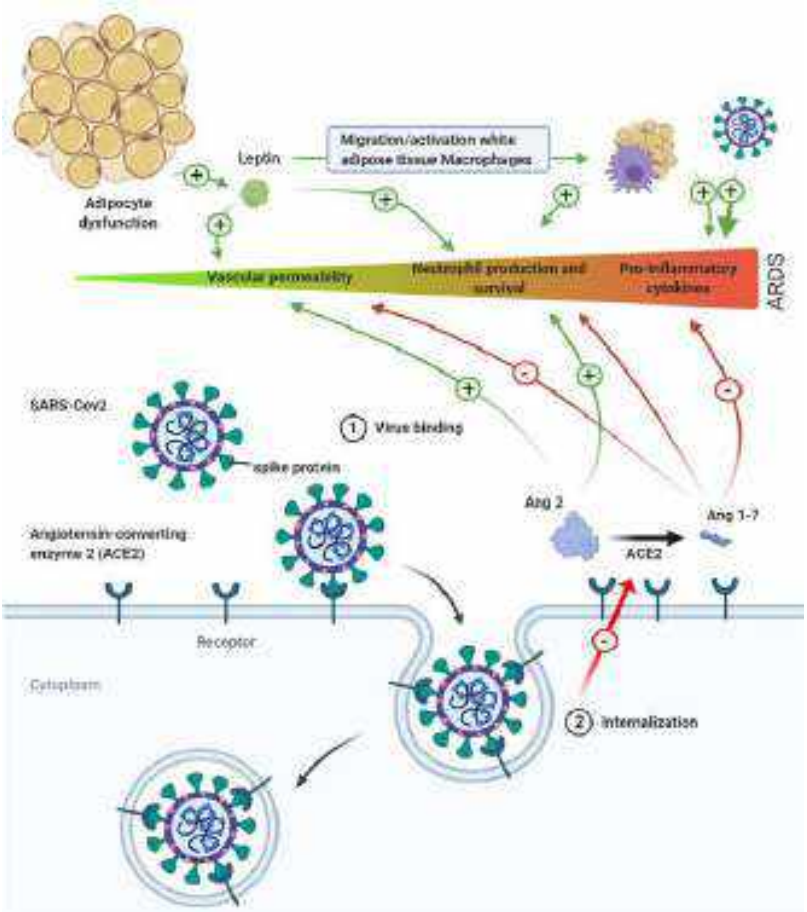
Patients with 'abdominal obesity' already have an inflammatory profile with an associated risk of low-grade persistent inflammation (meta-inflammation) and metabolic disorders such as type 2 diabetes. These patient are the most at risk of developing a severe inflammatory episode. *"Our hypothesis is that these patients either have a naturally low level of Ang1-7 which explains the background meta-inflammation and means that these patients just don't have the resources to fight the inflammation caused by COVID-19, or their Ang1-7 levels increase proportionally with the meta-inflammation to try to control it and when COVID-19 causes the Ang1-7 levels to drop drastically, the resulting inflammation is severe,"* explains Méry. Ang1-7 supplementation, already used in clinical trials with safe outcomes, could therefore adjust the levels of Ang1-7 and balance the inflammation.

Though the initial research carried out by the group was fundamental, they have quickly progressed to translational research that links the testbench right to the patient. The blood samples of COVID-19 patients at CHU-GA have formed a biobank that is constantly being added to. Having observed that patients with metabolic disorders risk developing

The research group is composed of (from left to right) Bertrand Toussaint, university professor and hospital practitioner in medical biology (UGA/CHU-GA), Olivier Epaulard, university professor and hospital practitioner in infectious diseases (UGA/CHU-GA), Audrey Le Gouellec, associate professor and hospital practitioner in medical biochemistry (UGA/CHU-GA) and (missing from the photo) Geoffroy Méry, intern at the department of pulmonology (CHU-GA).

severe inflammation, an innovative analysis of the profile of metabolites present in the blood samples has been put in place. The objective is to detect which metabolites are correlated with a severe form of COVID-19. *"The idea is that from a patient's blood sample, we could warn of a potentially severe COVID-19 infection,"* explains Dr. Le Gouellec. *"We have already carried out a pilot study on 20 patients and the results are promising. We're now studying the next 200 patients and we're also trying to set up a national project in collaboration with MetaboHub (the national infrastructure in metabolomics and fluxomics) to study the metabolite profile of patients infected with COVID-19 across France."*

State of the art equipment is required to measure the metabolite profile and this equipment is generally installed in research laboratories such as CNRS or Inserm. When lockdown happened, the laboratories were closed and the equipment was put on stand-by meaning that very little data is available from this period. *"The equipment that we have in the Grenoble Expertise in Metabolomics platform (GEMELI-GExiM) here at the Institute of Biology and Pathology at CHU-GA was financed by the IDEX « Initiative d'excellence » and the Auvergne-Rhône-Alpes region. It is unusual to have such equipment installed in a hospital but it meant that this work could continue during the lockdown enabling a continuity of research that otherwise wouldn't have been possible and it means that people are really keen to see what results we've obtained!"* says Dr. Le Gouellec.



Impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on pathways promoting acute respiratory distress syndrome (ARDS).

Expertise in Metabolomics platform (GEMELI-GExiM) at the Institute of Biology and Pathology at CHU-GA.

GIANT EFFECT

The work carried out was funded by the UGA Foundation and achieved by a collaboration between different individuals bringing together a number of different institutes: the Grenoble-Alpes University Hospital (CHU-GA), the TIMC-IMAG laboratory (Université Grenoble Alpes, UGA; Grenoble Institute of Engineering and Management, Grenoble INP; French National Centre for Scientific Research, CNRS; Veterinary Campus of Lyon, VetAgro Sup) and the Institute of Structural Biology (IBS - French Alternative Energies and Atomic Energy Commission, CEA / CNRS / UGA).

TRUST IN TIMES OF CRISIS

Modern society cannot function without the ability to trust. Yet trusting is becoming more difficult during the current period of increased risk and vulnerability caused by the pandemic. Charles-Clemens Rüling, professor at Grenoble Ecole de Management (GEM) and group leader of the Chair for Public Trust in Health, explains how such a crisis has the potential to polarize levels of trust across a society already witnessing a tendency towards an erosion of trust.

#Research — #Healthcare — #Society

CHARLES-CLEMENS RÜLING
Director of Research at Grenoble Ecole de Management and Coordinator of the Chair Public Trust in Health

"Trust, from a theoretical perspective, is the ability or willingness to accept your vulnerability when interacting with an individual or a collective that you do not intimately know," explains Rüling. Trust is normally not an issue for traditional societies, where members tend to know each other very well. However, it is critical for the functioning of modern societies that have a high division of labor and where interacting with multiple individuals and organizations that we do not know is an everyday occurrence. Indeed, it is trust that enables interaction, collaboration and cooperation within our society.

The decision to trust is based on a largely unconscious evaluation of another actor's ability, benevolence and integrity. Entering a medical practice, for example, we look for cues that indicate medical competence and professionalism (ability), that a medical professional is working, at least to some extent, with our best interests in mind (benevolence), and that the person adheres to principles that we find acceptable (integrity). *"Trust is a multi-dimensional evaluation,"* explains Rüling, *"you can recognize that somebody is highly skilled and proficient but if you perceive cues that you interpret as a misalignment of values or that they are acting mainly out of self-interest, that is detrimental to trust."*

Yet how we interpret these cues is influenced by a non-evaluative mechanism that reflects our personal frames of reference, values and culture. Considering the current pandemic, though the general opinion may be that the crisis was relatively well-managed in France, individuals will be attuned to cues that confirm their initial perspective. *"An individual politically aligned with the current government, will note that hospital capacity was not overwhelmed, while, an individual who is generally critical of the current government, will retain that a lack of preparation caused an initial severe shortage of personal protective equipment,"* explains Rüling. As a consequence, any given situation can yield very different individual-level trust outcomes.

> ***The current pandemic has caused a level of disruption not seen since the Second World War to aspects of everyday life in France that were taken for granted - leaving our homes, going to work in an office, children going to school, restaurants, cinemas, traveling.***

This disruption and the risk associated with the pandemic has dramatically increased the sense of personal vulnerability.

GIANT EFFECT

Trust within the domain of health innovation, where connected devices and implants fundamentally alter the relationship between patients, healthcare professionals and caregivers, is currently being studied by GEM in collaboration with SentinHealth (a Grenoble-based MedTech startup), the Université Grenoble Alpes (UGA), the Grenoble-Alpes University Hospital (CHU-GA) and several international partners, within the framework of the EIT Health project 'RealWorld4Clinic'.

As vulnerability increases, the ability to trust is reduced and an erosion of trust occurs during a time when the need for trust is greater than ever for society to follow advice from health professionals, scientists and authorities. Indeed, the paradoxical situation was observed during the lockdown of public displays of trust in the healthcare system, while at the same time, individuals delayed or stopped seeking treatment.

For individuals generally aligned with the position expressed by current political authorities, the pandemic may have increased their level of trust. Inversely, the level of trust of those who were already critical of public authorities, and by extension their handling of the crisis, may have decreased. *"The same event can cause a polarization within society, with very different outcomes on the level of trust of different individuals,"* explains Rüling. The level of trust will also have an impact on behavior, with an increased sense of vulnerability causing some individuals to seek a greater sense of control. *"Instead of trusting their doctor and following their advice, people might search for second opinions on-line,"* explains Rüling.

"Erosion of trust in the aftermath of the acute stage of the COVID-19 crisis and the increased search for alternative opinions could have an impact later on when we have a vaccine."

The seriousness of the potentially polarizing nature of the current pandemic with its impact on levels of trust should not be underestimated considering the long-term tendency towards an erosion of trust in society, evident in the decrease of trust in mainstream political parties and a growing distrust of experts. *"The less we take the risk of trusting, the more we actually lose our ability to trust,"* cautions Rüling.

Grenoble Ecole de Management

Preparing for THE NEXT PANDEMIC(S)

Before the arrival of SARS-CoV-2, it was generally considered that the greatest pandemic risk was posed by the influenza (flu) virus. Influenza vaccines require annual updating as the virus constantly evolves to escape the immune system. Research at the European Molecular Biology Laboratory (EMBL) in Grenoble is providing critical information for the development of new antiviral drugs that target a key component of the virus, the polymerase, that is not only much less variable but whose core structure is the same across most RNA viruses.

#European Large Scale Facilities — #Influenza — #Pandemic

STEPHEN CUSACK
Head of EMBL Grenoble and group leader in the structural biology of protein-RNA complexes and viral proteins

The most outstanding and troublesome characteristic of influenza viruses is their ability to change, both rapidly and frequently, meaning that hundreds of different strains of the virus exist. Seasonal flu epidemics occur each winter, infecting millions and causing hundreds of thousands of deaths worldwide each year. They are caused by already circulating viruses that have acquired mutations enabling them to escape the immunity that many people have developed.

A pandemic occurs when a new influenza virus emerges from non-human animal sources such as birds or pigs that can infect and transmit between humans.

Being different from any previous human strain, most people have no immunity and the virus can spread easily.

Each year, a new version of the influenza vaccine has to be formulated that includes the three or four influenza strains that the World Health Organization (WHO) has identified as being the most likely to cause significant human disease in the coming season. The vaccine stimulates the generation of antibodies that mainly target the proteins on the surface of the virus, but mutations in those proteins render the vaccine quickly ineffective. What if drugs could be developed that target a more stable protein of the virus?

The influenza virus is an RNA virus whose viral RNA genome is copied by a key enzyme called an RNA-dependent RNA polymerase. If the polymerase can be stopped then the virus can no longer replicate and spread. Drugs that target the polymerase have two notable advantages. The first is that the polymerase is a well-optimized enzyme, meaning that it is relatively constant and difficult to change.

"It is possible that the polymerase will evolve resistance if you target it with a drug, but the idea is that it is less easy for the virus to change the polymerase while still ensuring that it carries out all its functions optimally," explains Stephen Cusack, group leader and head of the EMBL in Grenoble, who has been studying the influenza polymerase for over a decade.

The second advantage is that the polymerase is relatively constant for all the different influenza strains that infect humans, birds, pigs and other animals. The developed drug could therefore, in principle, target any influenza strain.

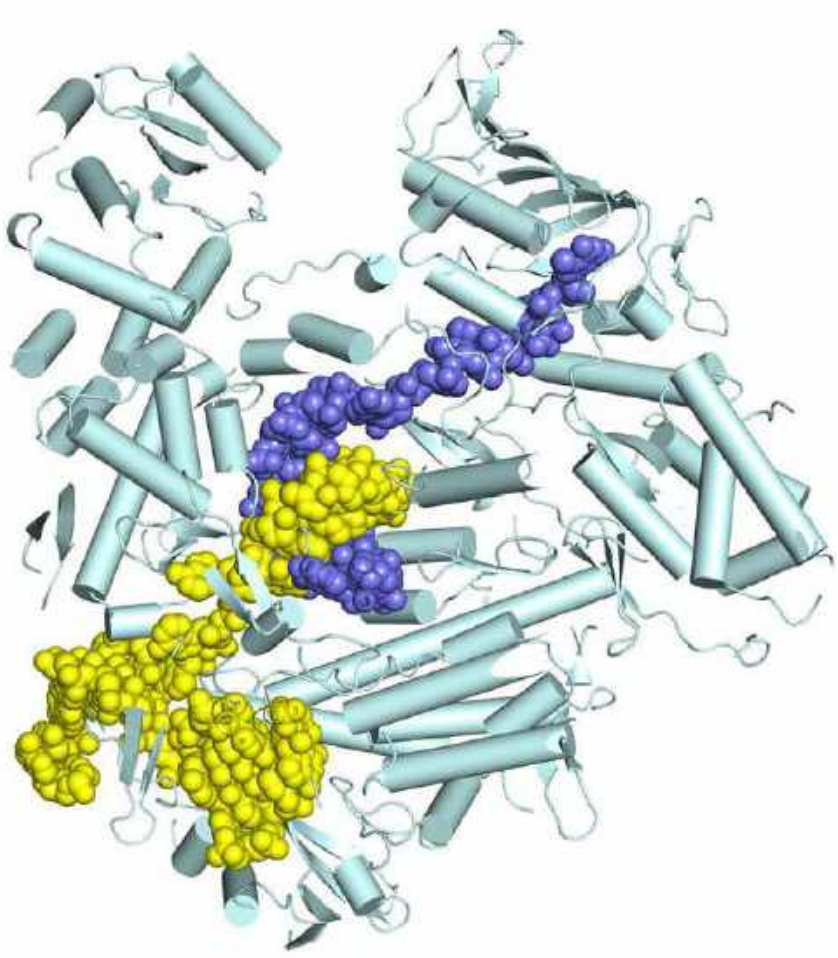
For the development of such antiviral drugs, the detailed structure of the complete influenza polymerase is required, which Cusack and his group achieved in 2014 using X-ray crystallography. This technique requires that the sample is crystallized, constraining the polymerase to one state.

GIANT EFFECT

X-ray crystallography beamlines at the European Synchrotron (ESRF) and the advanced cryo-electron microscope shared between the EMBL, ESRF, the Institut Laue-Langevin (ILL) and the Institute of Structural Biology (IBS) were used for the structural analysis.

But the structure of one state is not enough to understand its mechanism. *"The polymerase is a molecular machine,"* explains Cusack, *"you need many snapshots of the machine in action to be able to figure out how it works."* These snapshots can now be obtained thanks to the latest advances in cryo-electron microscopy (cryo-EM), where the sample is rapidly frozen before structure determination, with no need for crystallization. *"We started a transcription reaction in the test tube and then used different viral RNAs and inhibitors to stall the reaction at particular points in the process,"* explains Joanna Wandzik, the PhD student working on the project under the supervision of Cusack. At each stalled point, cryo-EM was used to determine the atomic structure of the polymerase in its current state.

The resulting series of snapshots of eight successive stages enabled the complete transcription process of the influenza polymerase to be visualized from beginning to end, like a movie. *"We could follow all the moving parts of the polymerase as it copies the viral RNA. This has never been achieved before in such detail for a large viral polymerase,"* says Tomas Kouba, a postdoctoral researcher working in the group.



Cryo-EM structure of the influenza polymerase (light cyan) in the process of synthesizing viral messenger RNA (slate blue) by copying the genomic viral RNA template (yellow),

The work achieved by Cusack and his group, which was published in the journal 'Cell' in May, provides critical information for the development of antiviral drugs that target the polymerase, not only of the influenza virus, but of many other RNA viruses. The common cold virus, Ebola, measles, dengue, Zika and SARS-CoV-2 all have an RNA-dependent RNA polymerase with a very similar core structure. Indeed, the world is waking up to the fact that due to altered human-animal interactions caused, for example, by climate change and habitat destruction, more and more RNA viruses could emerge from the essentially infinite animal reservoir to potentially cause pandemics.

"The virus responsible for the flu pandemic in 2009 was relatively mild even though many people died. But there could be one that's much worse and it could be tomorrow," says Cusack.

"I hope that this research area will now be taken more seriously, with increased resources for the basic research underpinning anti-viral drug and vaccine development."

PepS: the PEPtide Saver

Widespread adoption of mass spectrometry (MS) based proteomics to analyze the proteins in a biological sample has been limited by the sample preparation required that is both laborious and time-consuming. Researchers at the French Alternative Energies and Atomic Energy Commission (CEA) have developed PepS, an innovative device that fully automates the sample preparation.

#Technological Research — #Sample Preparation — #Innovation

MARIE-LINE COSNIER
Research Engineer and Project leader at CEA-Leti

MS analysis enables the proteins in a blood sample to be identified, characterized and quantified, but prior preparation of the sample is required to first break the proteins down into peptides. The current situation, in which sample preparation is carried out manually by professionals with a processing time of 24-48 hours, is about to change with the launch of the innovative device PepS.

Developed at CEA, the compact, transportable device operates a single-use microfluidic cartridge to automate the preparation of blood samples collected from patients.

Though other research groups have managed to automate and integrate some of the sample preparation steps, with the rest being carried out manually, PepS is the first device to integrate the entire sample preparation process into one automated instrument. Indeed, with more than 14 preparation steps included in the device, the sample preparation can be optimized for each particular application by computer-programming and modification of the cartridge that enables the definition of the number and sequence of steps to be carried out.

Advantages of the device include a reduction in the processing time from 24-48 hours to 2 hours and by removing human intervention and the associated possibility of error, a guarantee that the sample preparation is robust and reproducible. *"Each step of the preparation has been integrated into the device, so you push a button and everything is done automatically,"* explains Marie-Line Cosnier, research engineer at CEA-Leti.

The advantages and flexibility offered by the PepS device will enable MS-based proteomic analysis to be employed far more widely. Clinical trials and the search for new biomarkers are two areas in particular that will benefit from the new device.

Novel treatments for cancer and autoimmune or liver diseases, involve the injection of an antibody or a protein into the patient.

Compact and transportable PepS device

GIANT EFFECT

This work was carried out in collaboration with the EDyP (Exploring the Dynamics of Proteomes) research group - jointly supported by CEA, Université Grenoble Alpes (UGA) and the French National Institute of Health and Medical Research (Inserm) – and Clinatec – founded by the CEA, UGA, Inserm and the Grenoble-Alpes University Hospital (CHU-GA).

The collaborative team that developed the PepS device

The patient's response to the treatment is tracked by the regular analysis of blood samples to evaluate the time taken for the injected substance to become active, the quantity of the substance present in the patient or the quantity of the proteins that indicate a response to the treatment. In each of these cases, the particular protein to be analyzed is known and the objective is to precisely measure the quantity present in the blood of the patient. Clinical trials assess these novel treatments by application of the therapy to a large number of patients, with numerous blood samples tested per patient. The PepS device enables the sample preparation protocol to be adapted to optimize the isolation and detection of the particular protein while ensuring that the large number of samples are prepared quickly. Furthermore, as the preparation is the same for each sample, the quantities measured in different samples from the same patient or from multiple patients are rendered comparable.

The search for new biomarkers involves the investigation of proteins that could be indicative of pathologies, or of the evolution of pathologies. It therefore requires the study of the widest profile possible of proteins present in the sample, concentrating in particular on proteins that are present in very low quantities. As the validation of a new biomarker involves the study of a large number of samples across a number of different laboratories, considerable variation is introduced if each laboratory employs a slightly different sample preparation protocol. Differences in the results obtained are therefore not necessarily due to the analysis but to how the sample was prepared. The PepS device ensures that the sample is prepared in exactly the same way by each laboratory. The measurement of the small quantities of biomarkers present is therefore robust and reproducible.

Single-use microfluidic PepS cartridge

A GIANT response to a global pandemic

The GIANT innovation campus was founded in 2009 on the principle of collaboration and in the years that have followed, the eight members have worked collectively to achieve common goals. The novel virus SARS-CoV-2 was first identified in Wuhan, China in December 2019. It rapidly spread around the world and was declared a global pandemic by the World Health Organization on March 11, 2020. The pandemic has caused hundreds of thousands of deaths and global social and economic disruption. It has also galvanized the campus to work together on an unprecedented scale.

Within the GIANT campus, fundamental research is underway to understand the virus and the disease it causes, therefore guiding the development of vaccines to stop the virus and drugs to treat the disease.

Urgent demands and novel requirements have seen the development of new and innovative products that have been designed, validated, produced and put to use in record time. Different ways of living and working have been tested and adopted and as we look to the future, it is hard to imagine that life can go back to how it was before.

From barely registering in the world's consciousness, COVID-19, the disease caused by SARS-CoV-2, has become the defining crisis of a generation. Yet the response it has induced demonstrates beyond any doubt both the capabilities that exist within the GIANT campus and the desire and capacity to work together.

Understanding the virus and the disease it causes

A virus is *"simply a piece of bad news wrapped up in protein"* wrote the biologists Jean and Peter Medawar in 1977. The expertise, state-of-the-art facilities and common platforms for structural biology and bioimaging at the European Molecular Biology Laboratory (EMBL), the European Synchrotron (ESRF) and the Institut Laue-Langevin (ILL) will be key to unwrapping and understanding that bad news.

Viruses are not capable of independent replication. In order to replicate and spread, they must hijack living cells. When SARS-CoV-2 finds a suitable cell, the virus binds to and penetrates the host cell. Neutron reflectometry techniques and expertise at the ILL can provide information on the mechanism of interaction of the virus with cell membranes or on the molecular structure and composition of the outer surface of the virus, enabling the process to be better understood, as research carried out in 2017 at the ILL achieved for the hepatitis C virus.

Once bound to the host cell, the virus injects a strand of RNA that recruits machinery inside the infected cell to read the RNA letters and translate them into proteins. RNA structures are notoriously difficult to study, but Marco Marcia, group leader at the EMBL, could be considered to be at the forefront of the field having recently published methods he has developed on how to study long RNA structures in the highly regarded scientific journal 'Nature Protocols'. Marcia's group are now studying parts of the SARS-CoV-2 RNA that could represent important targets for drug development.

The RNA-dependent RNA polymerase is the protein that transcribes and replicates the viral RNA. *"If you can stop this enzyme from working, you can stop the virus from propagating,"* explains Stephen Cusack, group leader and head of the EMBL in Grenoble, who has been studying the influenza (flu) polymerase for over a decade (details of this work can be found in the article on pages 10-11) and is now working on the SARS-CoV-2 polymerase. Viral RNA polymerases all work in fundamentally the same way, so that known drugs that inhibit the flu or Ebola polymerases, broad-spectrum antivirals such as favipiravir or remdesivir, are therefore potentially useful against SARS-CoV-2.

The first viral protein created by the infected cell is a polyprotein – a single chain of 16 non-functional proteins that are crucial to the function and life-cycle of the virus. Two of those proteins – NSP3 and NSP5 – cut the chain at specific locations, in a process called cleavage, which activates the individual proteins to carry out their tasks. NSP3 and NSP5 are also therefore both interesting targets for antiviral research. If appropriate antiviral drugs can be found to inhibit the cleavage then the polyprotein remains in its original state and the virus replication machinery is blocked. As NSP5 does most of the cutting and is a protein that is conserved across different viruses, it is the focus of many research groups. However, Sagar Bhogaraju, group leader at the EMBL, is focusing on NSP3. Bhogaraju's group specializes in the study of a small protein called ubiquitin, which healthy cells use to tag old proteins for destruction. It just so happens that the second role of NSP3 is to remove those tags, thereby disturbing the balance of proteins in the infected cell. *"It was a natural transition for each of the four groups working on SARS-CoV-2 at the EMBL,"* explains Bhogaraju. *"The aspects of SARS-CoV-2 being studied are very closely aligned to the usual research subjects of each of the groups."*

This NSP3 protein has also intrigued Eaazhisai Kandiah, a beamline scientist at the cryo-electron microscopy (cryo-EM) facility at the ESRF. Kandiah, in collaboration with the Institute of Structural Biology (IBS), has been awarded funding from the French National Research Agency (ANR) to study the structure of NSP3 to explore whether it could be used as a potential drug target, thereby stopping the production of several functional proteins contained in the polyprotein.

The EPN (European Photon and Neutron) Science campus, which includes the ESRF, EMBL, ILL and IBS, offers a unique portfolio of techniques for structural biology. *"X-ray crystallography and cryo-EM will be used, and when possible combined, to determine the detailed atomic-resolution structure of the virus or parts of the virus,"* explains Jean Susini, director of research for life sciences at the ESRF. This synergistic approach can be further extended by using small angle neutron scattering (SANS) at the ILL which will enable the bigger picture to be studied at lower resolution. Indeed, neutrons offer the enormous advantage that individual subunits can be marked by deuteration, enabling specific regions in the complex to be distinguished. *"We are able to see, at a very small scale, the interactions between two materials that have very similar chemical compositions,"* explains Giovanna Fragneto, Large Scales Structures group leader and head of the Soft Matter Science and Support group at the ILL.

If the results of Kandiah's work are promising, her project will also benefit from the fragment screening platform that has been developed by the Marquez group at the EMBL. A chemical database of thousands of compounds is used to evaluate what type of compound binds to a particular protein. Such information is crucial for finding compounds that bind to and inhibit the protein. *"This would be a big lead for any pharmaceutical company or academic institution that are interested in drug development,"* explains Kandiah.

For the developed antiviral drug to be efficient, the inhibition needs to be robust, that is, the drug should be strongly bound to the protease (the protein responsible for the cleavage). This increases the likelihood of the treatment being effective in the long-term despite mutations of the protein. Neutron crystallography techniques at the ILL can provide key details about the hydrogen atoms that play an essential role in the binding of such drugs to their target protein through hydrogen bonding. *"How do the inhibitors position themselves, how exactly are the bonds that they've made with the protein,"* explains Fragneto. *"This is how neutron crystallography can help improve the development of antiviral drugs, it's what we've done in the past with the HIV-1 protease."*

Researchers at the ESRF are also studying the impact that the virus has on the body. For some people, the virus induces a 'cytokine storm' which is a destructive over-reaction of the immune system that causes immune cells to attack the body. 3D X-ray imaging will be used to study the effect of the virus on the lungs of patients that suffered the storm. *"It's like a super resolution medical CT scan of the lungs,"* explains Jean Susini. *"The multi-resolution approach means we can go from centimeters to view the entire pulmonary lobe, down to sub-micrometers to zoom in and visualize the impact of the storm on the microstructure of the infected lungs."*

New and innovative products to meet urgent demands and novel requirements

The arrival of the pandemic was accompanied, in France and many other countries, by a severe shortage of personal protective equipment. Visors are part of the equipment that healthcare workers rely on to protect themselves while caring for COVID-19 patients. A reusable piece of equipment that protects the mask, they also enable masks be worn longer than is usually recommended in case of a shortage of masks.

While masks and visors were in shortage, a group of engineers, technicians, professors and researchers from the Grenoble Institute of Engineering and Management (Grenoble INP) and the Université Grenoble Alpes (UGA) came together with one objective, *"We wanted to help,"* explains Alain Di Donato, technical manager of the GINOVA platform at the Grenoble-Alpes center of the S.mart network.

Already accustomed to working together, using collaborative tools and sharing data, the group were able to react quickly to find a technical solution for an urgent need. A visor was designed, and once the Grenoble-Alpes University Hospital (CHU-GA) had validated that the product was conform, 3D printing was used to make hundreds of the visors which were then distributed. *"It wasn't a massive revolution,"* says Di Donato, *"the revolution was that there were 28 of us!"*

While protective equipment is critical for healthcare workers, public health experts are strongly encouraging the widespread use of face masks in public to slow the spread of the virus. Reuse and recycle are two well-known concepts that have been innovatively applied to meet the unprecedented demand for face masks.

'OCOV®' is the name of the reusable mask that has been developed and produced in record time by a consortium that includes the French Alternative Energies and Atomic Energy Commission (CEA), the CHU-GA and numerous companies and public institutions. The mask comes with a filter that can be reused and replaced meaning that each mask can be used up to 100 times. Careful design means that a flexible part of the mask that covers the nose, mouth and chin molds to the shape of the face, reducing the degree of leakage around the edges compared to reusable cotton masks.

Concerning surgical and FFP2 face masks, the recommendation is that they should be discarded after a few hours of use. The possibility of recycling the masks is being studied by a consortium that includes the French National Centre for Scientific Research (CNRS), UGA and a number of other institutions, universities and university hospitals. The objective is to determine a disinfection protocol that eliminates the viral load after the mask has been used while guaranteeing that the recycled mask maintains the same performance level as a new mask. Though the French High Council of Public Health (HCSP) initially advised against taking steps to recycle masks, they now recommend that research should be continued though recycled masks should not be used in healthcare settings.

The pandemic has called for the development of solutions for novel requirements and the GIANT campus has demonstrated its ability to innovate, even when under lockdown. One such example is the quarantine bubble - a transparent PVC bubble, supported by an inox frame, it covers the patient's head and is attached directly to the patient. Slightly depressurized and with the air exhaled by the patient extracted using a pump and filtered before being evacuated, the patient is isolated and healthcare workers and nearby patients are provided with FFP2, or even FFP3, mask level of protection. Though initially devised for the transfer of COVID-19 patients by helicopter (where the usual material is too bulky for use), it was quickly realized that the device could be used right from when the patient was collected, through transportation and arrival at the hospital. The device, collaboratively developed by doctors, researchers and engineers from the CNRS, Grenoble INP, UGA and CHU-GA, has been approved and adopted by the Grenoble ambulance service.

Another example of innovation is the analysis device to monitor for the presence of SARS-CoV-2 in the air, which is under development at CEA-Leti in collaboration with the Pasteur Institute and with ANR funding. An electrostatic air sampler that collects micron and submicron-sized particles, with a microfluidic module containing lyophilized biological reagents to perform a rapid isothermal amplification of viral nucleic acids, should together enable a reliable detection of the virus in less than 30 minutes. Compact and light, the device is designed for semi-continuous monitoring of the air in at-risk or confined spaces.

Finally, though the spread of COVID-19 can be slowed by wearing face masks and practicing social distancing, the only way to prevent people from catching COVID-19 is with a vaccine. A candidate COVID-19 vaccine is currently being developed by collaborative research carried out by the CEA-Leti and the Institute for Advanced Biosciences (IAB), which is a research center jointly supported by the CNRS, UGA and the French National Institute of Health and Medical Research (Inserm). The vaccine candidate uses an innovative delivery system involving lipid nanoparticles. Small droplets of lipids are produced which can load fragments of the virus. Once administered, they are picked up by immune cells provoking an immune response, that will then protect the individual from being infected by the virus.

Different ways of living and working – the new future?

The crisis has caused different ways of living and working to be tested. Some have been adopted, while others have made us appreciate aspects of life previously taken for granted. Indeed, it is not the virus that has changed over the past few months, but how we coexist with it.

"Humans have survived because they are collaborative," says Dominique Steiler, professor at Grenoble Ecole de Management (GEM). The current crisis has certainly induced more collaboration and closer collaboration. The different institutes of the GIANT campus have worked together to manage shared services and buildings, ensuring that similar rules and protocols are put in place across the campus. Valerie Barrett, Head of Administration at the EMBL Grenoble, observes that, *"Science is really important, but if we can't eat, we can't advance science."* With the canteen being managed, scientists should be able to make the most of a new collaborative scheme that has been put in place by the EMBL and the ESRF that enables researchers to submit one proposal for access to both the automatic crystallization platform at the EMBL and the high-brilliance X-ray beams for crystal structure determination at the ESRF.

Thibault Daudigeos, professor at GEM and group leader of the Chair for Inclusive Sustainability: Territorial Ecosystems in Transition, considers that the crisis has induced a momentum for change, increasing awareness and ambition. Though as budgets are likely to be reduced, the transition will now, more than ever, rely on individuals changing their behavior. Social research being carried out by Corinne Faure, professor at GEM, aims to better understand behavioral changes at the local level, by questioning people living in the Grenoble-Alpes Metropole on a variety of topics that are of relevance to local policy and to the inhabitants. *"The idea is to collect local data on the reactions of people to initiatives or policy that are planned or happening in the metropole,"* explains Faure. The results of a survey carried out in May and June give an insight into people's reactions to some of the new ways of living and working. For example, of those that tried an online consultation with a doctor, the majority prefer the in-person visit. While people are open to considering working staggered hours to avoid everybody arriving and leaving at the same time, few appear interested in working on weekends.

The single biggest change to many people's working lives has been the shift to remote working which offers advantages that are both individual (facilitating tasks that require a high level of concentration) and collective (reducing the number of vehicles on the road). Though, as Shakespeare warned against too much of a good thing, so Barrett advises vigilance against the number of working hours that tends to increase as the separation between work and home becomes blurred. Thierry Ménissier, professor at the Grenoble Institute of Philosophy (IPhiG), UGA and scientific leader of the Chair for Ethics and Artificial Intelligence within the Multidisciplinary Institute in Artificial Intelligence (MIAI), calls for the socialization aspect of work to be considered. Despite the demonstrated efficiency of remote working, it remains fundamentally incompatible with socialization that is based on physical presence and emotional exchange. *"We have realized that a task can be simultaneously carried out well and frustrating to carry out when working remotely,"* explains Ménissier. Daudigeos further cautions that too much remote working could encourage urban sprawl, resulting in those fewer vehicles covering more kilometers.

It is not just work that can be carried out remotely, the crisis has forced many of the conferences and training sessions organized every year in Grenoble to be held virtually. Barrett has found them to be surprisingly successful, *"The diversity of the participants has increased because people who due to financial or time constraints wouldn't have been able to travel could participate."* The lower carbon footprint is another undeniable advantage. Though no one denies the importance of meeting in person, Barrett believes that the need to travel or to hold a conference in-person will be reassessed from now on. The need to travel, with the associated carbon footprint, will be similarly reassessed for scientists carrying out experiments at the ESRF.

Remote access has been operational for nearly 20 years at the ESRF for structural biology, meaning that users can mail-in samples, follow experiments and then download the data when it is available without needing to visit the facility. Indeed, the crisis has raised the question of the environmental ethics of remote working; though the pollution associated with travelling is reduced, Ménissier questions whether a person's internet connection should be limited in order to control the carbon footprint generated by continuous connection and the manufacture of the associated devices (computer, smartphone, tablet).

Despite these different changes, Daudigeos emphasizes that, *"A transition cannot be achieved by behavioral changes exclusively, infrastructural change is necessary to help people to change their behavior."* Indeed, the need for territorial coordination was highlighted by the crisis and one such form being studied by the chair are territorial exchange platforms that employ new organizational models to offer services that are not currently available. The 'outdoor' retirement home is one such example currently being experimented. The idea is to bring quality care to dependent elderly in their homes, wherever they live in the territory, while opening the homes up for non-residents to participate in activities thereby encouraging the circulation of people and evolving the role of the home beyond end-of-life care.

To achieve fundamental change, Steiler believes that work needs to have been done before a crisis arrives, *"If you read a fantastic book on marathons, and then decide to go run the Paris marathon without any training, nothing will happen."* The current crisis should, though, be the wake-up call to start reflecting on how we are going to do things afterwards such that when this crisis is over, the necessary transformations are started before the next crisis arrives.

Economic Peace is one transformation that Steiler has been working towards since the creation of the Chair that he leads on Economic Peace, Mindfulness and Well-being at Work in 2012. To explain the concept of economic peace, he recounts this topical anecdote, *"During the lockdown, a company suffering a serious drop in activity, received a large order to produce bins with an airtight lid for a hospital. When it was suggested that a lack of competition would enable the company to increase their prices, the owner replied that it was completely out of the question to take advantage of the crisis. Rather, he planned to apply the principles of economic peace to resolve how his company could best contribute while still surviving."*

Indeed, the profits of a company are often presented as a financial result, but the result may have been obtained while causing harm: damage to people's health and well-being, damage to nature and the environment, population displacement. *"So long as our model is that the generation of financial wealth is the sole objective of a company, that is what we'll do. The role of this chair is to transform the conception of the company such that it considers itself as an active participant of the community, that is capable of improving society by contributing to the common good,"* explains Steiler.

As this crisis period progresses and eventually passes, let us hope that the coordination, collaboration and solidarity demonstrated across the GIANT campus form the basis for a new and better future together. *"We will not go back to how it was before, we will keep the positive elements of what we have learned and developed,"* affirms Barrett.

Could you **DEUTERATE** that for me?

Just in case the most powerful neutron source available in the world wasn't enough, Institut Laue Langevin (ILL) scientist Krishna Chaithanya Batchu is producing deuterated molecules that aren't available anywhere else and that will soon be proposed to scientists coming to work at the ILL.

#European Large Scale Facilities — #Neutrons — #Deuteration

KRISHNA CHAITHANYA BATCHU
Scientist, Soft Matter Science
and Support group, ILL

Imagine you want to understand how a cell works – like many of the 700 or so researchers that come every year from all over the world to study soft and biological matter at the ILL. Well, you might have to look at the cell membrane, the bit that surrounds and holds the cell together.

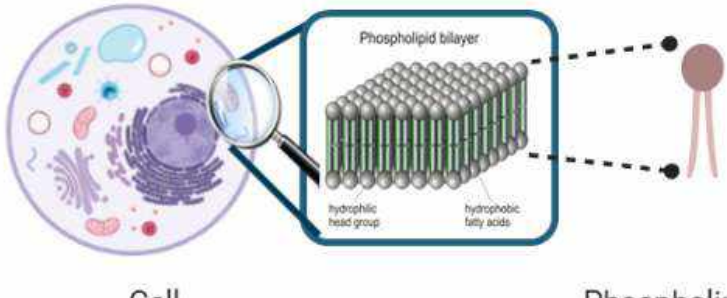
A major component of that membrane is something called a phospholipid.

But you don't want to look only at the cell by itself. What you're often interested in, is looking at how a specific protein interacts with the cell membrane. If the protein and the membrane are both the same color, it's going to be difficult to distinguish them from each other. Imagine though if the neutrons used in the experiments at the ILL could show the protein in blue and the membrane in yellow... that trick can be achieved through deuteration. Biological materials contain many hydrogens.

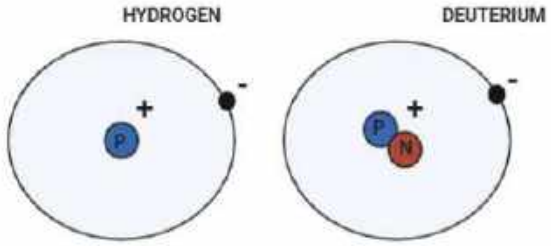
Deuteration involves replacing the hydrogen atoms of a molecule which have one proton in their nucleus, with deuterium atoms which have one proton and one neutron in their nucleus. The deuterated protein (blue) can now be differentiated from the membrane (yellow).

The deuteration laboratory at the ILL, run within the Life Sciences group, produces deuterated proteins. But imagine that for our experiment we want to swap the colors, that is, instead of a blue protein and a yellow membrane, we want a yellow protein and a blue membrane. We're going to need deuterated phospholipids. Where can we get them? One option is to buy them, but out of the thousands of phospholipids that exist naturally, there are only a few that are available to buy deuterated. And the ones for sale are all synthetic, that is, they've been made using chemical deuteration, which requires extremely toxic reagents. In fact, the synthesis of many phospholipids found in cell membranes is impossible using the chemical deuteration techniques that currently exist. Still hesitating? Consider that a few milligrams of the most interesting ones is going to cost you about 7-10k€.

What's the alternative? Well, if you want to understand how a cell works in natural circumstances, using a naturally produced lipid environment for your experiment would be a good start. Natural deuteration involves growing cells under deuterated conditions. That means, for example, that instead of giving natural nutrients that contain hydrogen, the cells are given deuterated nutrients. Everything produced by the cell is thus deuterated.



Lipids and cellular membranes: the zoom shows that phospholipids are a major component of the cell membrane



Deuteration involves replacing hydrogen (1 proton in nucleus), with deuterium (1 proton and 1 neutron in nucleus)

The lipids can then be removed from the deuterated cell, separated out into their different types and a list is made of each type present. This is the work being carried out by Krishna Batchu in the Soft Matter Science and Support group at the ILL under the supervision of Giovanna Fragneto.

Natural deuteration also has the advantage of having a much lower environmental impact than chemical deuteration.

The green chemistry methods employed at the ILL make use of the best techniques to maximize the lipid extraction yield while minimizing the quantity of toxic solvents required. And who said that going green costs more? Batchu estimates that optimization has enabled them to reduce the production cost to 300-400€ for about 100 mg of a range of deuterated phospholipids.

The phospholipid deuteration, extraction and purification platform is up and running at the ILL and the phospholipids are already available to ILL scientists. Indeed, scientific articles on experiments that used these naturally deuterated phospholipids have already been submitted to various journals. The next step is to make the phospholipids available to external scientists coming to the ILL in the next few months. Work is also underway to extract more from what remains after removing the phospholipids, as everything produced by the cell is deuterated.

Sounds like everything is going pretty well? *"I would say we are actually now miles ahead,"* summarizes Batchu. He's not planning on taking a break anytime soon though. A recent grant, supplied by the League of European Nations for Neutrons (LENS), is financing work to use the produced lipids to study specific diseases, such as Alzheimer's disease, which is the most common neurodegenerative disorder. Impaired lipid metabolism in the brain has been implicated in Alzheimer's disease. That means that if you take a neuron (cells found in the brain and spinal cord) from a healthy person and a neuron from a person with Alzheimer's disease, the lipid composition of the neurons will not be the same. The idea is to use the naturally deuterated phospholipids to create membranes that mimic the lipid composition of a healthy neuron and a neurodegenerative neuron and then study the interaction of these membranes with proteins that are known to play a major role in triggering Alzheimer's disease.

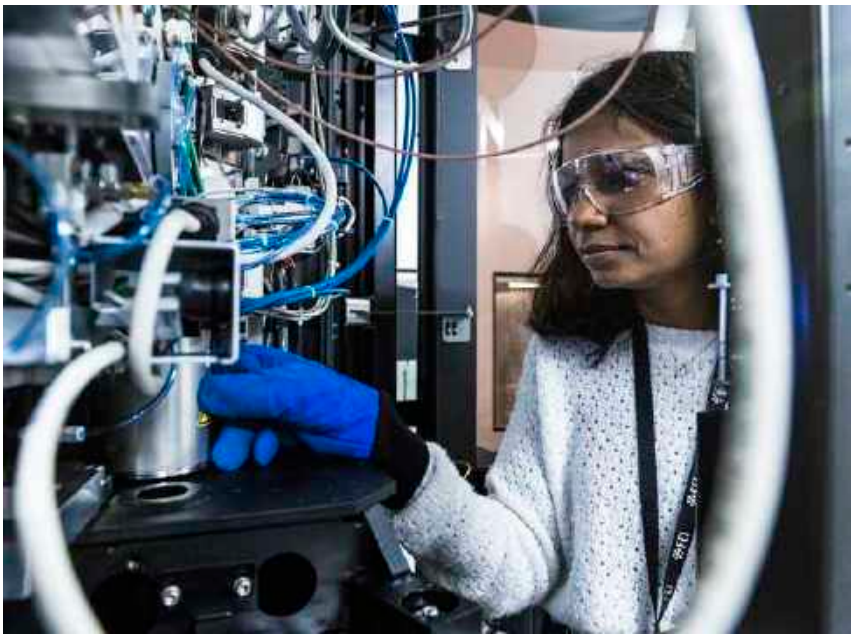
GIANT EFFECT

The characterization and cross validation of the deuterated molecules produced was carried out using the mass spectrometry platform located within the Cell & Plant Physiology Laboratory (LPCV) at CEA Grenoble in collaboration with Juliette Jouhet, CNRS researcher at the LPCV laboratory.

Resolution revolution reveals A FLEXIBLE VIRUS STRUCTURE

The cryo-electron microscope (cryo-EM) at the European Synchrotron (ESRF) has revealed the structure of the potato virus X at a resolution of 2.2 Å, the highest resolution ever achieved for a flexible, filamentous virus and one of the highest obtained using cryo-EM.

#European Large Scale Facilities — #Virus — #Cryo-EM



EAAZHISAI KANDIAH
Cryo-EM (CM01) beamline scientist, ESRF

Potato virus X (PVX) is a plant virus that infects potatoes, which are the world's number one non-grain food commodity and are worth billions to the global economy. Further understanding PVX could therefore have a significant economic impact, but also a health impact. The nanotechnology sector is currently investigating PVX as a potential nanocarrier, a particle that can be modified to efficiently transport drugs within the body. As a plant virus, it is non-infectious in humans and thus inherently safe. A very high resolution structure of the virus is required though in order to understand how to modify the structure for efficient use as a nanocarrier.

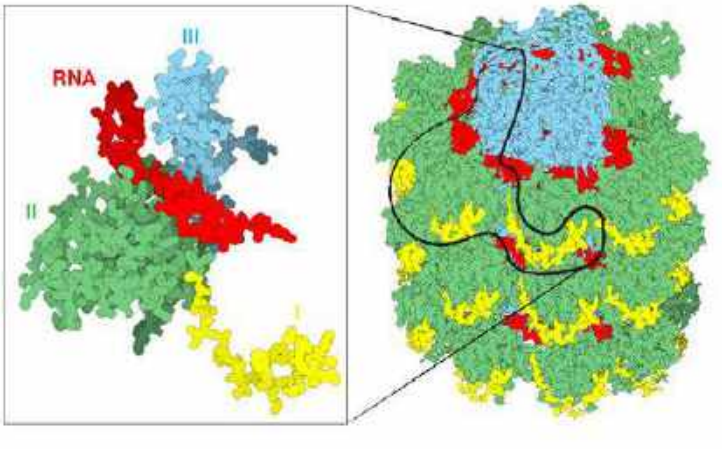
X-ray crystallography is traditionally used to study protein structures at high resolution. However, the technique requires that the sample is first crystallized. *"For crystallography, you need a crystal, where the same object is sitting in a regular pattern,"* explains Eaazhisai Kandiah, beamline scientist at the cryo-EM facility at the ESRF.

"PVX is a filamentous virus of varying length and is therefore impossible to crystallize."

With cryo-EM, the samples to be studied are directly frozen in amorphous ice thereby removing the need for crystallization and rendering possible the structural study of samples that cannot be crystallized.

Though cryo-EM technology is almost as old as X-ray crystallography, it is only recently that it has become a complementary technique. *"The technology wasn't as developed - the microscope, the detectors, the sample preparation - every aspect had several hindrances which meant that we could usually achieve a resolution of 20-30 Å,"* explains Kandiah. Cryo-EM involves passing electrons through the area of the sample to study, but the high energy electrons heat the ice embedding the particles (protein molecules or viruses) and as it melts, the particles start moving which introduces blurring or positional inaccuracy. To minimize particle movement, only low doses of electrons can be used and this low signal-to-noise ratio (SNR) impedes high resolution.

That has now changed thanks to the 'resolution revolution' that has occurred in the last 5-8 years and is largely due to improvement in microscopes, the development of direct electron detectors and associated progress in image processing. Previously, detectors worked by converting electrons into photons and back into electrons. The development of direct electron detectors, that directly measure each electron that touches a pixel of the



PVX coat protein-RNA packing in the filament. Inset: Domain 1 (yellow) of the coat protein embraces the neighboring subunits to strengthen the filament while domain 2 (green) and domain 3 (blue) forms a crevice in which the RNA is bound. The beautiful stitching of each of these components gives rise to the growing PVX filament shown above. Photo courtesy of Alessandro Grinzato, University of Padua.

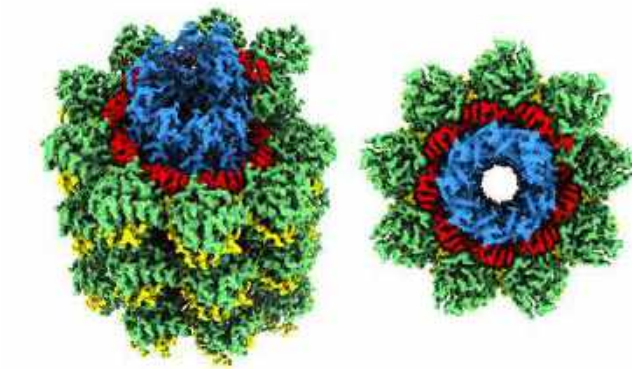
detector, eliminates the signal loss observed with the classical detectors and enables high electron detection accuracy and resolution. Moreover, to account for particle movement, each acquisition is separated into multiple frames. For example, a 10 second acquisition is separated into 10 frames which each last 1 second. The dose and induced particle movement per frame are therefore limited. The frames are then aligned using an image processing technique called motion correction and added together to increase the SNR. The direct detection of electrons and a high SNR ensure that the resultant image - the micrograph - is high-resolution. The particles are isolated in each of the micrographs and analysis enables the different particles to be aligned and combined together in order to achieve a 3D reconstruction of the sample.

All these innovations have been integrated into the Titan Krios cryo-EM microscope at the ESRF.

Operational since 2017, the microscope has a high brilliance and coherent electron beam with thermal and mechanical stability to ensure excellent optical performance, both of which are key parameters for producing high resolution images. Using this state-of-the-art technology, a collaboration between scientists from the ESRF and the University of Padua has enabled the structure of the PVX to be obtained at a resolution of 2.2 Å, which represents the highest resolution ever achieved for a flexible, filamentous virus using cryo-EM and one of the highest ever obtained for cryo-EM in general.

"It is the flexible aspect of the virus that makes it very difficult to achieve a high resolution," explains Kandiah. *"The cryo-EM data is analyzed using helical image processing which means that small segments of the filament are considered and these segments are then analyzed along the entire length of the filament. If the filament is curved, it is difficult to continue building these blocks of segments along the filament."*

The high resolution PVX structure obtained has shown that the virus is composed of repeating units of 8.8 coat proteins that wrap around the RNA genome. The identification of these crucial protein-RNA interactions aids the development of anti-viral drugs and advances the investigation of PVX as a potential nanocarrier.



Cryo-EM reconstruction of PVX in the (left) side and (right) top views enables the spatial arrangement of each of the PVX components to be appreciated. The component coloring is as follows: RNA (red), domain 1 (yellow), domain 2 (green) and domain 3 (blue).

GIANT EFFECT

Users of the cryo-EM facility are supported by a team of scientists from four different institutes – the ESRF, the Institute of Structural Biology (IBS), the European Molecular Biology Laboratory (EMBL) and the Institut Laue-Langevin (ILL).

SUPERHERO HANDS
made in Grenoble

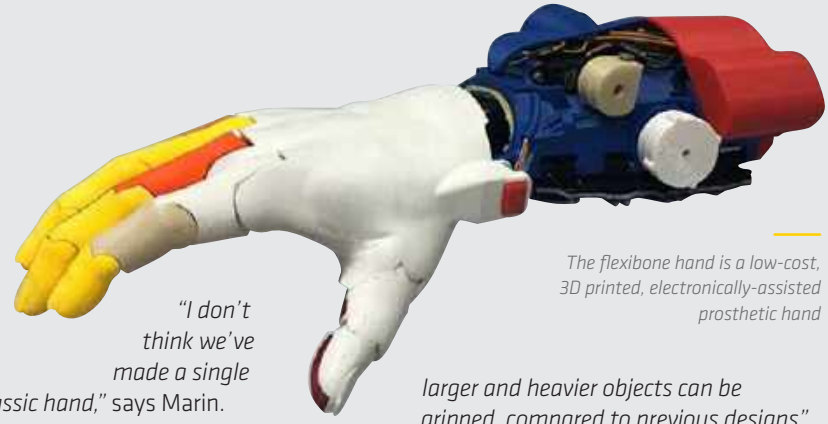
A novel design for a low-cost, 3D printed, electronically-assisted prosthetic hand has been developed by a team that includes researchers and professors from the Grenoble Institute of Engineering and Management (Grenoble INP). An undeniable technical achievement, the prostheses developed also represent an important psychological support for many of the children that receive them.

#Engineering — #3D Printing — #Prostheses

PHILIPPE MARIN
Associate professor and researcher at the G-SCOP laboratory of Grenoble INP

More than 300 children are born each year in France with a malformation of their upper or lower limbs. While there has been significant research and industrial development of lower limb prostheses, there is a limited number of options available for the upper limb. The association 'e-NABLE', a worldwide network of volunteers, works to mitigate this shortage by using 3D printers to make low-cost prostheses that are gifted to children and adults who were born without or who have lost fingers and hands.

A team of engineers, researchers and professors wanted to offer more than a size-modified version of the same model. *"We very quickly felt that each situation, each child, adolescent or adult, each handicap was particular and required an adaptation of the classic hand,"* explains Philippe Marin, associate professor and researcher at the G-SCOP laboratory of Grenoble INP. The 'Gre-Nable' team has been using their expertise to design and develop fully customized solutions, tailored to specific needs - to hold a pen, fork or paintbrush, to ride a bicycle.



The flexibone hand is a low-cost, 3D printed, electronically-assisted prosthetic hand

"I don't think we've made a single classic hand," says Marin. *"The requests we receive from 'e-Nable France' always concern particular situations for which they know, right from the beginning, that the classic hand model will not suit."*

The team has developed novel adaptations of the hand model for each new request and their latest design integrates electrical assistance for the first time.

Flexible 'bones' pass through the center of each finger and thumb and are covered by a harder shell with three articulation axes. These fingers can be contracted by fishing wire, used to mimic tendons, attached to servo motors, with the grip force being applied measured using a pressure sensor integrated into the tip of the index finger and indicated to the user by means of vibration. *"These new flexibone fingers mean that smaller, larger and heavier objects can be gripped, compared to previous designs"* explains Marin.

Electronically-assisted prostheses are usually controlled using myoelectric sensors that measure the electrical tension generated every time a muscle contracts, however they can make the prosthesis difficult to control, with an often noisy signal worsened by sweat between the sensor and the user's skin. Indeed, the recipient of the novel flexibone hand had been struggling not only with the weight (1.5 kg) but also the difficulty of controlling the €48,000 myoelectric prosthesis that she had been supplied with. An alternative solution was found to control the flexibone hand by positioning a joystick inside the palm that the user could operate with the mobility of her residual thumb joint. With an approximate weight and cost of 0.5kg and €200, the technical advances of this latest design are indisputable.

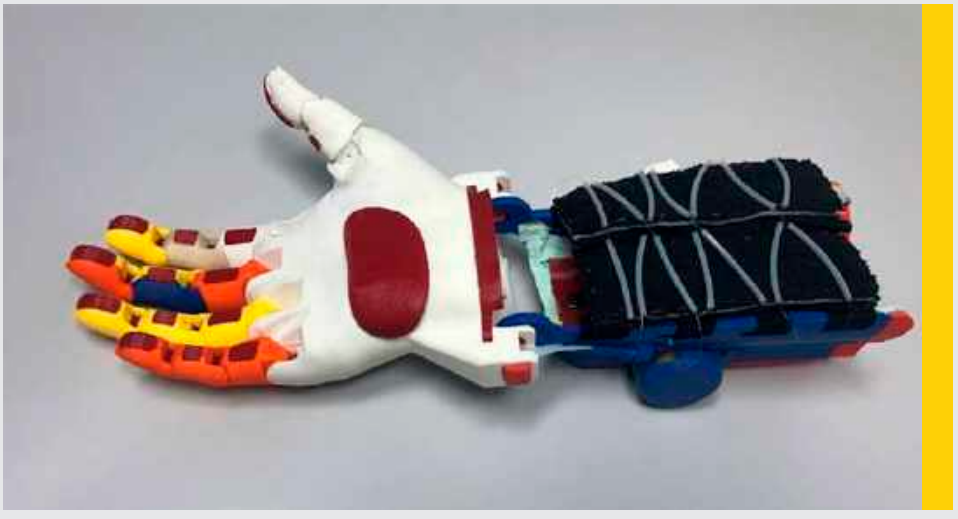
Furthermore, with the open-source design and technical details shared on-line (the project is Open Source Hardware certified under the OSHW reference FR000008), this low-cost, electronically-assisted prosthetic hand can be made by anyone with a 3D printer.

Beyond the technical achievement, Marin mentions that many of the prostheses developed have been for children, for whom the psychological role is far more significant than the limited functional role. *"The prosthesis looks like a superhero hand with nice colors and though it does help them somewhat, there are many things that they don't manage to do with it,"* explains Marin. *"The prothesis enables them to realize that since their birth, they have learned to use what they have of their hand or arm in their daily life and that for many movements they're actually more at ease without the prothesis."* Indeed, Marin has noticed that many of the children will stop using the prothesis after a few days or weeks. *"It doesn't matter, because it has helped them to accept their difference,"* he explains.

The novel flexibone fingers enable smaller, larger and heavier objects to be gripped, compared to previous designs.

GIANT EFFECT

The flexibone prosthetic hand was developed using the digital and prototyping facilities of S.mart Grenoble Alpes, an interuniversity department of Grenoble INP, Université Grenoble Alpes (UGA) and the University Savoie Mont Blanc. Technical CAD/CAM (computer-aided design and computer-aided manufacturing) tools from the Tricholome platform were used and functional devices were created using rapid prototyping CNC (computer numerical control) machines from the GINOVA platform.

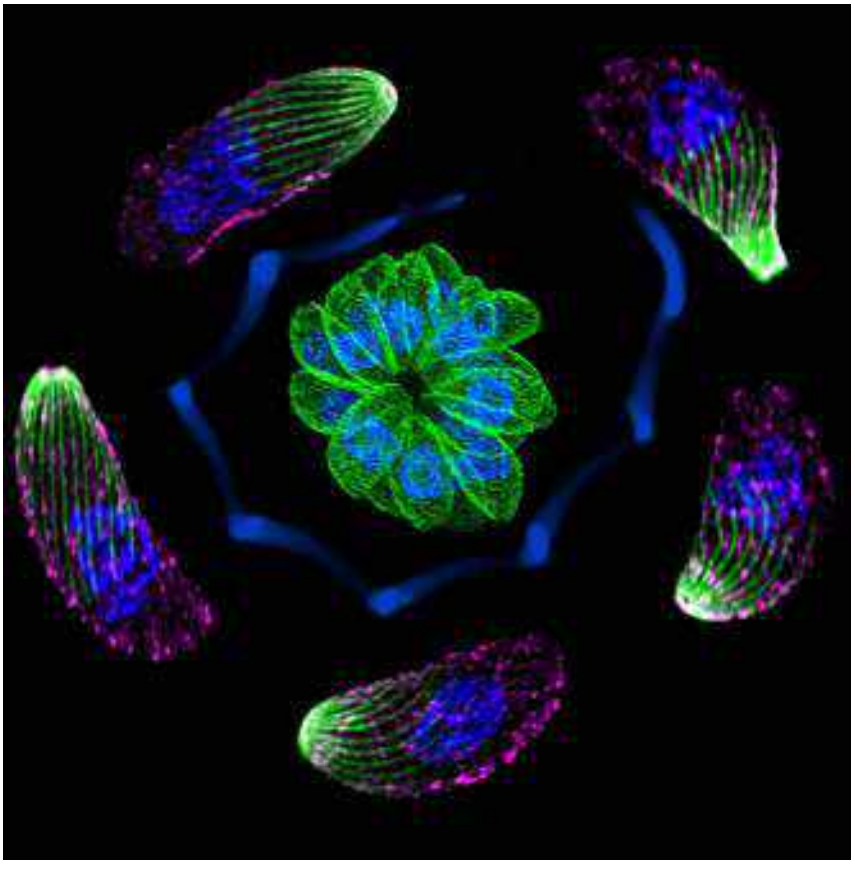


Electronically-assisted flexibone hand

TOXOPLASMA: the Usain Bolt of parasites

Toxoplasma – the eukaryotic parasite responsible for the infectious disease called toxoplasmosis – is a tiny banana-shaped single-cell microbe with a unique ability to move in a corkscrew-like helical motion at impressive speeds. Research carried out by Isabelle Tardieux, research director at the French National Centre for Scientific Research (CNRS), and her team at the Institute for Advanced Biosciences (IAB), has enabled the forces that power the movement to be measured for the first time to better understand just how this parasitic cell manages to achieve speeds that are ten times greater than the fastest cells in humans.

#Fundamental Research — #Parasite — #Biosciences



From the periphery to the center, images of (i) the spring-like force generated by the cytoskeleton of polarized Toxoplasma in motion within extracellular matrix (ECM) tissue; (ii) material released at the basal pole of ECM-moving parasites, forming a trail; (iii) endpoint of the parasite intracellular proliferative phase with the typical rosette organization of the descendance.

ISABELLE TARDIEUX
CNRS research director and group leader of the Biomechanics of Host-Parasite Interactions group, IAB

"The impressive motility capacity of Toxoplasma is directly associated with its ability to navigate among the extracellular matrix of cell tissue and enter targeted cells where it can reproduce," explains Tardieux. Transmitted through contaminated food and water, Toxoplasma is present in approximately one third of the human population across the entire planet. Though the infection is harmless for most people, it can be serious for pregnant women as the parasite crosses the placenta and colonizes the fetus potentially causing miscarriage or birth defects. The latent parasites persist in particular in the brain and retina for decades, reactivating a proliferative developmental phase with serious consequences at a later date if an individual becomes immunocompromised, induced for example by immunosuppressive drugs for transplant patients or for the treatment of a broad repertoire

GIANT EFFECT

The research carried out was made possible by collaboration with Mohamed-Ali Hakimi and his team at the IAB who work on Toxoplasma molecular genetics and with the Interdisciplinary Laboratory of Physics (LiPhy) - a joint CNRS and Université Grenoble Alpes (UGA) structure – in particular with Martial Balland, an expert in traction force microscopy, and Delphine Debarre, an expert in reflection interference contrast microscopy.

of pathologies such as cancer or rheumatoid arthritis.

In order to understand how the parasite moves forward in the extracellular matrix tissue, Tardieux and her team employed the use of traction force microscopy. For this technique, the sample, free to move and adhere, is placed on a soft material containing fluorescent beads that can be detected by the microscope. High speed image acquisition enables both the movement of the sample and the displacement of the beads – correlated with the force exerted by the sample to move – to be followed in real-time. Though the technique has existed for a number of years, it is generally used for much larger samples. *"Toxoplasma is a very small polarized cell, about 5-7 µm long, and moves very fast meaning that adherence is low,"* explains Tardieux. *"These conditions created unique constraints and it was not trivial to adapt the technique for Toxoplasma. For example, for the beads to displace when the parasite moved, it was necessary to have very small beads – about 0.2 µm in size – in a very soft, linearly elastic gel. But the parasite doesn't like it much when it's soft, it moves much less efficiently. Although very challenging, Georgios Pavlou, a talented PhD student in the team, managed to establish the conditions in which the displacement of the beads could be detected while still enabling the movement of the parasite."*

Combined with quantitative high resolution reflection interference contrast microscopy, micropatterning and the recently developed expansion microscopy technique, the team was able to reveal the ingenious mechanism evolved by the parasite to power its distinctive gliding movement. First, a single tight attachment is formed between the front of the parasite and the surface. The parasite pulls on this attachment, using it as an anchor, and causing a build-up of forces in the cytoskeleton. As energy is loaded into the spring microtubule system, the body contracts and a kink forms in the front part of the parasite's body. The rear of the body is slowly dragged forward and when the parasite detaches from the surface, the spring is released and the parasite suddenly surges forward in a super-fast helical glide. *"This is the first time that the change of shape of the parasite has been tracked in parallel with the measurement of the forces exerted by the parasite. By combining a number of techniques that have never been used at this spatiotemporal resolution level in this field of work, we were able to put together a comprehensive explanation of the movement that showed that the theoretical model accepted up until now lacked the spring function of the Toxoplasma cytoskeleton,"* explains Tardieux.

The results achieved have been recently published in the journal 'ACS Nano', with the movement of Toxoplasma visible in a short video produced by the journal (*youtu.be/kG146bHn4qw*). The team are now collaborating with a group in the Unites States in order to further advance their proposed model by the application of imaging techniques in 3D. It is hoped that by understanding the biomechanical aspects of the movement of the parasite, the knowledge could be integrated into the development of future ultra-high performance nano- or microrobots for medical or industrial use.

Isabelle Tardieux with Georgios Pavlou, respectively group leader and PhD student of the 'Biomechanics of Host-Parasite Interactions' team at the IAB.

PEOPLE OF GIANT

Karen AMRAM

welcomes innovation ecosystems from around the world to the GIANT campus.

The High Level Forum (HLF) was founded in 2012 to promote and strengthen international cooperation between the leading innovation ecosystems. Dr Karen Amram, Head of International Foresight (CEA Technology Research Unit) and the new Chair of the HLF, is responsible for the coordination of the annual international summit devoted to 'Leading Innovation Ecosystems', which is organized and managed by the Grenoble innovation ecosystem GIANT. Hosted in Grenoble every two years, the HLF Annual Summit is attended by representatives from innovation ecosystems located around the world, all committed to the management or promotion of innovation within their regional ecosystem.

How would you describe the HLF Annual Summit?

The HLF is a close-knit international community that groups together 45 innovation ecosystems from around the world. The meeting point of this family of ecosystems is the HLF Annual Summit which is either held in Grenoble or is hosted every second year at one of the partner ecosystems abroad. By bringing together representatives from industry, research and higher education, as well as entrepreneurs and members of the regional government and local authority, the summit offers a unique opportunity to meet and discuss in-person, to inspire and to learn from how others are doing things. Successful elements of partner ecosystems can be developed and adapted to local constraints and requirements thereby enabling each ecosystem to progress and improve.

How important is this summit?

I measure the importance of the summit by the fact that I see influential people who have very busy schedules stop everything once a year to come and participate in the HLF Annual Summit. When I ask them what they come for, they reply that they want to leave with their heads full of idea – and that is what happens! Grenoble is a very dynamic ecosystem and the summit participants really want to come back to Grenoble every two years to see what's new and what has changed since the last summit.

As the new Chair of the HLF, do you plan to make any changes?

My objective is to create a new dynamic to increase the interaction and collaboration of the ecosystems between each annual summit. I don't want us to have to wait an entire year to exchange and debate! To better connect the HLF ecosystems together and further stimulate exchange, a long-distance, continuous thread of interaction between the ecosystems is being put in place, called HLF Connect.

The other new aspect this year is the creation of the HLF Senior Level Group (SLG) and the HLF Steering Committee (SCOM). The SLG has responsibility for the governance of the HLF and is composed of the members of the GIANT council as well as representatives from a number of companies based on the campus. The SCOM includes representatives from ten different innovation ecosystems who act as ambassadors for the High Level Forum around the world. I hope that this international governance will help to guarantee the quality of the HLF Annual Summit and to enrich the HLF community.

The theme of the 2020 summit was presented by Dr Karen Amram during the closing ceremony of the 2019 HLF summit held in Lund, Sweden

More than 100 people representing more than 20 innovation ecosystems from around the world took part in the 2019 HLF Annual Summit held in Lund, Sweden

What can you tell us about the summit this year?

The 2020 HLF Annual Summit was scheduled to be held in Grenoble from the 29th of November to the 2ndof December under the theme 'Innovation Ecosystems: key players in reinventing industry to support a resilient society'. Considering the current health crisis, the HLF Senior Level Group has decided to postpone the summit until next year. Indeed, as the strength of the summit lies in the in-person dialogue that the event facilitates, we preferred to postpone rather than replace the summit with an entirely virtual event. I am pleased to confirm however, that the postponed summit will be replaced by a 100% online HLF Connect conference during which the ten ecosystems of the SCOM (including GIANT) will discuss critical issues of our time in front of a large international virtual audience.

hlf-giant-grenoble.org

HLF UPCOMING EVENTS

The postponement of the 2020 HLF Summit has been an opportunity to focus on some new interactions that combine collaboration, innovation and valuable content all-year long. Following this strategy, here are the two upcoming events on the HLF Community's agenda:

HLF @ III INTERNATIONAL TRIPLE HELIX VIRTUAL SUMMIT

2020, 24-25 November

The HLF will be at the next International Triple Helix Virtual Summit on 24-26 November 2020 to explore the theme *"Designing globally connected regional innovation ecosystems: overcoming barriers and opening pathways"*.

HLF CONNECT, 1ST ONLINE BRIEFING

2020, 1 December

The first HLF Connect Briefing hosted online from Grenoble on Dec 1st, invites Innovation Ecosystems of the HLF to discuss three critical issues of our time:

- Innovation ecosystem resilience: impacts in the short to long term
- New collaborations and alliances: strategies for integrative innovation
- Winning innovations in the time of Covid and beyond

An Awarded-Startups show & contest and highlights from HLF leading Innovation Ecosystems will punctuate this free HLF event that will be broadcast worldwide.

GIANT

AT A GLANCE

40
COMPANIES
on-site

More than **7,000**
SCIENTIFIC PUBLICATIONS
per year

More than **10,000**
INDUSTRIAL JOBS

More than
10,000
RESEARCH JOBS

More than
10,000
STUDENTS

More than **700**
PATENTS filed per year

Annual direct and indirect
ECONOMIC IMPACT:
€4,1 BILLION

About **10,000**
INHABITANTS ON CAMPUS

More than **9,000**
INTERNATIONAL VISITORS

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