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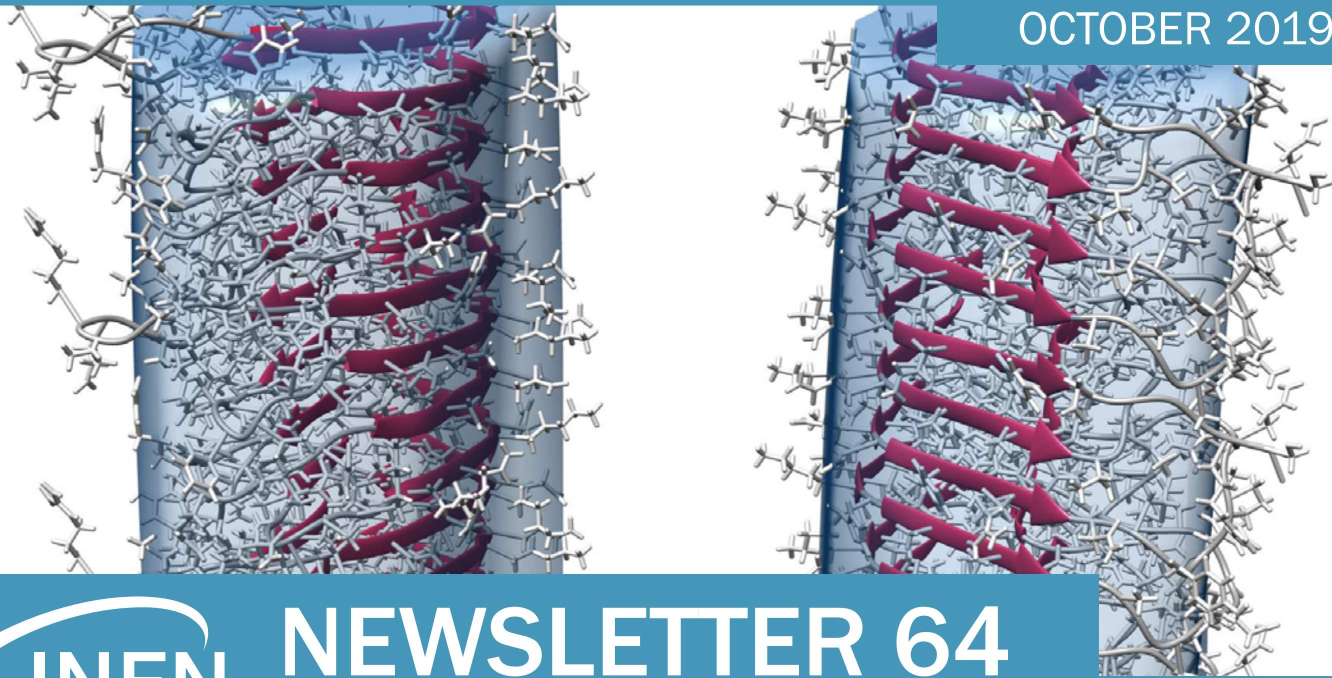

NEWSLETTER 64

Istituto Nazionale di Fisica Nucleare

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FROM QUANTUM MECHANICS A SPIN-OFF TO DISCOVER NEW DRUGS

Interview with Lidia Pieri, CEO of the INFN spin-off Sibylla Biotech

Discovering new drugs thanks to innovative drug design protocols and powerful algorithms starting from mathematical methods derived from theoretical physics, originally developed to study the typical phenomena of the subatomic world, such as the quantum tunnel effect. This is the challenge launched by the newly established Sibylla Biotech, a spin-off company of the Italian National Institute for Nuclear Physics (INFN), of the Universities of Trento and Perugia, and on which the Vertis Venture 3 Tech Transfer fund has decided to invest 2.4 million euros. Sibylla Biotech is one of the projects selected for the US-Italy Innovation Forum held on October 17th and 18th in San Francisco. The event also hosted the visit of the President of the Italian Republic, Sergio Mattarella. We asked Lidia Pieri, CEO of Sibylla Biotech to tell us what the company consists in and what is the strength of the technology that led to the creation of the company and what the future prospects are.

Sibylla Biotech recently received the interest and funding of investors, in particular for a technology that could enable the identification of new drugs using algorithms developed from mathematical methods of theoretical physics. What is the relationship between innovative drugs and theoretical physics? What does the technology you have developed consist of and what is its strength?

Today, among the many unresolved scientific questions, is the understanding of how biologically significant proteins are formed. Produced by the ribosome in the form of a chain of amino acids by translating DNA information, they then fold into defined forms to carry out their biological activity, a process called folding. The world's largest supercomputer, built to perform molecular dynamics, can only study the folding of small proteins or small portions of proteins. It would take hundreds of thousands of years of calculation to simulate the folding of a biologically interesting protein.

Sibylla overcomes this obstacle, thanks to the invention of two scientists who are among the founding members of the company: Pietro Faccioli, theoretical nuclear physicist, Professor at the Department

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of Physics in Trento and INFN researcher, and Emiliano Biasini, molecular biologist specialised in neurodegenerative diseases, researcher at the Dulbecco Telethon Institute and Professor at the CIBIO in Trento. Faccioli and Biasini have combined their talent, courage and perseverance, taking a potentially revolutionary and certainly engaging multidisciplinary journey.

The scientific journey started more than ten years ago, when Faccioli realised that, using the mathematics of quantum mechanics, and in particular that which describes the passage of a quantum particle through an energy barrier - the so-called tunnel effect - it is possible to find a short cut and to simulate this type of event.

The protein comes out of the ribosome as a chain of amino acids, and then goes through one or more conformational changes to reach its biologically active shape. The protein vibrates around a certain shape because of the interactions between its atoms and the atoms of the surrounding environment. It takes some time, from milliseconds up to minutes, until the protein finds the most energetically favourable state and rapidly changes (in microseconds) its shape. We're talking about the interactions of thousands of atoms of a protein and of around half a million of atoms of the liquid in which it is immersed. Molecular dynamics is forced to simulate all the time the protein spends in a given conformational shape. This simulated time does not give us any information on protein folding but it greatly increases the time a simulation takes, that can become greater than the time of a human life, making the simulation impossible. With Faccioli's method, as long the final conformational shape is known, we can directly simulate the exact moment in which the protein changes its shape, and two weeks are enough to run the protein folding simulation with atomic detail on a small cluster. Moreover we realised that, biologically relevant proteins can take intermediate states as they fold towards their biologically active form. And now we know how to characterise these states at an atomic level. I underline it: only now and only we know how to characterise these states at an atomic level. This uniqueness is the strength of our method.

Now let's go back to Trento, where Biasini has been working for some time on a protein responsible for various neurodegenerative diseases. Here, while he and Faccioli are working together on an interdepartmental thesis project, the biologist in front of the physics equations and the physicist in front of the complexity of the cellular environment, intuition hits. If a drug were to be bound in the intermediate state of that protein (and this could not be done before because the structure of the intermediate states was unknown), it would inhibit folding, and the cell's control system would eliminate it before it was converted into its pathological form, thus preventing it from causing the disease. The first molecules linked to an intermediate state, which may be the starting point for the pharmacological research of a cure, are now being patented. The method of suppressing the toxic activity of a protein through a drug linked to the intermediate folding state can be generalised to all proteins that have an intermediate state, and has been patented. We know

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that this could revolutionise pharmacology, which is applicable, in principle, to all therapeutic areas and therefore also to those that contain incurable diseases, such as certain types of cancer or Alzheimer's disease. We do not yet know whether it will work on other proteins, but it is certainly worth investigating this possibility.

This idea led to the foundation of Sibylla Biotech, a spin-off of INFN, of the Universities of Trento and Perugia. What kind of support did you receive from INFN and what importance did this have for Sibylla?

Sibylla has licensed both the molecular simulation platform and the method patent, and aims to develop an innovative drug discovery platform.

INFN’s contribution was fundamental not only for the scientific background underlying the discovery, but also for the support we received from the Technology Transfer Department from the very outset. The INFN wanted to get to know us when our business ideas were still embryonic; it believed in the method’s potential and in the possible revolutionary impact on society of an invention that stemmed from the basic research. Sibylla is a true proof that basic research is one of the foundations on which the scientific culture of today must be based, together with the need to be able to address complex issues with a multidisciplinary approach.

Sibylla and INFN have signed a collaborative research agreement that has allowed us to use fundamental computing resources to take the first steps in the search for investment.

Based on your experience, what are the favourable and necessary conditions for the creation of a spin-off?

The necessary conditions for the creation of a spin-off are an excellent and motivated team, and a surrounding cultural environment that is an ally in technology transfer and that teaches those who do another job how to do business. We were able to count on the support of INFN and to follow the Bootstrap path with HIT (Hub Innovation Trentino), which brought us closer to the business world and its mechanisms and complexities. This provided us with the basics in order to navigate what is a completely new system for those coming from the academic context.

I would like to see the culture of creating a company to exploit an idea implemented and rooted more strongly in the academic environment (from where I come). Instead, I feel there is still a fundamental wariness, as if doing business were, in fact, a violation of an ethical principle of scientific sharing. I firmly believe that founding a company means giving an idea the opportunity to receive funding and the necessary support to develop and exploit its potential to the full, at the cost of postponing the dissemination of the idea just for

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the time necessary to get it patented (a necessary step to acquire the value that is sought by the investor). Only having founded Sibylla do we now have the opportunity to investigate new pharmacological targets and to proceed towards the development of new drugs. If we had not founded the company, we would simply not have had the millions of euros needed to do this.
The profession of a university professor and researcher is a wonderful, stimulating and rewarding one, which I have pursued for many years. I am a physicist, moreover in the INFN area. For personal reasons I left the academic world five years ago, after a PhD and ten years of research. My training has allowed me to follow the scientific evolution of the method for identifying folding intermediates and its application to pharmacology, to fall in love with this idea and to be able to pass it on to non-experts. The fact of not working in the academic world, however, gave me the time, the opportunity (no academic can have operational positions in a spin-off) and the perspective necessary to lead the company in this initial phase. Managing a company, coming from outside the academic world, has been a very interesting experience for me, both professionally and personally. I have been able to exploit my scientific but also managerial and multitasking skills which research had already trained me in. I have been able to address a challenge with significant responsibilities, that I had to constantly confront.
I believe it would be useful to train scientists. I would like Universities to consider that, starting with master's degree students, they should organise meetings or even business development courses. These would introduce the concept of technology transfer and create the culture of this process - an alternative process that is not in opposition to the academic career, one that enriches and does not impoverish scientific knowledge, one that allows ideas and projects to be implemented without destroying any ideal.

What are Sibylla Biotech's next objectives?
Sibylla has received 2.4 million euros in funding from the Vertis Venture 3 Tech Transfer fund, which believed in the team and in the potential of the idea. This is significant funding that will allow us to validate the technology and, thus, finalise the proprietary drug discovery protocol in order to collaborate with large pharmaceutical companies.
Our first objective is to prove that our technology works, that we can detect at least one other unknown pharmacological target in a protein responsible for a disease and identify molecules that bind to this new target, eliminating the protein before it becomes toxic. We want to produce a result that can mark the beginning of a ten-year journey towards the discovery of a cure for that disease. Our long journey begins here and, I'm sure that the Sibylla team is the best possible to complete it. ■

INTERNATIONAL COLLABORATIONS

KAGRA JOINS THE GLOBAL NETWORK FOR THE SEARCH OF GRAVITATIONAL WAVES

The gravitational observatories VIRGO (in operation in Italy at the European Gravitational Observatory, EGO), LIGO (two twin detectors in Louisiana and in the state of Washington, USA) and the Japanese KAGRA have signed a scientific collaboration agreement that covers scientific collaboration, including joint observation of gravitational waves and data sharing, for the coming years.

KAGRA is a gravitational-wave observatory developed in Japan under the leadership of the University of Tokyo's Institute for Cosmic Ray Research (ICRR) with contributions from the National Astronomical Observatory of Japan (NAOJ) and the High Energy Accelerator Research Organization (KEK). Construction started in 2010, and now the highly-sensitive instrument is nearing readiness to join VIRGO and LIGO, the interferometers that led to the discovery of gravitational waves and the birth of multimessenger astronomy. The three detectors are taking data since April 2019 for the third observation campaign called O3, that will last one year.

The agreement signed is a Memorandum of Agreement (MOA), valid until 2023, and foresees the possible extension of the collaboration with the inclusion of new scientific observers. Furthermore, from 2025 LIGO India should become part of the network for the observation of gravitational waves from the Earth as well. ■

PUBLIC ENGAGEMENT

FESTIVAL AND EXHIBITIONS

Three major public events opened in October with the participation of the INFN.

In Genoa, the 17th edition of the Science Festival, dedicated to the theme "Elements", has started and will end on November 4th. INFN participates with the exhibition *The cosmos in a glass*, *Art & Science: the elements of creativity*, the science show *The universe in a box* and the conferences *The factory of the elements*, *The scream of the universe*, *All the colours of the cosmos*, and the laboratory *When the cards tell the truth*.

In Rome, at the Palazzo delle Esposizioni, the exhibition *Sublimi Anatomie* was inaugurated on October 21st and will remain open to the public until January 6th. The exhibition traces the secular and spectacular history of human body observation that involves the senses in the first place, but also tools and technologies, such as those of the most advanced medical imaging, which the INFN has contributed to narrate. On show are works, artifacts and documents of historical and artistic importance that, between art and science, tell the evolution of knowledge on human anatomy in close dialogue with contemporary artistic research on the materiality of the body.

In Pisa, at the Museo della Grafica, it opened its doors on October 12th and will be open until December 8th the exhibition entitled *Rhythm of space*. From the discovery of gravitational waves to contemporary art: the exhibition offers a fascinating journey between art and science in the context of the last exciting discoveries in physics. The recent detection of gravitational waves, produced by the fusion of black holes and neutron stars, allows us today not only to observe the cosmos but also, we could say, to "listen to it". This new possibility of knowledge has led international artists to reflect on our relationship with the universe, with our planet and with society. ■

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MINI-EUSO, FIRST DATA FROM THE EXPERIMENT ON BOARD THE ISS

Last 7 October, the astronauts on board the International Space Station (ISS), led by Luca Parmitano, switched on the Mini-EUSO (Multiwavelength Imaging New Instrument for Extreme Universe Space Observatory) ultraviolet telescope for the first time. The telescope is the result of an agreement between the Italian Space Agency, the funding body, and the Russian Space Agency Rosocosmos, and it was assembled in the laboratories of the INFN division and Physics Department of the University of Rome Tor Vergata. This first switching-on was followed by a second on 19 October. The two preliminary observation phases demonstrated the correct operation of the experiment and have already produced a considerable amount of data, which will be analysed in depth by the experiment collaboration once on Earth.
The Mini-EUSO experiment arrived on the ISS on 27 August on board the Soyuz MS14 spacecraft, which was launched on 22 August from the Baikonur cosmodrome. Now it is installed inside the Russian Zvezda module, from where it is observing the Earth. Its scientific objectives are many and extend over several fields. For the first time, a map of the Earth's nocturnal emissions in the ultraviolet spectrum and of their variations, both anthropogenic and bioluminescent, i.e. linked to particular plankton and algae behaviour, will be obtained. Phenomena in the upper atmosphere and the possibility of identifying and removing space debris will also be studied.
In addition, meteors will be studied to search for signals from a particular, very dense state of nuclear matter, in their traces as they enter the atmosphere. This nuclear matter, strange matter, has not yet been observed but it is predicted by various theoretical models. Mini-EUSO is also able to observe very high energy cosmic rays.
The new generation optical system and focal surface allow Mini-EUSO to achieve unprecedented sensitivity, being able to detect each photon emitted in a 40-degree field of view at a rate of 400,000 images per

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second. One of the main characteristics of the device is its ability to make observations on different time scales, from a few microseconds upwards, and to be able to correlate data with those from two ancillary cameras, which are sensitive in the visible and near infrared bands. Mini-EUSO also contains a series of new generation detectors, such as the silicon-photomultipliers, with the aim of studying their behaviour and their ability to withstand the space environment. The technology developed within the scope of this experiment - the result of the work of a broad international collaboration of researchers - will be used in future space missions and on stratospheric balloons. One example of the latter is the NASA SPB-2 project, which is scheduled to be launched from New Zealand in 2022. ■

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Prion structural model superimposed on cryo-electron microscopy maps, credit Sibylla Biotech.

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