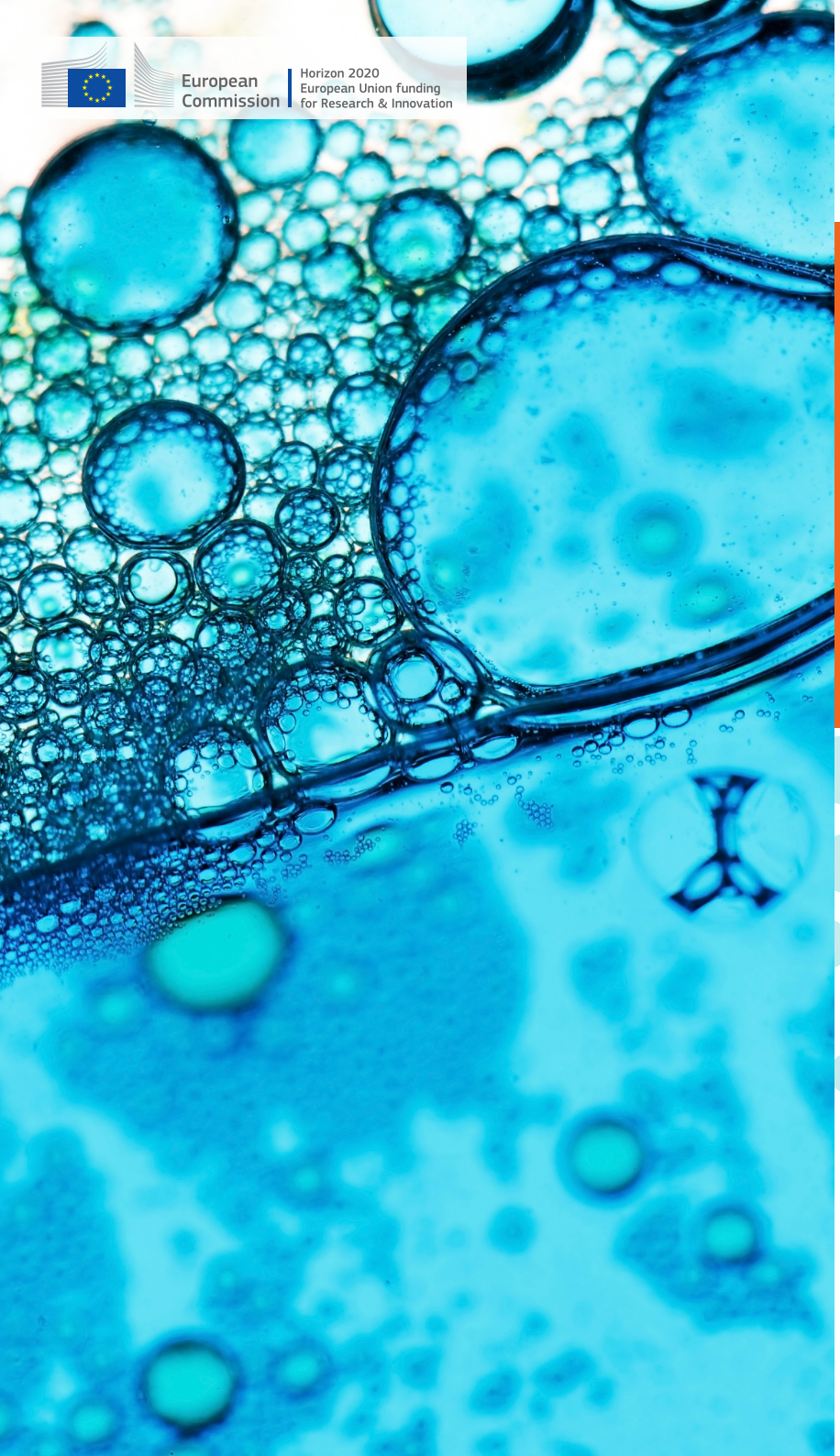

European Commission

Horizon 2020
European Union funding
for Research & Innovation

Computational biology

Spotlight on ERC projects

2017

10 years erc

European Research Council

Established by the European Commission

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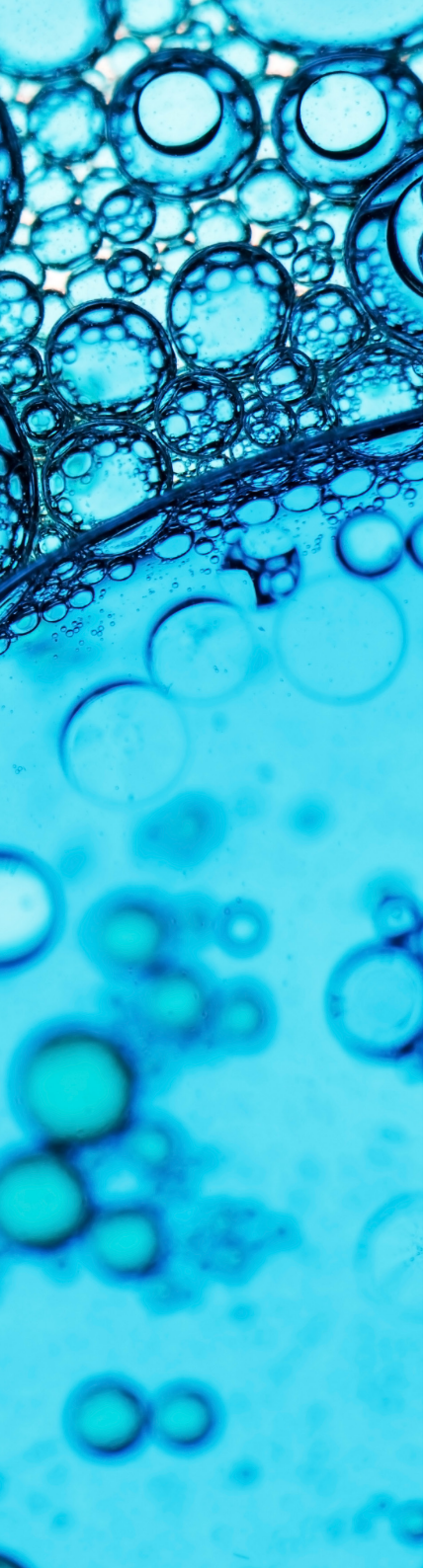
Set up in 2007, the ERC is the first pan-European funding body designed to support investigator-driven frontier research and to stimulate scientific excellence across Europe. It aims to support the best and most creative scientists to identify and explore new directions in any field of research (Physical Sciences and Engineering, Life Sciences and Social Sciences and Humanities) with no thematic priorities and the only evaluation criterion being excellence. With more than 7 500 projects funded, it has now been 10 years that the ERC awards long-term grants to individual researchers of any nationality and age who wish to carry out their research projects in Europe.



Introduction

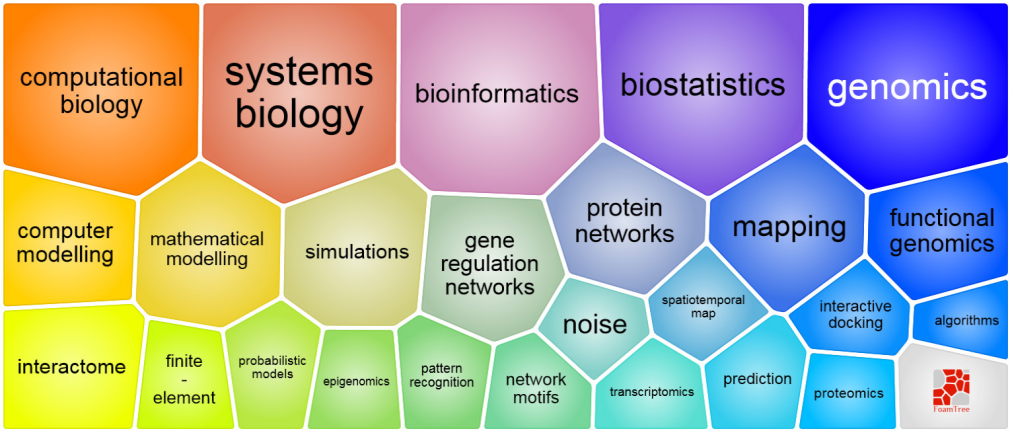
Computational and systems biology are interdisciplinary sciences that have been greatly advancing in the last decades by harnessing the increased power of computation and mathematics. Their aim is to apply large-scale computational and numerical methods to the fields of molecular, cellular and structural biology, in order to answer emerging biological questions that were not possible to tackle with traditional approaches.

The foundations of these disciplines lie in computer science, applied mathematics, statistics, biochemistry, chemistry, biophysics, molecular biology, genetics, genomics, ecology, evolution, anatomy, neuroscience, visualization, animation, etc.

In this context, thousands of researchers around the world work on a wide range of computational, analytical and theoretical methods, to study amongst others gene regulation, structure prediction, protein design, analysis of cell signalling and metabolic networks. They focus on the design, prediction and discovery of emergent properties of cells, tissues and organisms, on studying and modelling complex interactions within biological systems, on developing algorithms and databases, and on the use of advanced computing.

To date, the European Research Council (ERC) has supported close to 350 projects in computational biology, systems biology, bioinformatics and biostatistics, representing more than EUR 700 million invested in these research areas.

This brochure has been published on the occasion of the 25th International Conference on Intelligent Systems for Molecular Biology / 16th European Conference on Computational Biology, taking place from 21 to 25 July 2017 in Prague (Czech Republic).



Cluster view of most used keywords in ERC projects in the field of computational biology

Leukaemia: an epigenetic disease?

All cancers carry epigenetic alterations. But the biological function of these alterations is not well understood. In his ERC project, Prof. Christoph Bock explores their functional role by introducing them into cancer and normal cells. Successful engineering of an epigenetic leukaemia could challenge the idea that all cancers are driven by genetic alterations.

Epigenetics research investigates heritable patterns of gene regulation that cannot be explained by the genetic code. Recent studies have found epigenetic alterations in all cancer types and in essentially every examined patient. Despite such high prevalence, their causal and/or consequential role in cancer development is largely unknown. This is in part due to the lack of suitable technology for programming a precise set of epigenetic alterations into individual cells.

Developing and applying cutting-edge experimental and bioinformatics technologies, Prof. Bock and his team work on engineering cancer-specific epigenetic aberrations into healthy cells. The goal is to reprogram cells between the normal and the cancerous state, which would provide evidence for the functional role of epigenetic alterations and a powerful model for drug screening and developing novel therapies.

The researchers, based at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences in Vienna (Austria), are developing methods and algorithms for rational epigenome programming, using CRISPR technology, epigenome sequencing, and bioinformatic modelling. Their study focuses on leukaemia as an important and experimentally accessible cancer, but the concepts and methods are broadly applicable for any disease with an epigenetic component.

This is a high-risk, high-impact project as it relies on new technologies and on the hypothesis that it is possible to induce a cancer state in a cell just by changing its epigenetic markers. If successful, it will not only challenge (or extend) the current view of cancer as genetic disease, but it will also provide a validated toolbox for epigenome programming in human cells.

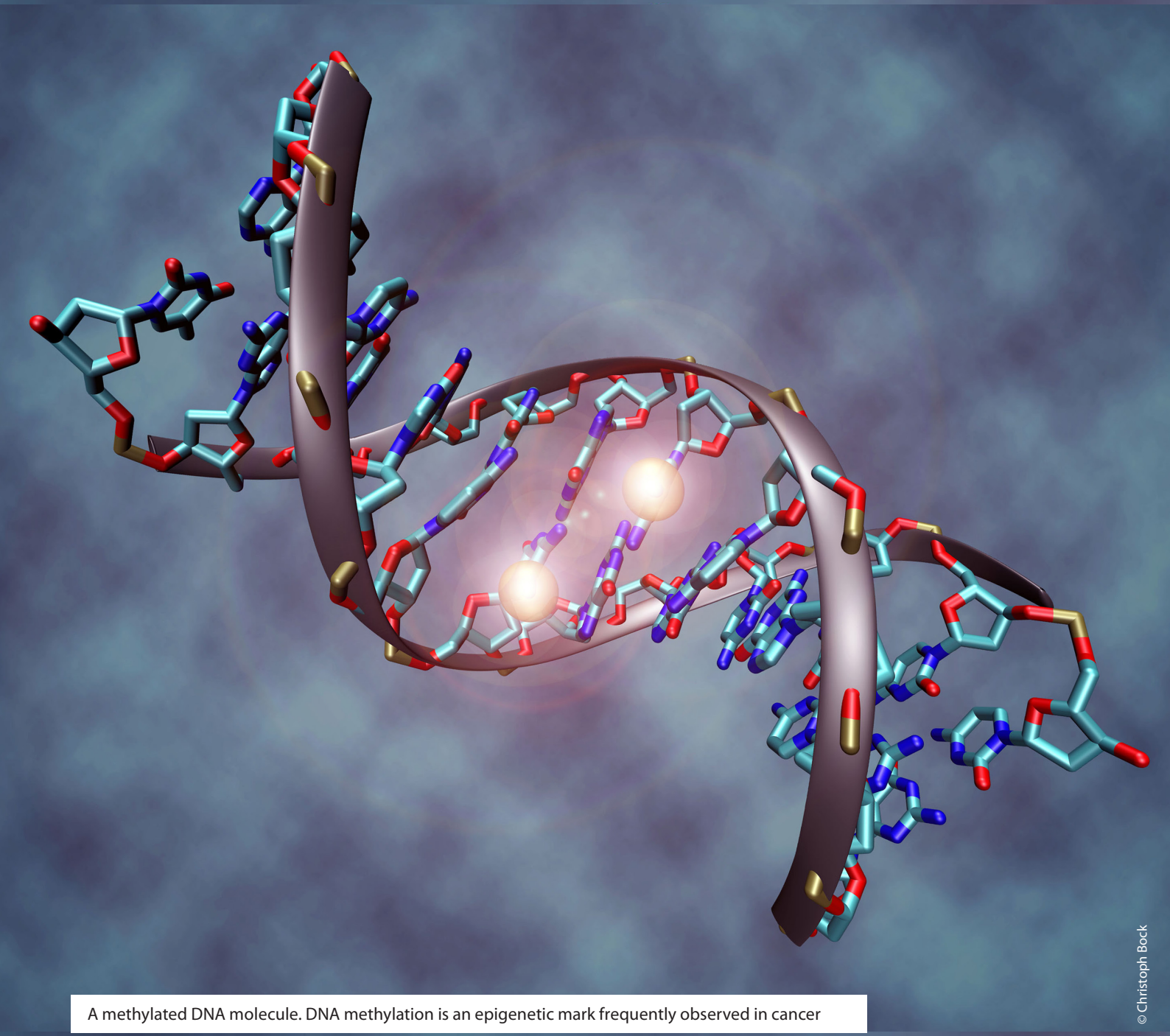
Finally, Christoph Bock expects that his research will eventually contribute to the development of innovative epigenetic therapies for leukaemia, which may have an important role to play in personalised cancer medicine.

Researcher: Christoph Bock

Host institution: CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences (Austria)

ERC Project: An experimental and bioinformatic toolbox for functional epigenomics and its application to epigenetically making and breaking a cancer cell (EpigenomeProgramming)

ERC funding: Starting Grant 2015, EUR 1.3 million (2016-2021)



A methylated DNA molecule. DNA methylation is an epigenetic mark frequently observed in cancer

Secrets of protein interactions unveiled

How do proteins trigger complex signal processing tasks, such as neurotransmission, in cells? Thanks to the development of innovative molecular simulation techniques, this ERC-funded project has brought new insights into the transmission of messages inside and between cells.

Cells are able to receive, process and send many signals, to other cells, simultaneously. This occurs thanks to proteins, called receptors, that bind signalling molecules and initiate a response. Practically, all life processes stem from the action of these proteins that move inside and around cells, associating and dissociating themselves to transmit information. Neurotransmitters, for example, are a class of signalling proteins that travel across the tiny spaces between adjacent neurons or between neurons and muscle cells.

But how do proteins find and bind their targets in extremely crowded cellular membranes? Prof. Frank Noé assembled a team of chemists, biologists, physicists, mathematicians and software engineers working together to answer this challenging question. The investigation carried out at the interface of various disciplines and combining different techniques – including molecular dynamics simulations and Markov modelling – has led to a ground-breaking outcome.

The researchers were able to visualize for the first time protein association and dissociation in atomistic resolution. This process cannot be directly observed by experiments, and a computer simulation without the team's novel simulation techniques would take thousands of years to complete. In the future, this achievement may open the path to the understanding of many biological processes with a tremendous impact on pharmaceutics, biotechnology and material sciences. Their observations, in collaboration with another research group led by Prof. Gianni De Fabritiis at Pompeu Fabra University in Barcelona (Spain), were reported in June 2017.

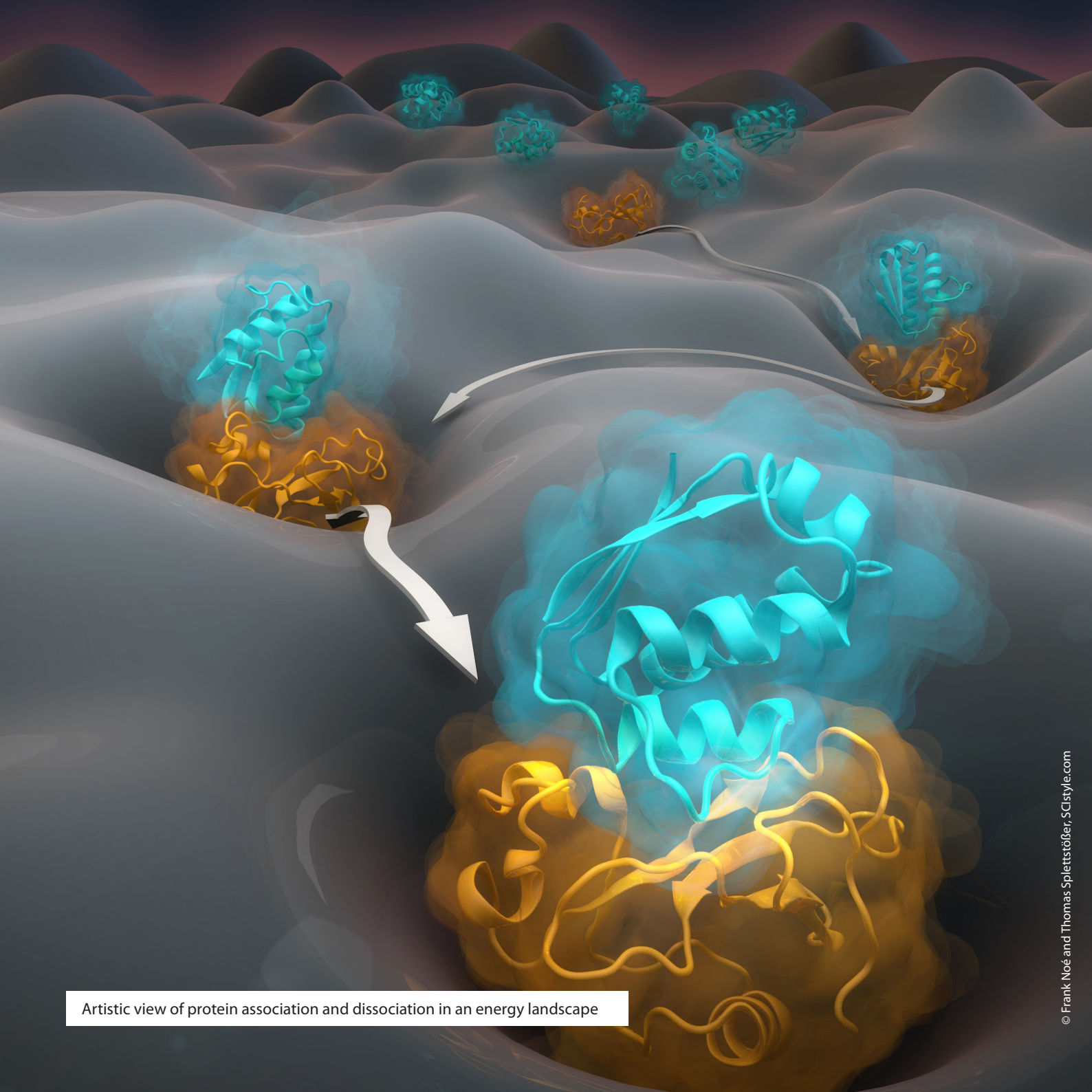
These results may revolutionize the field of computational biology. Prof. Noé declared: *"This is the kind of high-risk project for which it is very difficult to get funding because at the beginning nobody believes it is possible".*

Researcher: Frank Noé

Host institution: Free University Berlin (Germany)

ERC Project: Physicochemical principles of efficient information processing in biological cells (pcCell)

ERC funding: Starting Grant 2012, EUR 1.4 million (2013-2017)



Artistic view of protein association and dissociation in an energy landscape

Always on call: how does the immune system perform?

Our immune system recognises and fights infections in a constantly changing environment, where new pathogenic threats emerge. At the crossroad between physics and biology, Prof. Aleksandra Walczak investigates the fascinating process that allows the immune system to be always ready to adapt and evolve to face new dangers.

The role of the immune system is to protect the organism from the many pathogens, such as bacteria, germs, viruses, it constantly encounters. To fulfil this function, it must maintain a diversity of specialised cells, each one targeting a subset of pathogens, including those to which it has never been exposed to. All together, these cells cover an array of potential threats.

The immune system basically relies on B and T cells, which, following maturation in the spleen (B cells) or thymus (T cells), are secreted into the bloodstream. The receptor proteins on the surface of B and T cells interact with pathogens, recognise them and initiate a response. These receptors are generated randomly, yet together form a diverse repertoire that allows the immune system to protect us against a wide range of diseases. This repertoire must adapt to the changing pathogenic environment, maintaining, at the same time, memory of the past infections.

The diversity of the composition of the immune repertoire is a self-organised process, whose nature has not been yet completely unveiled. Applying a combination of data analysis and statistical mechanics modelling, this ERC-funded project focuses on the mechanisms underlying the recognition of pathogens at a molecular and evolutionary level to build new probabilistic and data-driven models.

Recent findings by Prof. Walczak's team, in collaboration with other research groups, suggest that, during pregnancy, twin embryos may exchange T cells through cord blood and that T cell clones produced before birth may persist in the body of a person for about 40 years.

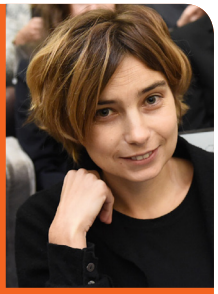
Making advances in the understanding of recognition of potential threats by the immune system will be fundamental for the development of new treatments against allergies and auto-immune diseases.

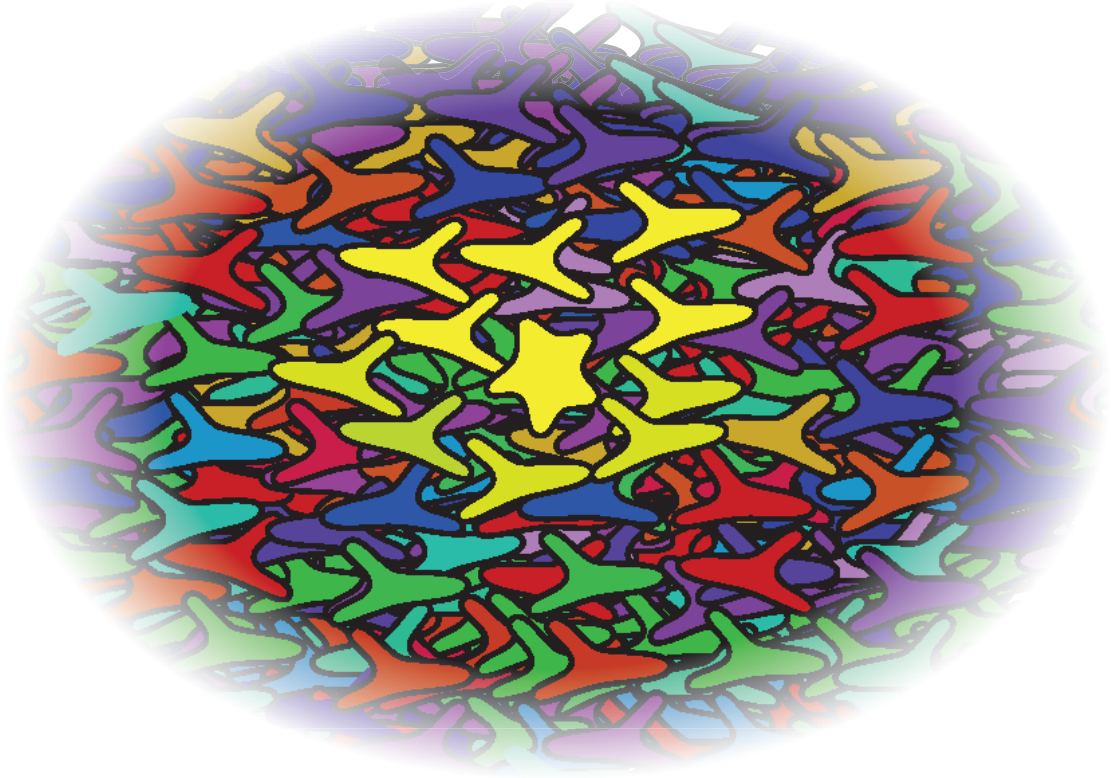
Researcher: Aleksandra Walczak

Host institution: CNRS (France)

ERC Project: Physical principles of recognition in the immune system (RECOGNIZE)

ERC funding: Starting Grant 2012, EUR 1.4 million (2012-2017)





Emergent function in a repertoire

Building a multi-level simulation of organogenesis

Organogenesis is the process by which different cells grow, differentiate and interact with each other to create large structures, such as the heart, the brain, a limb. But what are the mechanisms behind these molecular, cellular and tissue interactions that lead to the construction of an organ? Prof. James Sharpe's team is developing the first 3D computer model to better understand this complex process.

Computational models are invaluable tools to investigate organ and tissue formation. So far, these models have allowed scientists to understand only some of the pieces of this big puzzle, such as the control of tissue growth. However, putting all the pieces together into a single multi-scale simulation remains problematic. The SIMBIONT project addresses this big technical challenge, working on the first ever multi-scale computer model of mammalian organogenesis, focusing on limb development.

In order to create this new tool, Prof. Sharpe and his team are applying a novel conceptual and experimental approach that, in many aspects, goes beyond the most recent modelling techniques and molecular signalling studies. The researchers use cutting-edge quantitative data-generation techniques to gather and integrate, in a single comprehensive framework, information about cell morphology, motility and tissue morphogenesis, all on a three-dimensional level. The challenge lies in the large amount of data to be collected as well as in the computational and mathematical hurdles that need to be solved, since the few existing computer simulations are mostly two-dimensional. Overcoming these difficulties will ultimately help to better understand how complex interactions at multiple scales (genes, molecules, cells and tissues) coordinate to build a carefully constructed three-dimensional organ.

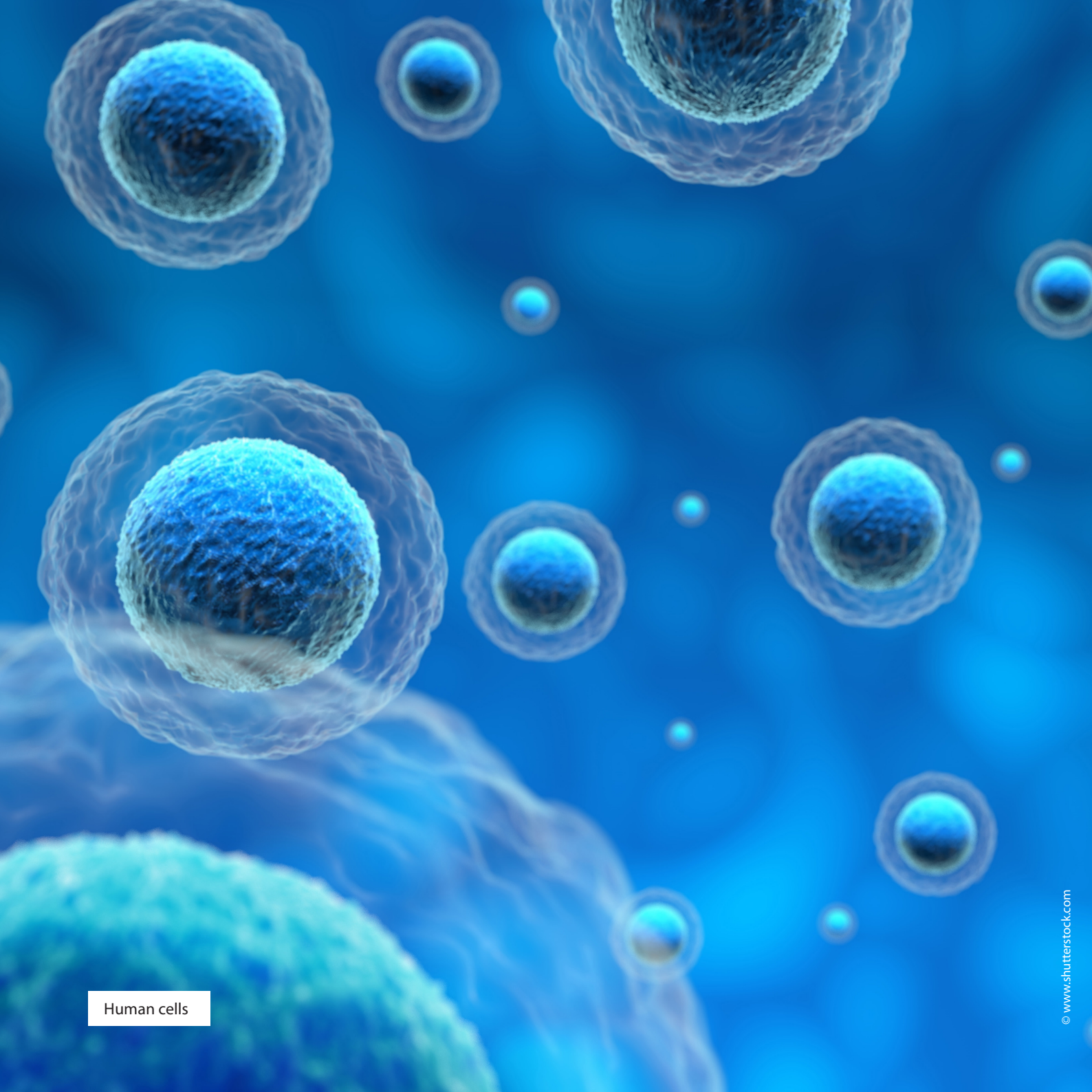
Prof. Sharpe, who has been appointed in May 2017 head of a new EMBL outstation in Barcelona (Spain), is confident that, in the future, this approach can be used to study other complex multicellular processes such as tissue engineering and organ regeneration. It could also provide scientists with new insights into the cellular and molecular alterations underlying human congenital malformations and the development of cancer and other diseases.

Researcher: James Alexander Sharpe

Host institution: Centre for Genomic Regulation (Spain)

ERC Project: A data-driven multiscale simulation of organogenesis (SIMBIONT)

ERC funding: Advanced Grant 2014, EUR 2.1 million (2015-2020)



Human cells

Understanding membrane trafficking in space and time

ERC grantee Prof. Maria Antonietta De Matteis studies membrane trafficking in cells and how its components interact and are regulated to guarantee a healthy cell function. Her work could revolutionise our understanding of this key biological process.

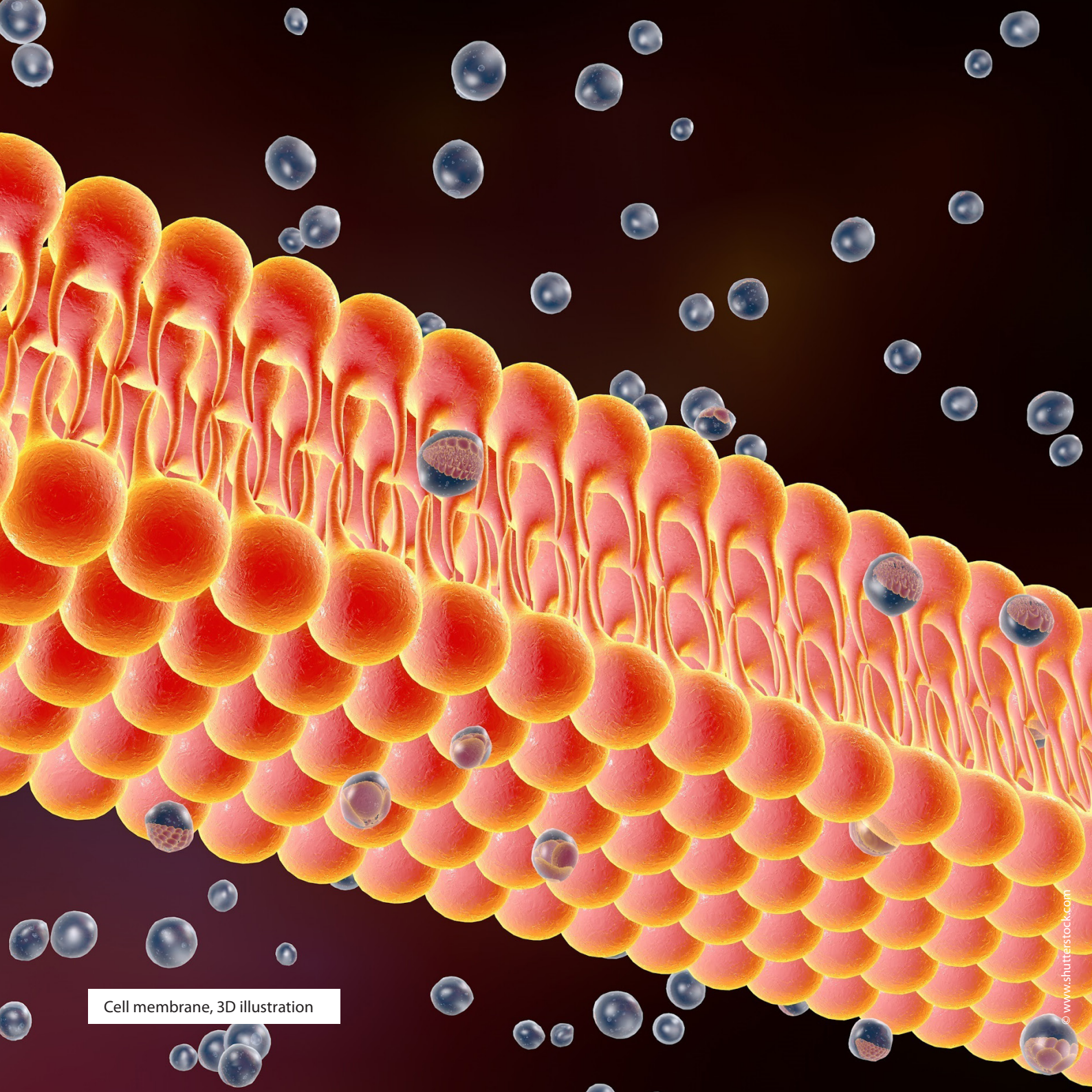
Membrane trafficking is the process by which proteins are distributed inside and outside the cell, as well as being one of the mechanisms that guarantee homeostasis. It is of key importance for cell organisation, communication and function. However, the knowledge available so far is limited to the identification of its main molecular components, rather than to the system as a whole which is considered as a simple strategy based on a small number of constitutive events.

Prof. De Matteis, from the Telethon Foundation (Italy), is working towards an understanding of the complexity of the overall membrane trafficking system. Following the observation that mutations in seemingly ubiquitous genes involved in trafficking cause distinct diseases depending on where they are in the body, and that the same genes can have different effects on the development of different tissues, she believes that membrane trafficking is more than the cell's "day-to-day house-keeping".

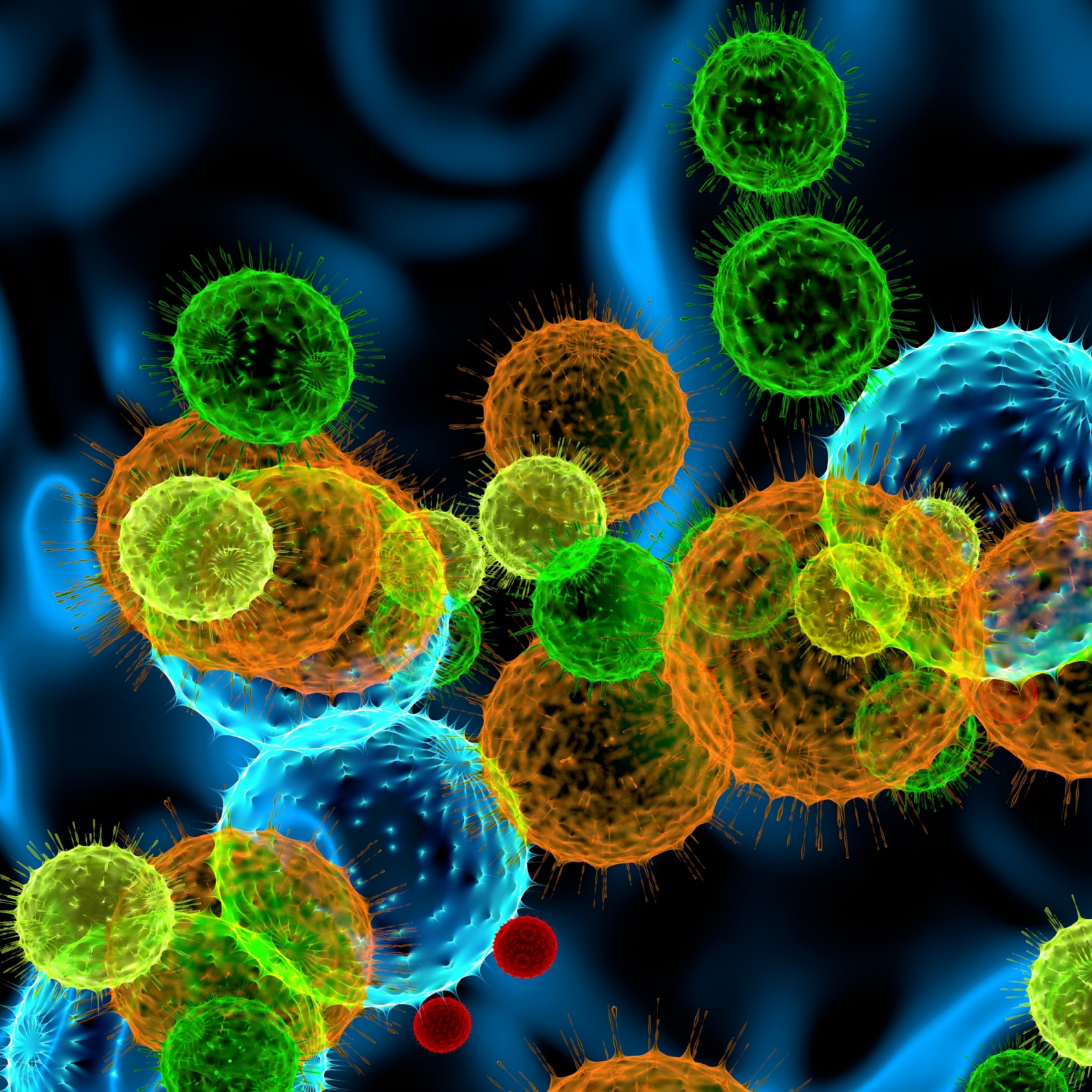
Her team created a list of 1 187 genes responsible for membrane trafficking in different parts of the cell. Using a multi-tool approach that combines functional genomics, proteomics and microscope-based high content screening, Prof. De Matteis and her team intend to create a spatiotemporal map of the elements and processes regulating membrane trafficking, based on an understanding of its modules – proteins and genes.

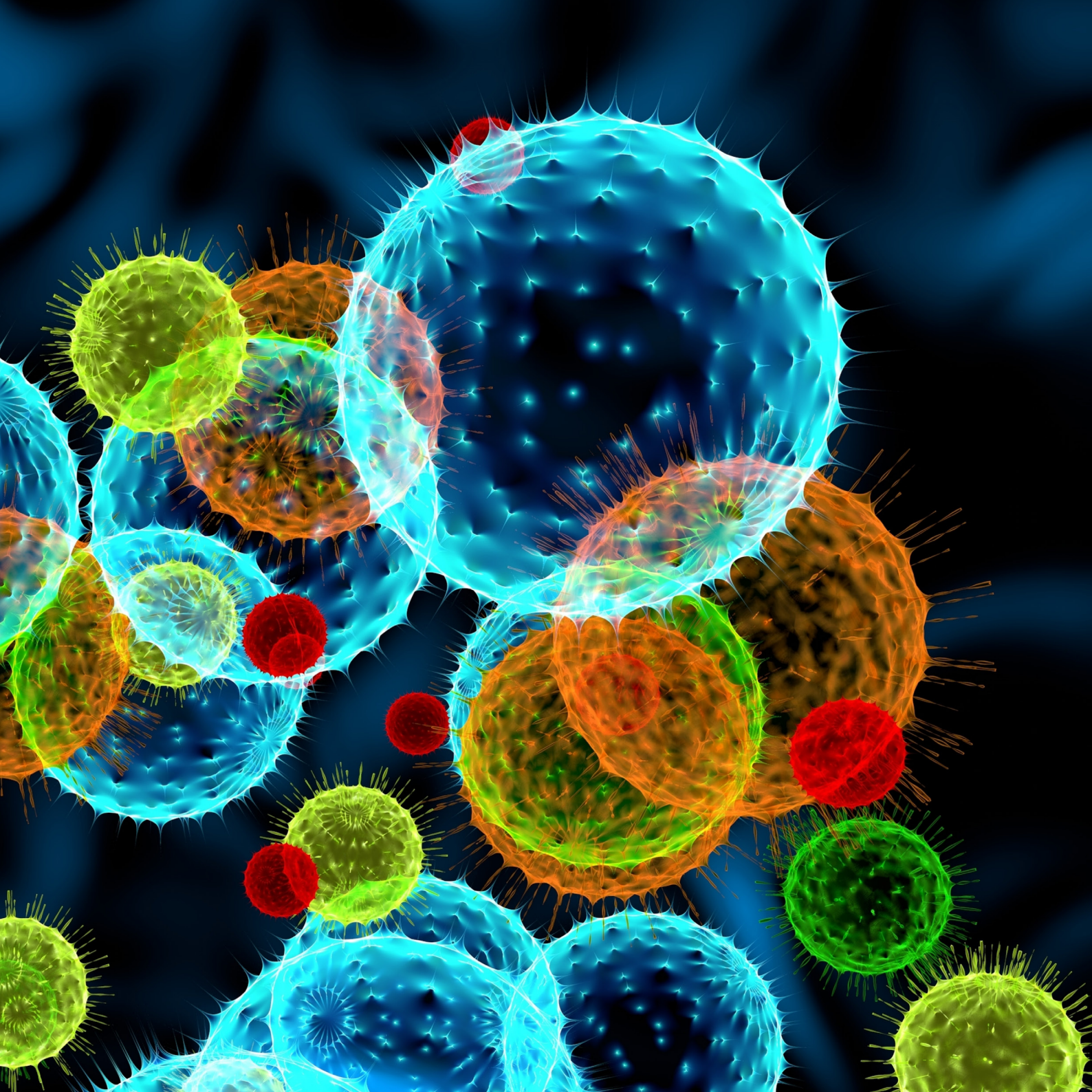
This work will provide a unique resource to evaluate the impact of the different trafficking regulatory mechanisms employed by the cell, with important implications for human health and the identification of drug targets for congenital disorders such as Lowe syndrome, a condition that primarily affects the eyes, brain, and kidneys, and spondylo-epiphyseal dysplasia, a bone growth disorder leading to dwarfism.

Researcher: Maria Antonietta De Matteis
Host institution: Telethon Institute of Genetics and Medicine (Italy)
ERC Project: Systems Biology of Membrane Trafficking (SYSMET)
ERC funding: Advanced Grant 2014, EUR 2.4 million (2016-2020)



Cell membrane, 3D illustration





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Jean-Pierre Bourguignon
ERC President and Chair of its Scientific Council

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