

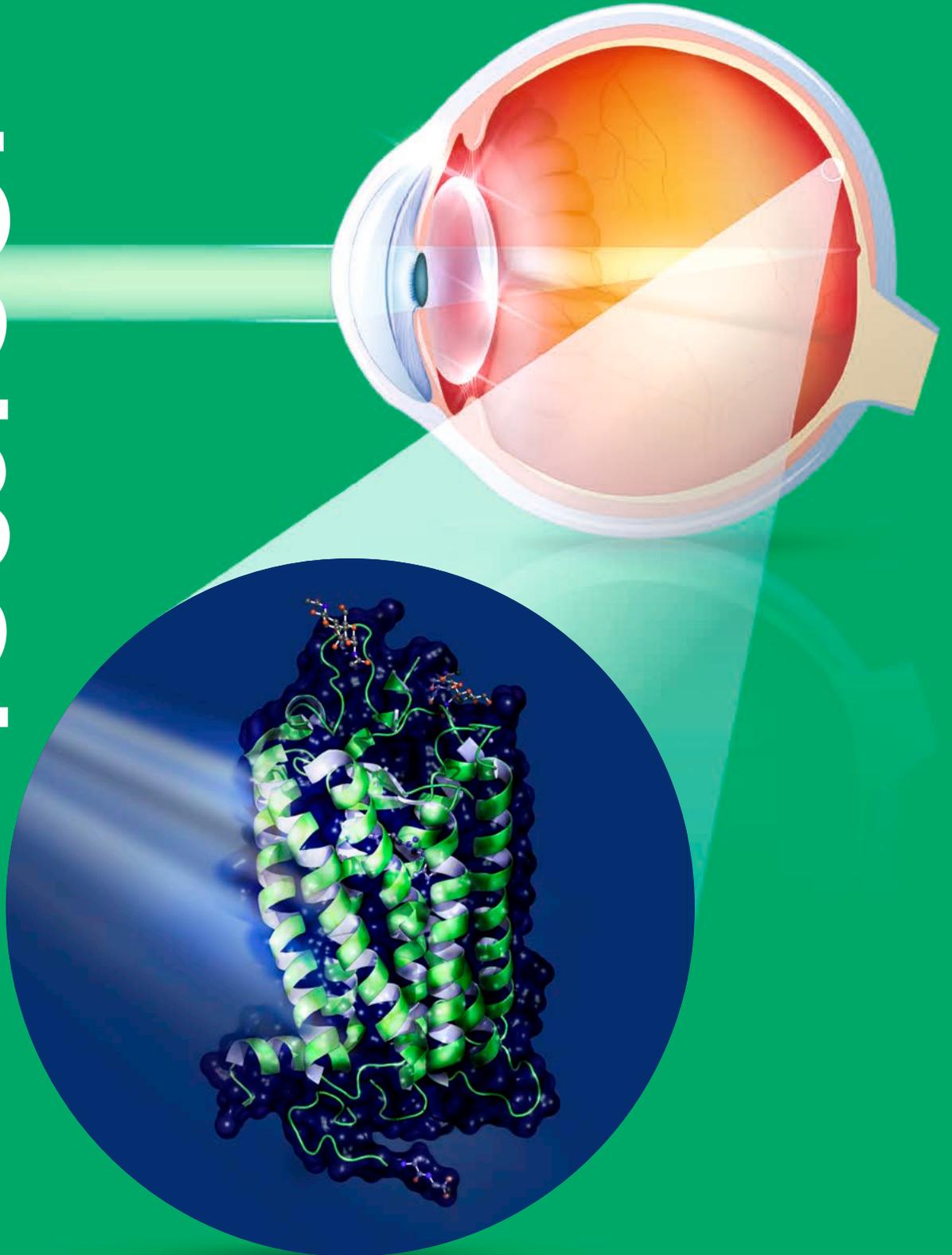
The magazine of the Paul Scherrer Institute

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2022

KEY TOPIC

LIGHT-SENSITIVE SWITCH IN THE EYE



KEY TOPIC: LIGHT-SENSITIVE SWITCH IN THE EYE



BACKGROUND

The wondrous world of light antennas

Without them our world would be dark: light receptors in our eye. At PSI, researchers are able to unlock the secrets of these unique biomolecules thanks to its special large research facilities, such as the X-ray free-electron laser SwissFEL and the Swiss Light Source SLS. This knowledge paves the way to new therapies for diseases and new possibilities for research on the human body.

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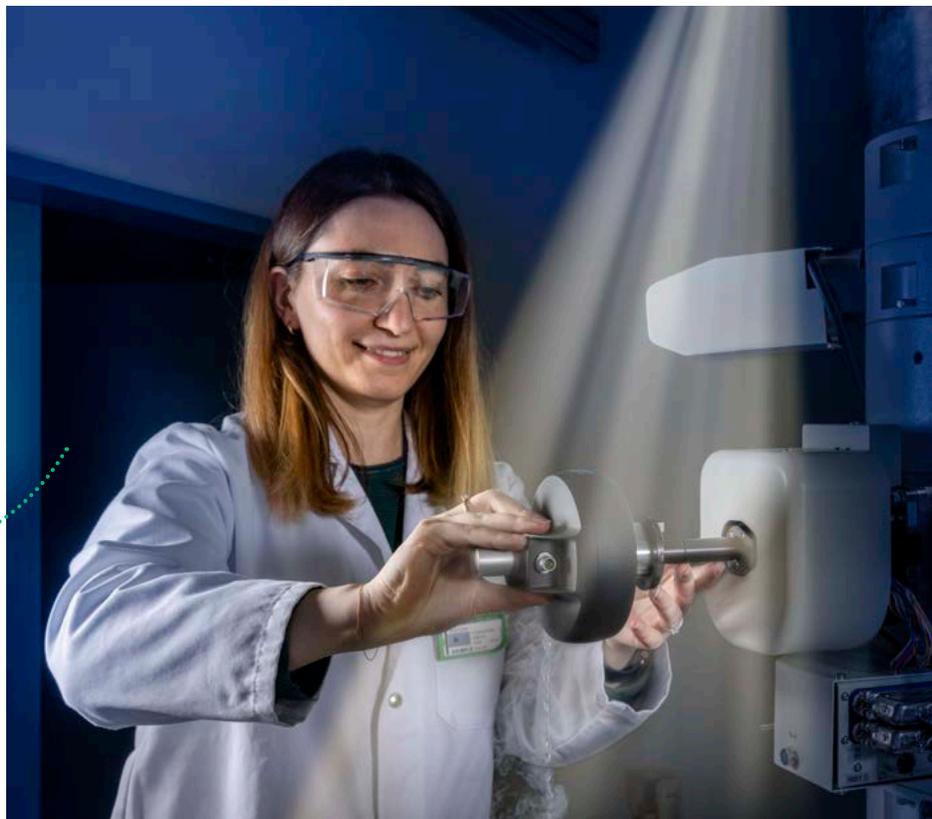
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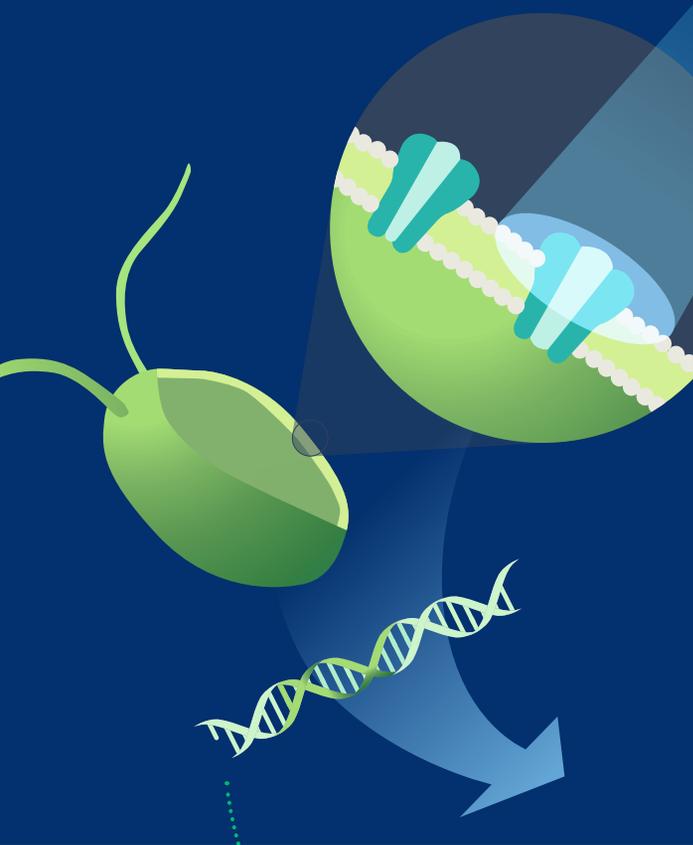
Cool newcomer

A relatively new method in electron microscopy complements perfectly the large research facilities of PSI and enables amazing insights into the world of light receptors.

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INFOGRAPHIC

Controlling cells with light

PSI researchers, as members of a multinational consortium, are taking part in a large-scale project to revolutionise a research area that is still in its early days: optogenetics.

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With the participation of PSI researchers, an international consortium wants to preserve ice cores from the earth's glaciers in the eternal ice.

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Fifteen years ago, she set up a beamline at SLS. Today Iris Schmid is in charge of product management for a company that makes control systems for trains.

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Mr. Rüegg, what does research at PSI have to do with our eyes?

Like so much in our body, we owe our sense of sight to proteins – large biological molecules that take on special, in most cases vital, tasks in every cell. It's no exaggeration to say that all life on earth is only possible with proteins. And yes, we humans can only see because we have such specialised proteins in our retina: the light receptors. When light hits them, they change their three-dimensional structure. This creates a signal that is ultimately processed in the brain into a visual impression. It's ingenious what has developed in the course of evolution. With our large research facilities, we specialise in investigating proteins, whether for the pharmaceutical industry's search for new active ingredients or for more basic research on proteins such as light receptors. The X-ray free-electron laser SwissFEL is particularly helpful in investigating these proteins.

Why is SwissFEL so well suited for this research?

It's never that tips the balance here. The process that takes place every time light hits our eye is one of the fastest responses that can occur in our body. Within quadrillionths of a second, it's as if a switch in the protein is turned on to signal: "I was in contact with a beam of light." So it's lightning fast. Such processes in biological molecules can be investigated particularly well with SwissFEL, for example at the Bernina experimental station, in whose control room I happen to be sitting. With SwissFEL, we have already solved many exciting mysteries about light-sensitive proteins and are confident that we will solve more in the future. Sight is perhaps the sense that most strongly shapes us as human beings, so it is amazing how much we still don't know about it – and thus how much remains to be explored at PSI.

Does this research take place exclusively at SwissFEL?

Oh no! It is precisely the variety of research facilities here at PSI and in the ETH Domain that enables our researchers to uncover so many secrets about proteins of all kinds. Our Swiss Light Source SLS, for example, is ideally suited to find out how proteins are structured and how they exist in three-dimensional space. More than 8,000 structures have already been solved at SLS. And let's not forget cryo-electron microscopy, which our researchers use, for example, in collaboration with ETH Zurich and the Biozentrum at the University of Basel. This technology has made amazing advances in recent years, for example when it comes to studying complexes made up of several proteins. It's absolutely clear: to investigate protein structures with X-ray light, there is almost no better place in the world than PSI.



TELL US MORE

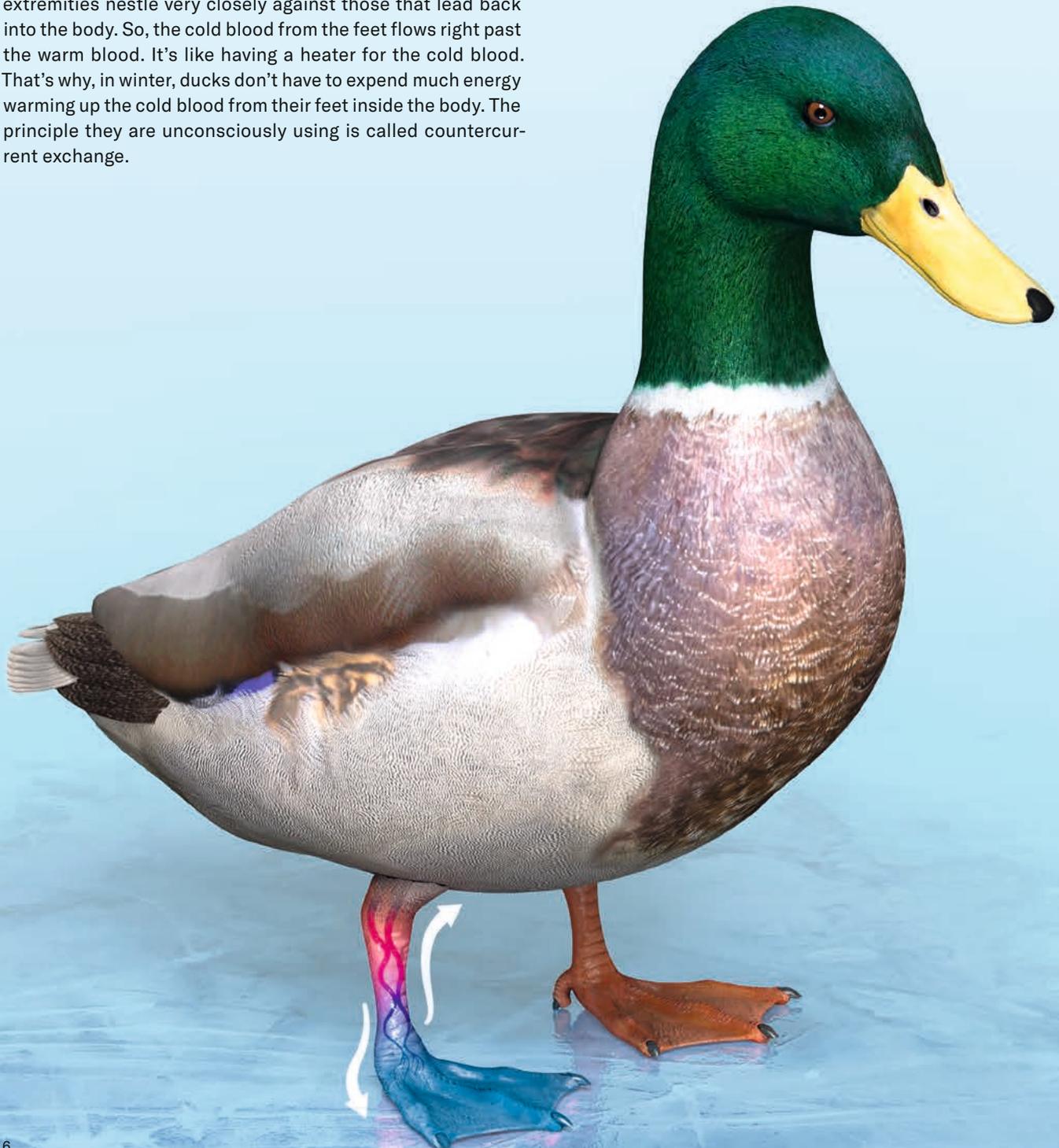
What are you up to, Mr Rüegg?

When it comes to research on proteins – for example, light receptors like those found in our eyes – the Paul Scherrer Institute is a world leader. Director Christian Rüegg explains why these biomolecules are such an excellent target for investigation at PSI.

Cold feet

Brrrrr. It can make you shiver to watch ducks or other waterfowl in the winter as they swim in icy water or waddle across a frozen pond. If we humans tried this with bare feet, it wouldn't be long before we were chilled through and through, and our body temperature would drop dangerously low. The fact that the same thing doesn't happen to ducks, which usually have an even higher body temperature than we do, is not due to their warming plumage alone.

To curb temperature loss through their feet, nature has furnished these birds with a very special mechanism. The blood vessels that transport warm blood from the body to the extremities nestle very closely against those that lead back into the body. So, the cold blood from the feet flows right past the warm blood. It's like having a heater for the cold blood. That's why, in winter, ducks don't have to expend much energy warming up the cold blood from their feet inside the body. The principle they are unconsciously using is called countercurrent exchange.



Clean fuel

Countercurrent exchange is put to use in many technical processes. Basically, two material flows are guided past each other in opposite directions to promote an exchange of heat or material. Researchers at PSI use it too, for example in the optimisation of biomethane production. Biogas, which is produced through the fermentation of biowaste, is a mixture of carbon dioxide and methane, as well as traces of other substances. Therefore it cannot be fed directly into the existing natural gas network.

For this, gases – for example methane, hydrogen, and carbon dioxide – must be consistently separated from one another. One possibility for this is offered by membranes that selectively filter gases whose constituents exceed a certain size – as shown in the graphic, for example, methane (brown-yellow spheres) and carbon dioxide (brown-blue spheres). The same approach works for the separation of methane, carbon dioxide, and hydrogen. In a study, researchers at PSI have shown how the separation of hydrogen and methane can be especially effective if the countercurrent exchange principle is applied.

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KEY TOPIC

Light-sensitive switch in the eye

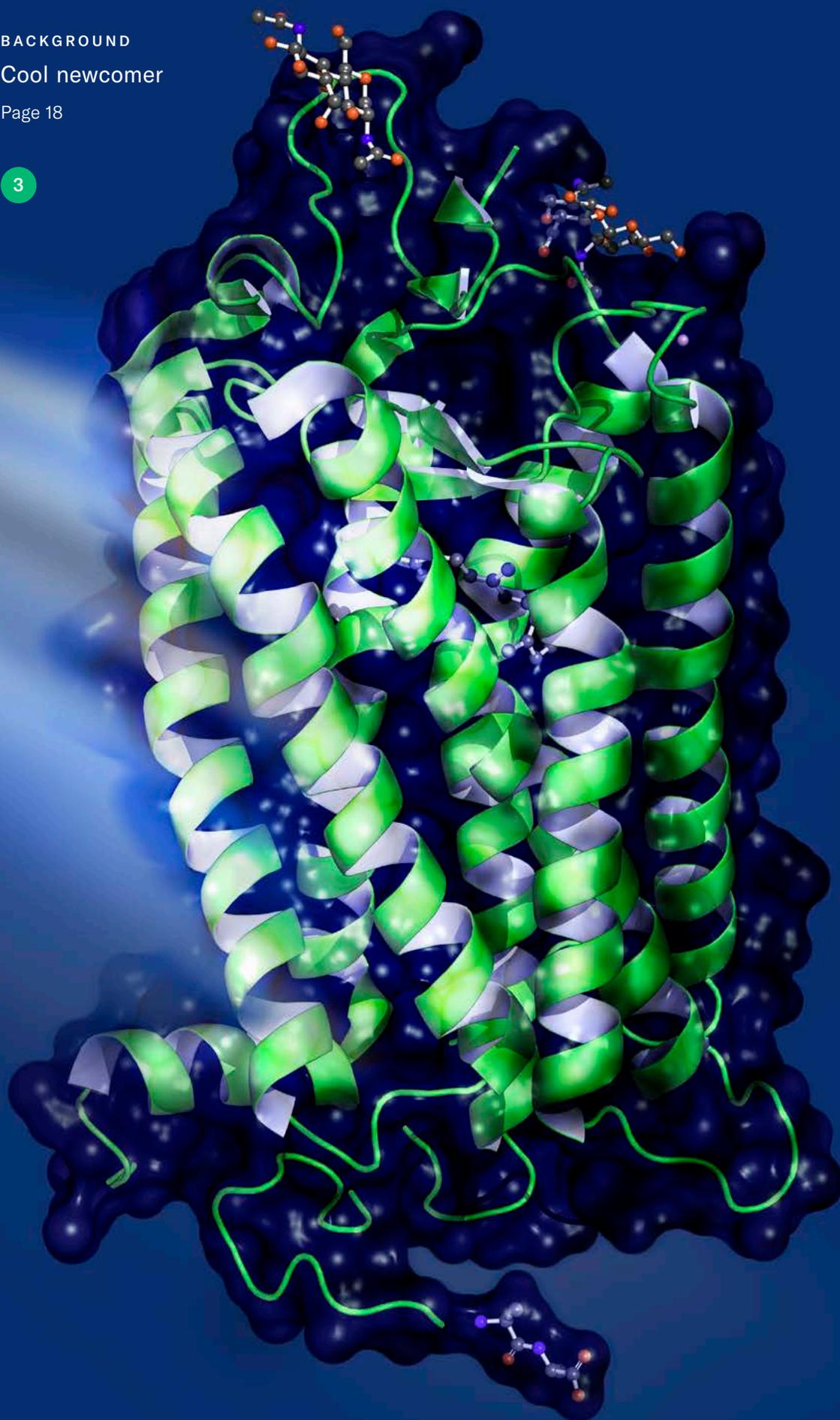
When light enters our eyes, it is registered by certain molecules in the cells of the retina. This is the starting point for vision. Yet this fascinating invention of nature can also be used to conduct very special research, because the cells can be controlled by these sensors.

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Cool newcomer

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The wondrous world of light antennas

In evolution, the development of light-sensitive proteins was a momentous step: it's only thanks to them that we can see. The large research facilities at PSI are helping scientists unravel the last major secrets concerning these extraordinary cellular components. The researchers have another goal as well: selectively switching processes in cells on and off with the help of light receptors.

Text: Brigitte Osterath



Gebhard Schertler, head of the Biology and Chemistry Division at PSI, explains what happens at the beginning of the visual process. Upon the incidence of light, the small molecule retinal in our eye changes its shape.

Without them, the entire world would always be black for us. The fact that we can look at the blue sky, read a book, or watch an action film on television we owe entirely to the photoreceptors: proteins that react to light.

Such proteins provide indispensable services to all life forms: single-celled algae, for example, use them to sense what direction it pays to swim in; plants can turn towards the sun thanks to these molecules. Many animals and humans, in turn, pick up light with highly developed organs, the eyes, and process the signals into complex impressions in the brain. Such light receptors also reset our internal clocks every day.

The principle is always the same: the proteins are integrated into the membranes – fatty envelopes around the cells – and convert light into a biological signal. The first and essential step of their activation is to flip a switch from off to on. But how exactly does the energy stored in a beam of light bring about the changes in photoreceptors that stand at the start of all further reactions? “So far, nobody has got to the bottom of this fundamental question,” explains Gebhard Schertler, head of PSI’s Biology and Chemistry Division, who has been investigating proteins of this type for more than 30 years. To solve this and other mysteries, PSI researchers are studying the structure of light-sensitive proteins and their dynamic transformations.

How a cat lands on its feet

The off-to-on switching processes that go on constantly in our eyes are incredibly fast, taking only quadrillionths of a second. To probe these lightning-like processes in depth, very special research facilities are required, such as the X-ray free-electron laser SwissFEL, which was inaugurated at the end of 2016 and is thus the newest of the large research facilities at PSI. “With SwissFEL, we are taking structural biology to the next level,” explains Jörg Standfuss, a scientist in the PSI Laboratory for Biomolecular Research. SwissFEL enables researchers to capture something like an ultra-high-resolution film of biochemical processes in order to study a process down to the last detail – no matter how fast it is. “In this way we really can fully and completely understand how these light-sensitive proteins work.”

One of the most important natural light receptors in humans and animals is the rhodopsin family. In the human eye, these proteins are part of the rod cells, the sensory cells that specialise in the perception of light and dark. Fixed in the middle of rhodopsins is a small elongated molecule: retinal, a derivative of vitamin A. When light hits retinal, the

molecule absorbs the energy and, as a result, is transformed (see illustration on the left). Retinal changes its three-dimensional shape. This in turn leads to structural changes in the protein, which now can bind to other proteins in the cell, the so-called G proteins. This sets in motion a cascade of biochemical and biophysical processes. The result might be, for example, the perception of a flash of light in the brain.

Valérie Panneels, a scientist in the PSI Laboratory for Biomolecular Research, wants to understand exactly how the structural change of the retinal takes place inside the protein. “Let’s compare retinal with a cat that falls back-first from a tree and lands on its feet. The question is: What states does the cat adopt during its fall, that is, while it is trying to right itself?” Even with cats, the process is so quick that it cannot be seen with the naked eye. All the more so in the case of retinal: intermediate states only exist for a few quadrillionths of a second.

Panneels knows that the retinal cat turns its shoulder first and then its stomach. But it’s still a big mystery why the transformation of retinal takes place so efficiently in the eye. “It’s one of the fastest and most directed reactions that occur in nature,” says Valérie Panneels. The reaction is only this efficient, however, when the molecule is bound in the protein, not if it is floating freely in solution.

So the protein exerts a strong influence on the direction of the reaction – but exactly how is not clear to science. “If this question could be answered, the construction of SwissFEL would already have been worth it,” says Standfuss. This knowledge would yield numerous new possibilities for further research and applications in medicine and biology.

Pumping instead of seeing

Evolution has also shaped light-sensitive proteins for a purpose other than seeing: they made it possible, for the first time, for living things to obtain energy from sunlight. Many bacteria and single-celled algae, for example, possess light-driven pumps in the cell membrane. These are proteins that, when exposed to light, change their shape in such a way as to transport ions – that is, small charged particles – out of the cell or into it. This enables the single-celled organisms to adjust themselves to the pH value, salinity, and other characteristics of their environment.

One such light-driven pump is bacteriorhodopsin. This protein transports protons and is found, for instance, in so-called halobacteria, a group of unicellular microorganisms that thrive in extremely salty lakes. Even though this single-celled organism



is not closely related to humans biologically, bacteriorhodopsin is not so different from human rhodopsin: it too binds retinal and changes its shape when exposed to light. It does not, however, bind to G proteins, and – despite the name it was given historically – it belongs to a different class of proteins, the microbial opsins.

In 2016, Jörg Standfuss made, for the first time, a film of the pumping process of bacteriorhodopsin. Then in 2020, his group captured the pumping process of another light-driven pump in action: the sodium pump of a marine bacterium.

“Thanks to SwissFEL, PSI is a world leader in research on rhodopsins and their structural dynamics,” says Przemyslaw Nogly, once a postdoc with Standfuss and now head of his own research group at ETH Zurich. With SwissFEL, Nogly is investigating the chloride pump halorhodopsin, which in halobacteria transports chloride ions into the cell from the outside. “We are particularly fascinated by the question of how the energy of the absorbed light is used to drive the transport of chloride,” explains Nogly. In the meantime, SwissFEL is contributing to the solution of this mystery as well.

On and off

Understanding natural light antennas advances not only basic research, but also so-called optogenetics. With this technology, researchers are trying to build light-sensitive proteins as tiny switches in animal or human cells. Processes inside the target cells could then be switched on and off simply by irradiating them with light. Hopefully this could provide the basis for a broader understanding of biological processes in our body and pave the way for new therapies.

In the early 2000s, for the first time, researchers in the USA and Europe introduced a light receptor into nerve cells in a targeted way to control their activity (see infographic on page 16). This was the channel protein channelrhodopsin from a freshwater alga. The genetic material for this channel was introduced into the nerve cells of rats so that these cells would produce the ion channel in a petri dish. The channelrhodopsin opened when irradiated with blue light and let positively charged ions flow into the cells, whereupon the cells were activated. By means of such newly introduced ion channels, nerve cells can be controlled in real time with light from the outside.

All previously developed optogenetic tools have one major disadvantage, explains Valérie Panneels: they are applicable almost exclusively in nerve cells. “We are now working on developing optogenetic proteins that can also be used in other

“We are working to develop optogenetic proteins that can be used in virtually every organ.”

Valérie Panneels, scientist in the PSI Laboratory for Biomolecular Research

cells and for other functions – in virtually every organ.” This would drastically expand the possibilities for applications of this technology.

The ideal target is the family of receptors that also includes rhodopsin: so-called G-protein-coupled receptors, GPCRs for short. They can be found in almost every cell in our body; they mediate numerous functions, from the senses of smell and taste, to regulating the heart rate, to initiating an inflammatory reaction. Therefore GPCRs are also extremely important targets for active ingredients in medicine. It is estimated that more than one-third of all currently approved drugs work by acting on this family of proteins.

Big plans

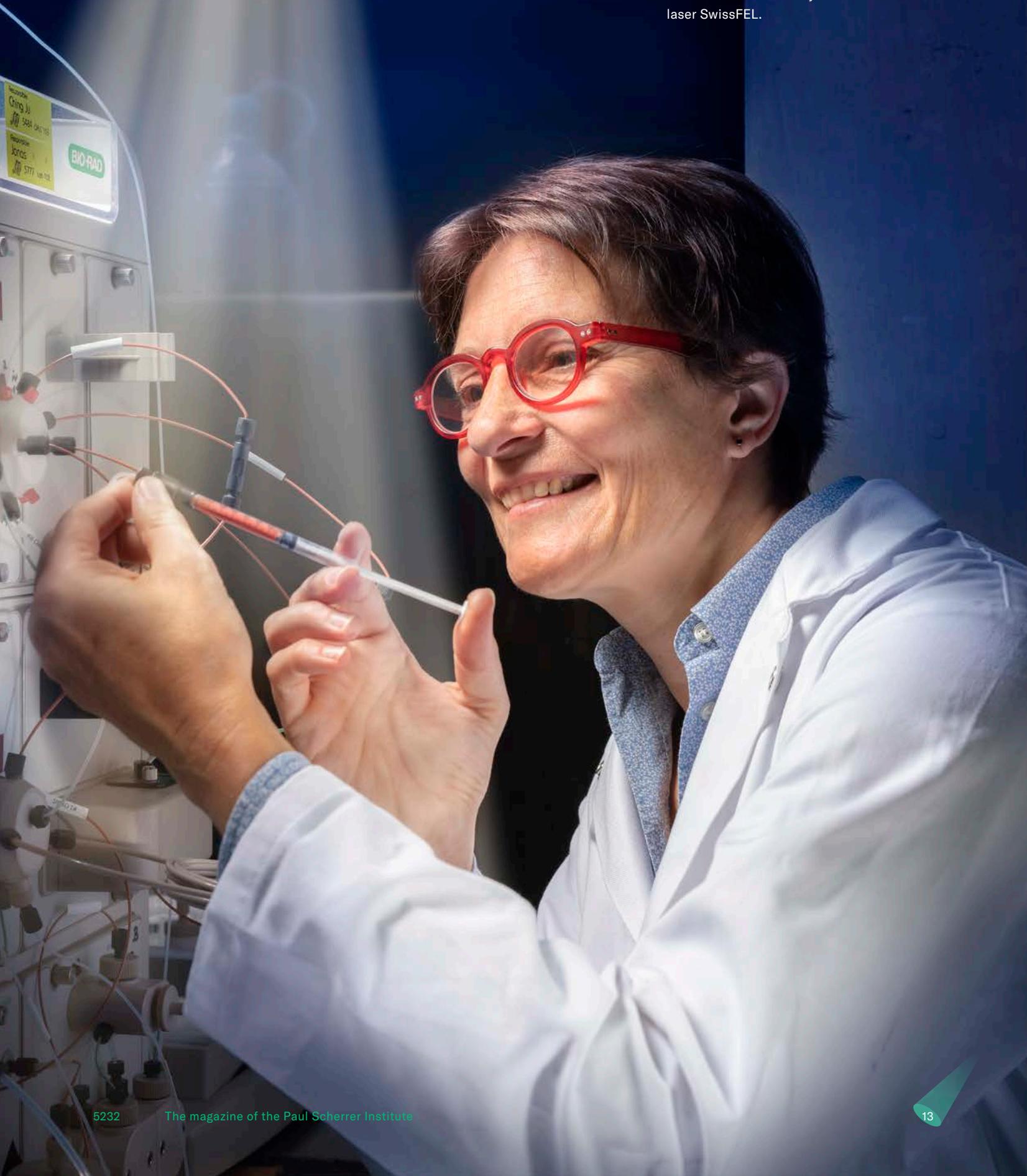
In the coming years Gebhard Schertler, working as part of a Swiss-European research team, wants to lay the foundations for developing light-controllable switches that can be used universally (see infographic on page 16). The consortium includes Peter Hegemann from the Humboldt University in Berlin, Sonja Kleinlogel from the University of Bern, and Rob Lucas from the University of Manchester in the United Kingdom.

The team wants to create so-called chimeric proteins, which are made up of two parts: a light-sensitive head that can be switched on and off by light, and a body that, when activated, switches on a very specific process in the cell.

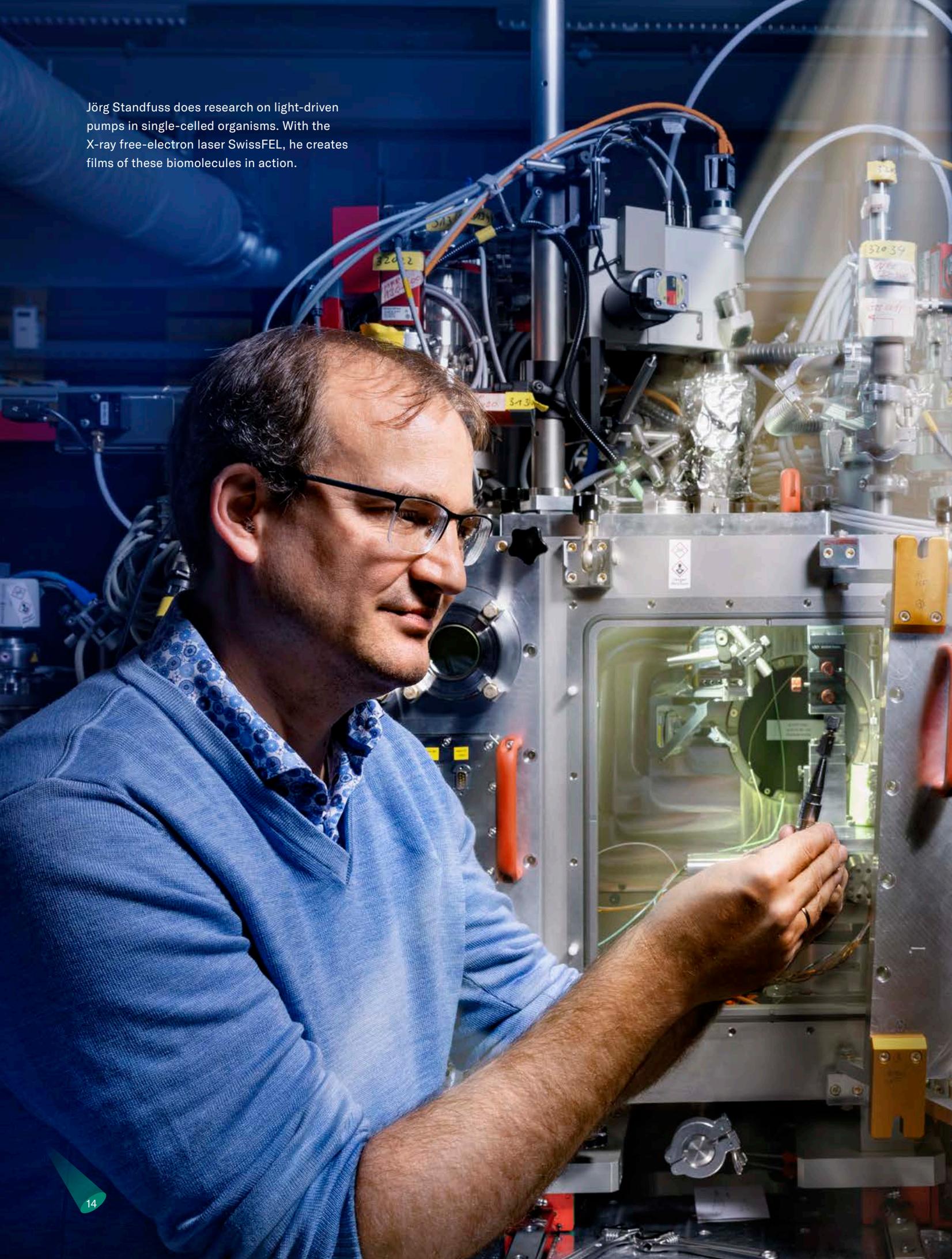
However, rhodopsin from vertebrates, including humans, is not suitable for tiny switches like this, explains Gebhard Schertler. “Every time a rhodopsin is activated in the human eye, the bond between protein and retinal is broken. To make the receptor sensitive to light again, it must first be regenerated.” This occurs within a single layer of cells in the retina, the retinal pigment epithelium. There the protein is reunited with a retinal molecule to form a functional light receptor. “Our light receptors can only be used once and then have to be regenerated in an elaborate process – it’s quite a complicated system.”

In the light receptors of cephalopods, insects and many other invertebrates, however, the retinal

Valérie Panneels is purifying the red, light-sensitive protein rhodopsin for later examination at the X-ray free-electron laser SwissFEL.



Jörg Standfuss does research on light-driven pumps in single-celled organisms. With the X-ray free-electron laser SwissFEL, he creates films of these biomolecules in action.



remains permanently bound to the protein. By absorbing a second light beam, the receptor converts itself back to its original state – and can then receive the next light beam right away. Rhodopsins of this type – termed bistable – can be switched on and off again and again. If the protein could then be modified in such a way that it is switched on with a blue light and switched off with a red light, for example, it would provide the ideal switch.

The secret of the jumping spider

Up until now, bistable light receptors have received little attention from science, but they are the focus of this research project. The bistable rhodopsin from the jumping spider *Hasarius adansoni*, which reacts to the colour green, has proven to be a particularly promising candidate for the laboratory work. The spider, which is only six millimetres in size, is commonly found in greenhouses all over the world. Of its eight eyes, two large ones point straight ahead. Four superimposed retinal levels in the front eyes allow the spider to precisely pinpoint the location of prey, to within a few millimetres, and to catch it while jumping.

“In contrast to many other rhodopsins, the jumping spider’s rhodopsin is stable and easy to crystallise and manipulate,” says Schertler. The researchers hope this protein will spur on the search for light-controlled molecular switches. Looking long-term, scientists consider light-sensitive human melanopsin to be particularly well suited. It regulates our day-night rhythm in special nerve cells in the eye, and it too is bistable. However, no one has yet succeeded in deciphering the structure of melanopsin because it is too unstable in laboratory vessels.

Light in sight

Sonja Kleinlogel of the University of Bern has already produced a chimeric bistable optogenetic protein: the head consists of the light antenna of melanopsin, and the body consists of a receptor found in the bipolar cells of the eye. These play an important role in relaying the signal from the retina to the brain. Using an optogenetics-based gene therapy on blind mice, the scientist managed to restore a large part of their eyesight. However, she constructed her optogenetic protein mainly through trial and error. Thus her method is not currently transferable to other receptors.

“We have to find out why Sonja Kleinlogel’s construct works,” says Gebhard Schertler. “And we ourselves need to acquire the knowledge of how we can modify proteins so that they do what we

want.” Using the Swiss Light Source SLS, SwissFEL, and cryo-electron microscopy (see article “Cool Newcomer” starting on page 18), the researchers want to investigate bistable light receptors and their mechanisms in the cell. Then, on the basis of these findings, they hope to develop additional prototypes for optogenetic tools.

The potential is enormous: such light-controllable switches could be used, for example, to probe higher brain functions. “Classic optogenetics changes the ion balance in nerve cells – we, on the other hand, could activate signal cascades in the brain, which is something completely new,” explains Schertler. The technology could one day enable better understanding of mental disorders such as depression and schizophrenia, and perhaps even facilitate the development of new drugs for these diseases.

If G-protein-coupled receptors in the body can be selectively switched on and off, this would also reveal which specific functions a particular receptor has. In drug development, the new technology could be used to check which receptors mediate the effect of a new active ingredient. Notably, this could minimise side-effects.

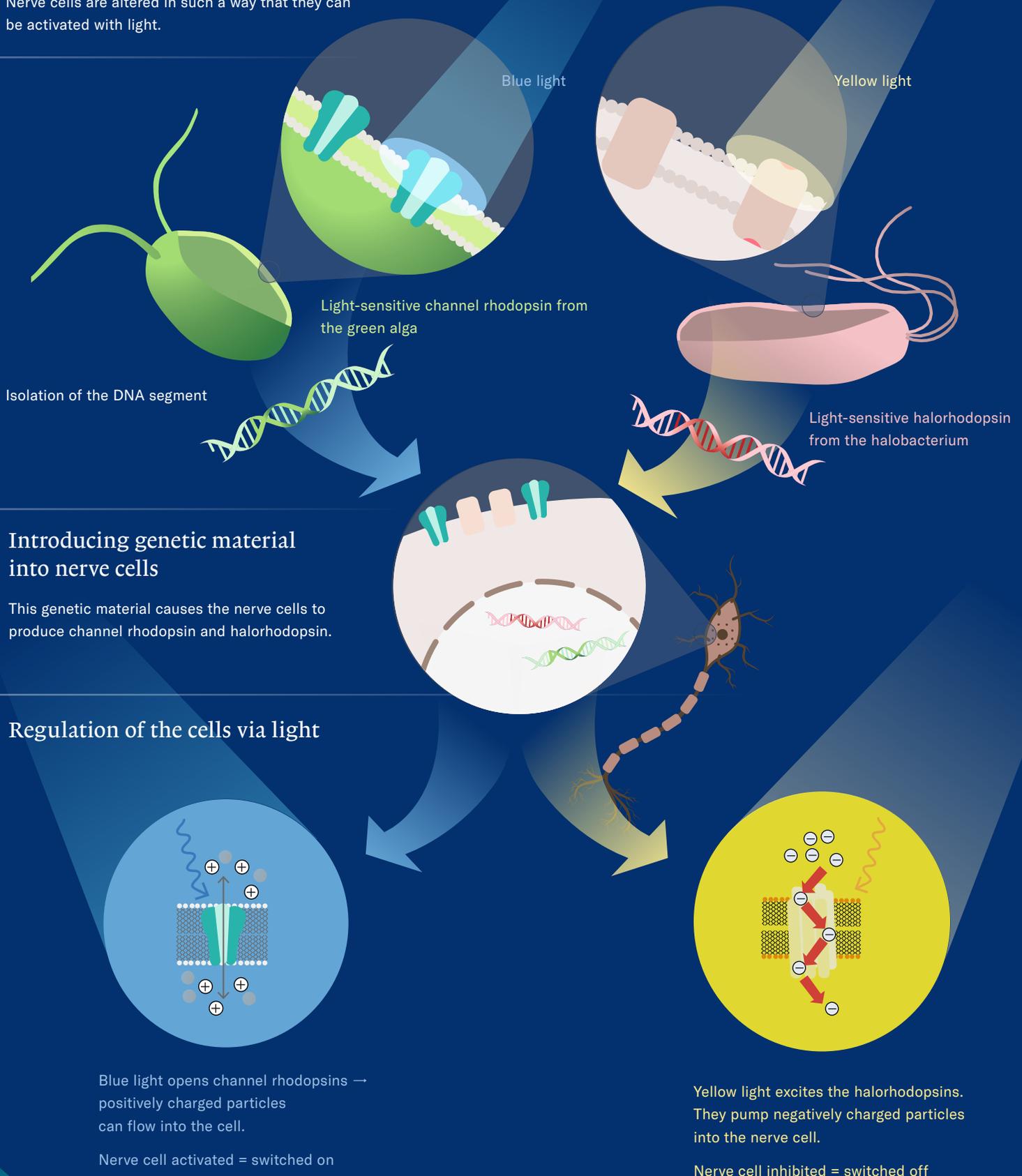
The development of new light-controlled molecular switches is highly valued by the European Research Council (ERC): in 2020 it awarded a grant of 10 million euros to the European joint project of Gebhard Schertler and his team.

Once the foundations have been laid, this technology will conquer the world of science, Schertler firmly believes. “We are still quite a long way from a toolbox of the kind that already exists for classic optogenetics. But in a few years we will be able to solve a lot of mysteries – and I think hundreds of laboratories will start using such universal light-sensitive GPCR switches.” ♦

Controlling cells with light

Classical optogenetics

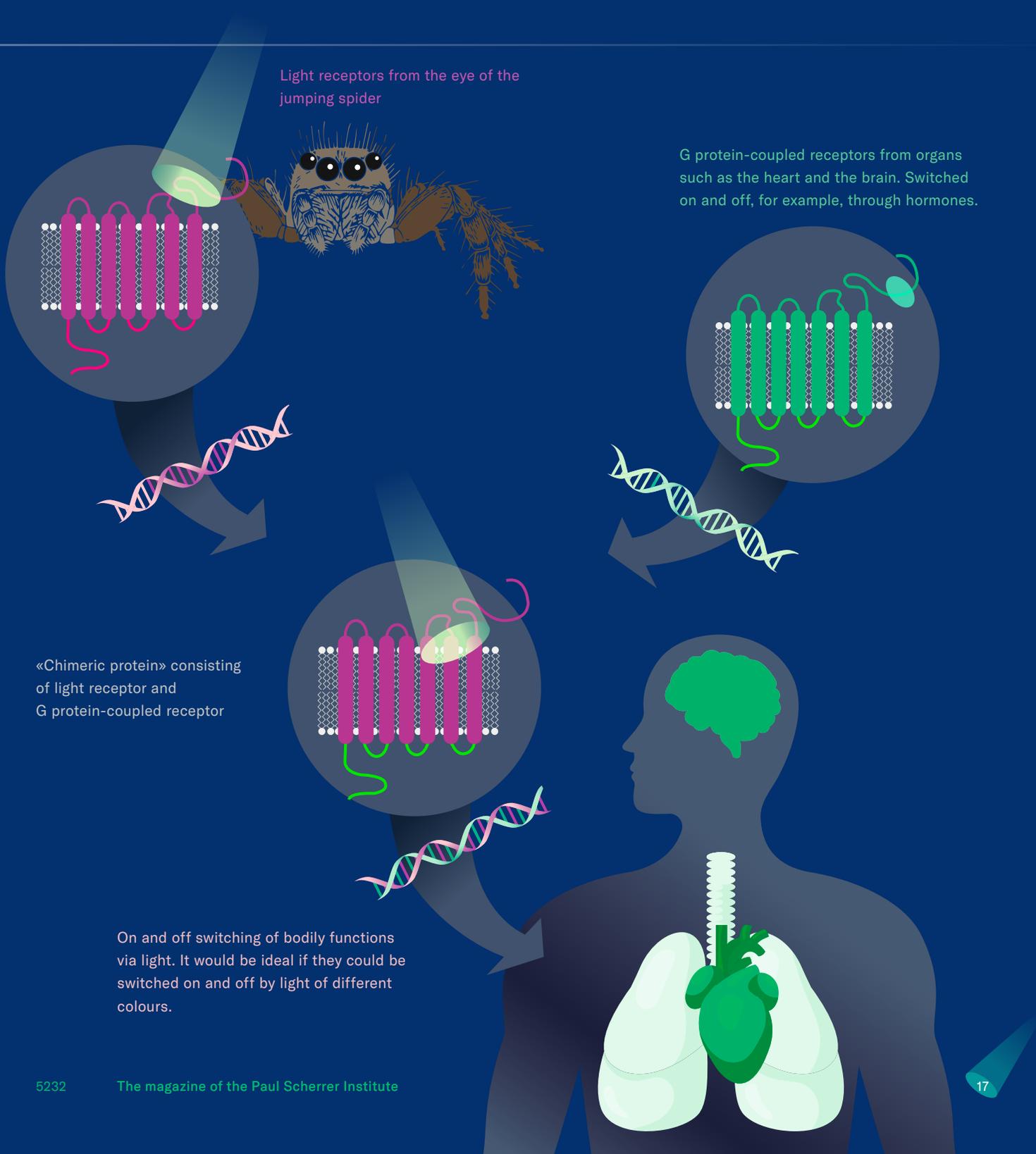
Nerve cells are altered in such a way that they can be activated with light.



With optogenetics, cells can be switched on or off with light. Classically these are nerve cells in the brain. New research, with PSI participation, aims to make this technology applicable to all types of cells in the body.

Novel optogenetics

Here, light receptors are to be combined with receptor proteins. In this way all types of cells in the body would be controllable.



Light receptors from the eye of the jumping spider

G protein-coupled receptors from organs such as the heart and the brain. Switched on and off, for example, through hormones.

«Chimeric protein» consisting of light receptor and G protein-coupled receptor

On and off switching of bodily functions via light. It would be ideal if they could be switched on and off by light of different colours.

Cool newcomer

Cryo-electron microscopy is still a comparatively new method for elucidating the three-dimensional structure of biomolecules. It can help researchers resolve many open questions about light-sensitive proteins, rapidly and with high precision.

Text: Brigitte Osterath

Scientist Emiliya Poghosyan is an expert in cryo-electron microscopy at PSI. Here she is pushing a sample – cooled with liquid nitrogen – into an apparatus as tall as a person.



Biophysicist Emiliya Poghosyan grips a tiny object with a pair of tweezers and holds it up to the light. A closer look reveals it to be a circular copper lattice, only three millimetres in diameter. These specimen holders, known as grids, are essential tools for all scientists who, like Poghosyan, use electron microscopy for their research. “We deposit our sample on the small grids – although in the end the sample layer may be no more than 100 nanometres thick,” Poghosyan explains. That is around five-hundredths the thickness of a human hair. Only in this way is it possible to capture and study individual molecules such as proteins under the microscope.

“It’s fascinating how rapidly electron microscopy has developed in recent years,” says Emiliya Poghosyan, a scientist in the Laboratory for Nanoscale Biology, who is responsible for the electron microscopy instruments at PSI.

Basically, an electron microscope works like an ordinary light microscope; instead of using normal light, however, the objects to be examined are irradiated with electrons in a vacuum, thus achieving a resolution that is 2,000 times higher than with the best light microscope, allowing much smaller objects to be examined.

“The resolution is now so powerful that we can use this method to determine the three-dimensional structure of proteins and other biomolecules.” The advances that have made this possible include a new generation of detectors that register electrons directly and analysis methods that compare the recordings of millions of molecules in a sample and, as it were, average them. This yields images with an improved signal-to-noise ratio, from which sharply defined molecular structures can then be determined. The so-called “resolution revolution” began less than ten years ago.

For biological samples, the breakthrough came with cryo-electron microscopy, the scientist explains. The samples are plunge-frozen before measurement. The cold protects the sensitive samples from damage that would inevitably be caused by the impact of the fast electrons. “Com-

pared to measurements at room temperature, we can shoot around a hundred times as many electrons at the sample before it is destroyed,” says Poghosyan. “And every additional electron increases the signal and the amount of information that we get during the measurement.”

No ice crystals allowed

Emiliya Poghosyan clamps the tweezers with the copper grid into an elongated device, the vitrobot. She applies a tiny drop of her sample solution through a circular opening on the side of the apparatus. Two parts of the device that look like headphones then close around the grid. “They remove excess water from the sample,” explains Poghosyan.

Then comes the temperature shock: the tweezers immerse the coated grid in a container with a liquid at a temperature of -196 degrees Celsius. This is ethane, cooled with liquid nitrogen. The sample freezes in a fraction of a second. “It is important for this to happen especially rapidly, because otherwise ice crystals can form and destroy the sample,” the scientist explains.

Electrons cannot penetrate thick ice crystals, so such areas would later appear black in the image – this part of the picture is then ruined. If, on the other hand, water is cooled very quickly, it solidifies without crystallising. The result is vitreous water which, like a liquid, exhibits a disordered molecular structure and will be penetrated by the electron beams.

The goal is for the sample molecules to be evenly distributed in the holes in the grid, surrounded by a layer of glass-like ice that is as thin as possible. For this, the sample films may not be thicker than the biomolecules themselves. “The preparation of the sample grids is a science in itself,” says the biophysicist. “There is no general-purpose recipe. You just have to keep trying new conditions until you have found the ideal one for a particular molecule.”

The developers of cryo-electron microscopy, Swiss chemist Jacques Dubochet as well as Joachim Frank and Richard Henderson, were awarded the Nobel Prize in Chemistry in 2017 for their work. It was Dubochet who discovered the trick with the crystal-free water.

The ‘Aha’ effect comes later

With nitrogen cooling and a suitable amount of water vapour, Emiliya Poghosyan transfers her grid to the chilled mount of the electron microscope and pushes it into the larger than man-sized device. Then she diligently pours in liquid nitrogen. “You need patience when you work with cryo-electron

“It’s fascinating how rapidly electron microscopy has developed.”

Emiliya Poghosyan, a biophysicist in the Laboratory for Nanoscale Biology at PSI

microscopy,” she says with a laugh. “If you don’t wait until all the equipment has cooled down sufficiently, the sample will be destroyed and all the work will have been in vain.”

Finally, in the room next door, she can look at her sample on the monitor and take pictures. One individual image is not very impressive: basically, you only see a lot of small greyish spots on a light background. These spots are the protein molecules.

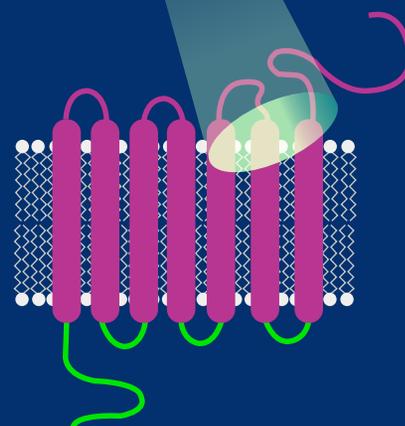
The ‘Aha’ effect comes with the subsequent data analysis: millions of molecules are averaged from a few thousand recordings. In this way, the protein is captured from all sides, since ideally a sample contains millions of molecules in many different orientations. Putting all this information together creates a three-dimensional model of the protein that is remarkably accurate. “It’s amazing how such precise 3D models can be created from these images,” says Emiliya Poghosyan.

A path to success even without a crystal

“Electron microscopy has revolutionised the way we get structural information from proteins,” says Jacopo Marino, a biologist in the PSI Laboratory for Biomolecular Research. “The whole process is advancing very rapidly.”

A few years ago, a team at PSI including Jacopo Marino solved the structure of a complex consisting of the light receptor rhodopsin and a G protein – proteins in the retina that enable us to see. Knowing how the receptor docks with the G protein provides clues as to how signal transmission works in the cell and how this process can be manipulated under certain circumstances (see infographic page 16). With cryo-electron microscopy, the structure was solved within four months. And even that is still relatively long. “With proteins that are biochemically easy to manipulate, we can even have the structure in our hands within a few days.”

The complex, which consists of several proteins is very flexible – a fact that stood in the way of X-ray crystallography. This flexibility means that obtaining crystals of the complex, essential for X-ray crystallography is extremely difficult, and couldn’t be obtained even with years of effort.



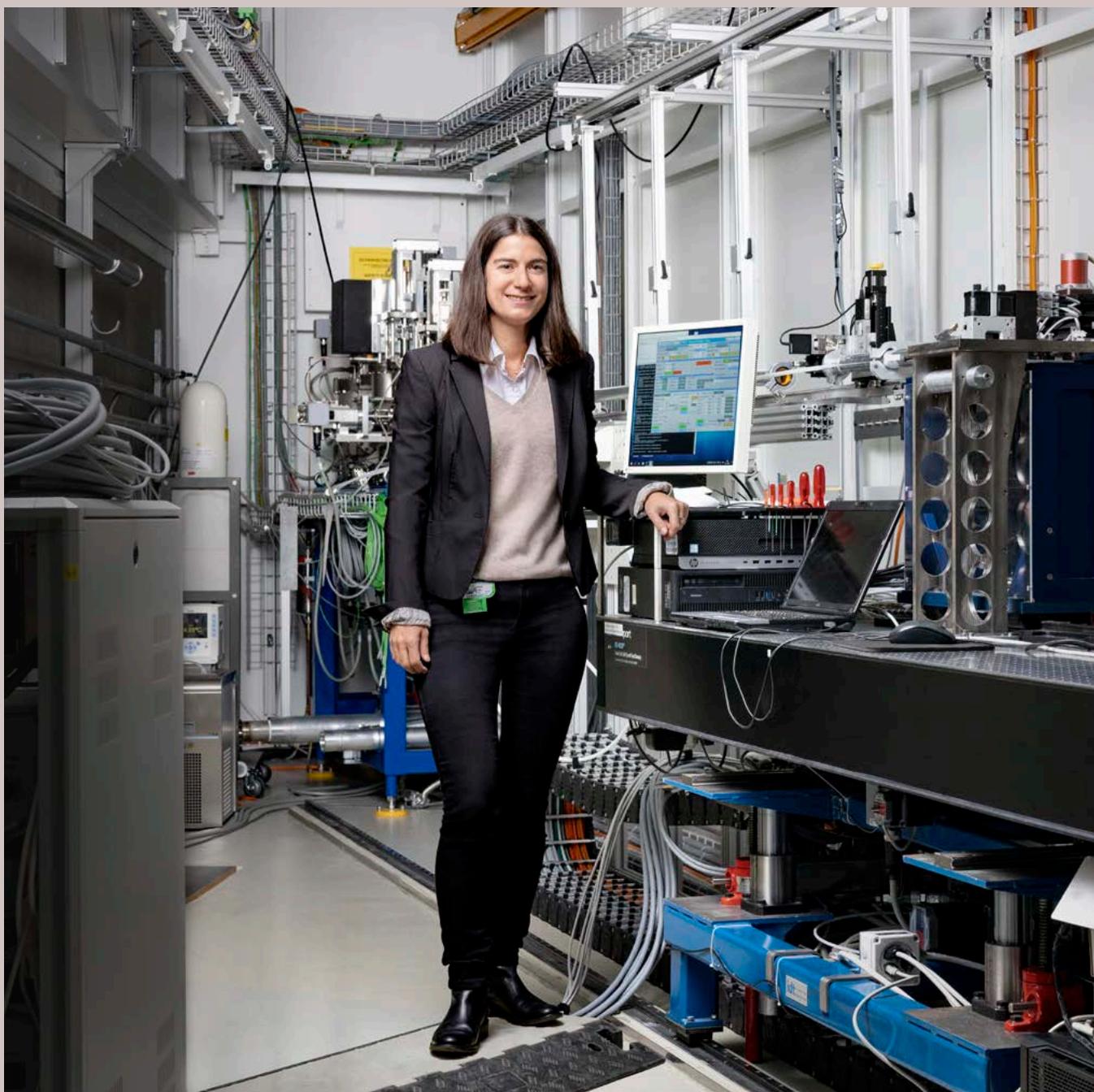
Currently, it is not possible to examine very small biomolecules with cryo-electron microscopy, says Emiliya Poghosyan. For instance, the structure of the protein rhodopsin alone cannot be deciphered in this way. In addition, the resolution is still marginally better in X-ray crystallography.

Complement, not replacement

Cryo-electron microscopy has enabled enormous progress in the investigation of membrane proteins such as receptors, which are naturally embedded in a cell membrane and are difficult to isolate in a pure form, let alone to make or to crystallise. One of the first proteins that Nobel Prize winner Richard Henderson worked with was bacteriorhodopsin, a membrane protein found in the cell wall of certain bacteria. Currently, Jacopo Marino is using this method to take a close look at an ion channel that plays a major role in signal transmission during the visual process.

Even very small amounts of protein are sufficient for cryo-electron microscopy. This makes the work easier and shortens the time it takes, especially with molecules that have to be laboriously isolated from tissues and cells. Also, the researchers don’t have to ensure their samples are meticulously clean.

However, cryo-electron microscopy will not replace the X-ray crystallography at SLS and SwissFEL. “The two are not in competition with each other,” emphasises Marino. “They complement each other. Both have their strengths, and their limitations.” ♦



Inside the heart

Anne Bonnin is a physicist at the Swiss Light Source SLS. With synchrotron light, she can non-destructively render the inner structure of objects visible in extremely high resolution, down to a few micrometres. The interaction between synchrotron light and the object rotating in the beam makes it possible to produce a digital 3D image or sectional images. With this so-called microtomography method, she analyses, among other things, tissue samples from the heart. By doing so she is tracking down the causes of heart failure and cardiovascular diseases, a prerequisite for better treatments and even personalised therapies.

Rescuing Earth's icy memory

Glacier ice holds valuable information about our planet's past. But as the glaciers melt in the course of climate change, this archive is disappearing. An international research team with PSI participation is rushing to preserve this scientific treasure for posterity.

Text: Brigitte Osterath



With this ice core, PSI researcher Margit Schwikowski also holds in her hands a piece of knowledge about our planet's past.



A race against time – this figure of speech perfectly describes the efforts of Margit Schwikowski and her team. The more inexorably climate change advances, the faster the glaciers shrink. Vanishing with them is the archive that has been accumulating inside them for many thousands of years: gases and particles locked in the depths of the ice layers. They reveal how the atmosphere was composed at the time the ice was deposited and allow conclusions to be drawn about past events. How warm was it in a particular time period? When did forest fires occur? Which plants did people cultivate in those days?

“We can look back 10,000 years, sometimes even more,” explains Schwikowski, head of the Laboratory for Environmental Chemistry at PSI. She is a member of the board of the international foundation Ice Memory. Its mission is to extract ice cores from selected glaciers worldwide and store them safely in Antarctica, as rapidly as possible: “We feel a certain pressure, because it is clear to us all what’s happening to these glaciers,” the chemist says. “We urgently need to act to prevent the valuable information they contain from being lost forever.”

Already today, analyses of glacier ice are yielding unique insights into past environmental conditions. But analytical methods are constantly advancing. In the future, researchers will surely be able to coax many more secrets from the ice – if it is still available to them. Ice Memory aims to ensure that it will be.

In addition to PSI, participating institutions, which are also founding members of the international foundation, include the Université Grenoble Alpes, Ca’ Foscari University of Venice, the French National Institute for Sustainable Development (IRD), the French National Centre for Scientific Research (CNRS), the National Research Council of Italy (CNR), and the French Polar Institute Paul-Émile Victor (IPEV). Ice Memory is supported by UNESCO, the United Nations Educational, Scientific and Cultural Organization.

Between altitude sickness and crevasses

The initiative was launched in 2015. It was logical that Margit Schwikowski should be asked to help establish the archive for ice cores: research on high mountain glaciers has been her specialty since 1992. “We are among the few research groups in the world that drill glaciers for ice cores,” she says. This is no easy task, and requires a lot of experience. “Every glacier and therefore every borehole is different.”

The expeditions to the glaciers, situated several thousand metres high, typically last a good week and are not without their dangers, adds Theo Jenk,

“It is clear to us all what’s happening to these glaciers.”

Margit Schwikowski, head of the Laboratory for Environmental Chemistry at PSI

a researcher at the PSI Laboratory for Environmental Chemistry and leader of the latest Ice Memory expedition. “The air is thin, and there’s always the risk of suffering from altitude sickness. We need to make sure we’re able to take sick members down again quickly in case of an emergency.”

Altitude sickness, which can occur during stays at 2,500 metres or higher, manifests itself in headaches, confusion, and hallucinations; it can also lead to life-threatening pulmonary or cerebral oedema.

Hidden crevasses are another danger that goes with the territory when researchers are working in the mountains. In many places the team doesn’t move without being secured by ropes and climbing harnesses.

The modular, two and a half metre-long ice-core drill with which the team gradually works its way down to bedrock under the glacier – often more than a hundred metres – is custom-made, developed and built by the company icedrill.ch in Biel, Switzerland. With the help of a winch – from which the drill is suspended by a cable and thus is controlled and supplied with electricity – the researchers pull 70-centimetre-long drill cores up from the depths, piece by piece.

“The work days up there are long,” explains Theo Jenk. “We also work at night sometimes if it is too warm during the day.” With too much exposure to the sun, the sensitive ice cores could be damaged through melting. There is also the danger that melt water will form on the drill, which then could freeze fast and get stuck in the borehole. To keep the arduously extracted cores cold enough, the researchers take insulation boxes up the mountain with them and bury them in the snow. The “cold chain” has to be maintained – using dry ice or refrigerated trucks if necessary – until the ice cores can be secured in cold storage.

Success at Colle Gnifetti

Last year the researchers managed to extract an ice core more than 80 metres long from a glacier in the Pennine Alps – to be precise, from the glacier saddle of Colle Gnifetti on the Monte Rosa massif at an elevation of 4,500 metres. For Ice Memory,

IN SWITZERLAND



obtaining a core like this was at the top of the list. “Here we have the highest glaciers in Europe, and these contain a lot of valuable information,” says Theo Jenk.

So many freshwater sources are fed by the alpine glaciers, some call Switzerland the *Wasserschloss* or “moated castle” of Europe. That makes it all the more important to know how the glaciers are likely to develop in the future – and to have samples in hand that will allow comparisons with the past.

Besides Colle Gnifetti, the Ice Memory team is already protecting ice cores extracted from the Illimani glacier in the Bolivian Andes, from Belucha in Siberia, from Elbrus in the Caucasus, and from Col du Dôme on Mont Blanc in France (see map).

An especially worthy target to pursue next would be Kilimanjaro in Tanzania, the site of the only remaining glacier archive in Africa. According to Schwikowski, though, it is taking a long time to get authorisation from the Tanzanian government. Also on the wish list are Mount Logan in Canada, various glaciers on the Tibetan Plateau, and the Fedchenko glacier in Central Asia.

Two years too late

In 2020, a team from Ice Memory was under way on a major expedition in the Pennine Alps – in this case, on the Grand Combin massif at an altitude of 4,100 metres. Test drilling in 2018 had identified the area as a suitable site.

Two years later, however, when the researchers returned fully equipped for drilling, they hit a snag: after only half a metre, they encountered a hard layer of ice, and at 25 metres the drill got stuck for good. The reason: freeze-thaw cycles had produced melt water in the glacier’s collecting basin. Evidently it had been so warm between 2018 and 2020 that a large quantity of melt water had been able to penetrate far into the depths. Even if an ice

core could have been extracted, it would have been useless for climate science. “We were totally shocked,” Schwikowski says, “because it became clear that for this glacier, we were already too late.”

According to the United Nations, almost all glaciers on Earth are shrinking – and with increasing speed. An international research team, with the participation of ETH Zurich and the Swiss Federal Institute for Forest, Snow and Landscape Research WSL, recently found that glaciers worldwide had lost 227 billion tonnes of ice annually between 2000 and 2004 – between 2015 and 2019 the average was 298 billion tonnes per year. The study reports that the fastest melting glaciers include those in Alaska, Iceland, and the Alps.

Safe at the South Pole

At each site, the researchers take at least two ice cores. One of them serves as a reference and is, among other things, analysed at PSI; the data are made publicly accessible.

The second core is meant to be stored in an ice grotto in Antarctica, where no electricity is required to keep things cold. Another advantage that justifies the long-distance transport to the South Pole: this part of Earth is politically neutral ground and under the terms of the Antarctic Treaty is reserved exclusively for peaceful use, especially scientific research.

Currently, experiments are under way to determine how best to set up the repository. What is planned is a kind of ice cave that should provide a safe home for the ice cores, so they won’t meet the same fate as the glaciers from which they come. For Antarctica, at least, deglaciation is not expected to occur within the next hundred years. ♦

Latest PSI research news

1 Protons against lung cancer

In November 2021, a 60-year-old patient with a lung tumour was irradiated with protons at the Centre for Proton Therapy in Switzerland. This is the first time in Switzerland that this type of radiation has been used to treat lung cancer. The seven-week course of therapy is part of an international study. PSI is taking part in the study together with the Radiooncology Centre of the Aarau and Baden cantonal hospitals – as the only participating institutions outside the USA. The study is comparing the treatment success of conventional radiation therapy with that of proton therapy for non-small cell bronchial carcinoma – the most common form of lung cancer – at an advanced, inoperable stage. This use of proton irradiation to treat a patient with lung cancer opens the next chapter in proton therapy at PSI.

Further information:
<http://psi.ch/en/node/48039>

25 years ago, the spot scanning technique in proton therapy was first used at PSI.

62 years old was the age of the world's first patient to be given this treatment at PSI.

2,000 patients, approximately, have received this therapy at PSI to date.



2 New active agent against parasites

Researchers at PSI have identified a chemical compound that is considered suitable for use as a drug against several single-celled parasites. These include the pathogens that cause malaria and toxoplasmosis – infectious diseases that affect many millions of people every year. The point of attack for this promising substance is the protein tubulin, which helps cells to divide and therefore is also essential for the parasites to multiply. “If this protein doesn’t work the way it should, it hits the parasite hard,” says PSI researcher Ashwani Sharma. PSI’s cooperation partners from the University of California, Irvine tested the new compound – called parabulin – on the toxoplasmosis pathogen in human cells. The pathogen almost completely lost its ability to reproduce. In contrast, human cells were virtually unaffected by parabulin – the best prerequisite for the development of a drug.

Further information:
<http://psi.ch/en/node/45951>

3 1,000 tomographic images per second

Computed tomography is familiar from medicine. This 3D imaging technique is more generally useful, however, for the non-destructive analysis of materials. When CT reaches microscopic resolution, it is called tomography. With the intense X-ray light from a synchrotron source, it is possible to obtain many tomographic images per second.

A team from the Helmholtz-Zentrum Berlin and researchers at the Swiss Light Source SLS at PSI have achieved a new world record: It is now possible to capture 1,000 tomographic images per second. These images have a spatial resolution of a few micrometres, the field of view is several square millimetres, and a continuous recording time of a few minutes is feasible.

This technology is of interest for material analysis, quality testing, and the development of new functional materials.

Further information:
<http://psi.ch/en/node/47742>

4 CO₂ as a valuable resource

In a new study, PSI researchers show that so-called carbon dioxide electrolysis can be profitable and can also contribute to climate protection. In this process, carbon dioxide (CO₂) is captured from the atmosphere or at the point where it is produced, for example in industrial manufacturing. Subsequent conversion using an electrolysis cell then makes this usable for the chemical industry. The CO₂ is converted to either carbon monoxide or formic acid. According to the study, the production of carbon monoxide is especially promising. Assuming the technology is developed further and costs go down as expected, carbon monoxide holds the greatest potential for the economical and ecological utilisation of CO₂.

Further information:
<http://psi.ch/en/node/48403>

Sounds of science

Can you see sounds? Obviously not. Nevertheless, this Gallery attempts the seemingly impossible, building a visual bridge to the soundscape the ear perceives all around PSI. Blurred movement hints at the acoustics of one of the world's most unusual research sites. If you follow the link next to the waveform profile, you can directly hear what you are seeing.

Text: Christian Heid

Tak-tak-tak-tak-tak-tak...

What does this noise remind you of? A sewing machine? A train rolling through a rail station? The orbital shaker sits in a biology lab and is used to cultivate eukaryotic cells, human cells for example. With its up to 200 revolutions per minute, it stirs cells and a reddish nutrient fluid in a smooth circular motion. The cells virtually float in the solution and thus are optimally supplied with nutrients and oxygen. Proteins that scientists want to know more about can be selectively extracted from the cell culture. Among these: the spike protein of Sars-CoV-2.

<http://psi.ch/en/node/49387#tak>







Iiiiiihhhhhhhhhhh...

This is what you hear in the ventilation center of SwissFEL, Switzerland's X-ray free-electron laser. It's the fan that revs up to supply fresh air to the 740-metre-long building, situated in the Würenlinger forest, not far from the PSI campus. At full load, it shovels up to 16,000 cubic metres of air per hour into the building. On the way inside, the air is conditioned to 20 degrees Celsius and precisely regulated to 24 degrees Celsius in the various rooms by means of dozens of air-conditioning units, because temperature fluctuations would falsify the research results. Thus the capability to use X-rays in this large research facility to trace extremely fast processes, such as the formation of molecules, depends in part on its well-tempered fresh air.

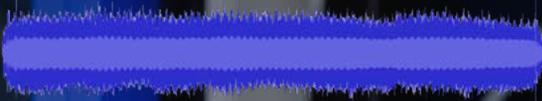
<http://psi.ch/en/node/49387#iih>



Whiiiiiiiiiiiiiiiiiiii...

Oh dear! That sounds like a dentist's drill... But in reality it is a telescopic tube that is part of a cryostat, a cooling device. The tube is extended, approaches a sample of protein crystals, and vaporises liquid nitrogen to keep the crystals chilled to their comfort temperature of minus 173,15 degrees Celsius. At this beamline the structure of proteins is investigated to improve the understanding of general biological processes and, in particular, to enable the development of new drugs. It is one of around 20 beamlines that belong to the Swiss Light Source SLS, which will be upgraded for higher performance by 2026.

<http://psi.ch/en/node/49387#whi>



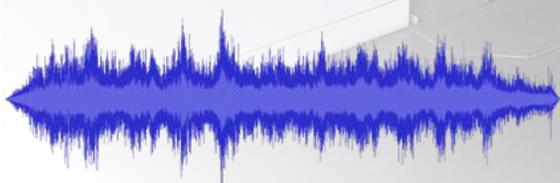


PAUL SCHERRER INSTITUT
PSI

Mmmwwwwhooooooooo wwwmm...

No doubt about it! That's a subway train that starts up slowly and comes to a halt a little later. You might think that... At least that's what we're told by patients with cancer diseases who come to PSI for treatment at the Centre for Proton Therapy (CPT). The noise is produced when the 180-tonne Gantry 2 is set in motion and a thin beam of protons precisely scans and destroys tumours inside the body. The beam only works where it's supposed to, so that healthy tissue on either side is protected. CPT has been treating cancer patients successfully for more than 25 years.

<http://psi.ch/en/node/49387#mwh>





Vvvvschschschs schschs...

Hm!? Maybe a tea kettle... or a bicycle tire that's losing air... This hissing belongs to a system where liquid nitrogen (LN₂) is transferred from a tank into smaller containers on wheels. At this filling station, the nitrogen is at a temperature of a little less than minus 196 degrees Celsius and thus is close to its boiling point. Even when the extensive operating instructions displayed on the sign next to the equipment are followed precisely, harmless amounts of nitrogen leak out, mix with the ambient air, and form a kind of ground fog. Nitrogen is frequently used where the lowest temperatures are required, for example to carry out specific experiments or to cool magnets and power lines.

<http://psi.ch/en/node/49387#vsch>





Tinkering and optimising

Fifteen years ago she set up the PSI beamline NanoXAS at the Swiss Light Source SLS. Today Iris Schmid is Head of Product Management at Selectron Systems AG, a manufacturer of automated control systems for trains. What she brought there: her penchant for optimisation.

Text: Christina Bonanati

Iris Schmid is sitting in an open-plan office, empty because of the pandemic, at Selectron Systems AG in Lyss, one of the leading manufacturers of train control systems. Colourful patterned socks are poking out of her jeans. The view out the large windows is lost in fog. After a year on the job here, the 46-year-old has become accustomed to this: “Where I live, in Bern, the sun is often shining while thick fog hangs over Lyss.” says the slender athlete. She used to be a marathon runner; today she has cut down a bit, though she still takes part in the annual Bern Grand Prix, a more than 16-kilometre run. She likes to work out in the mountains by hiking, going on climbing tours, or skiing cross-country.

Iris Schmid grew up in the Bernese Oberland. Her interest in technology and the natural sciences was awakened at an early age through her family, who ran an auto repair business, and her three brothers. As a student, she worked on the side in the chemical industry, at F. Hoffmann-La Roche. While attending a business-oriented secondary school in francophone La Neuveville, she came to a realisation: “Physics was a subject that everybody hated – except me.” And so, after passing her school-leaving exam in Neuchâtel, she studied experimental physics at the University of Basel, with a subsidiary subject that allowed her to pursue her passion for astronomy. After earning her diploma in 2001, she travelled through South America for a year, studied Spanish and Portuguese, and learned jewellery-making from local artisans. She felt most at home in the Andes of Peru and Bolivia.

Upon her return, she encountered a tough job market in Swiss industry, a result of the recession

triggered by the bursting of the dot-com bubble. She went back to the University of Basel as a doctoral candidate. With Hans Joseph Hug, who had supervised her diploma thesis – and who in the meantime had been appointed to a professorship at EMPA, the Swiss Federal Laboratories for Materials Science and Technology – she did research on interactions in hard drives: between layers that record information, in the form of magnetic polarisation of bits, and the antimagnetic layers responsible for retaining the data. The goal was to scale down the size of the bits without making them thermally unstable, thereby increasing the storage capacity of the hard drives – interesting for computer manufacturers and motivating for Schmid. She herself finds it hard to explain how she managed to successfully complete her doctoral thesis in 2006, just one year after the birth of her son: “Somehow, it all worked out.”

Not a normal “measurement postdoc”

With a fresh doctorate, Schmid took over scientific leadership of the project NanoXAS. This experimental installation of a new beamline and end station at PSI’s Swiss Light Source SLS was designed to combine atomic force microscopy with X-ray absorption spectroscopy. That would make it possible to simultaneously map the surface structure of materials and determine their chemical composition.

After ten years in Basel, Schmid and her family moved to the Aargau. In the first phase of the project, the mechanical design and construction of the new microscope were completed at EMPA, while the beamline was built at SLS.

With this successful project, the physicist proved her leadership skills early in her career. And being a good leader, Schmid is quick to share the credit: “I was surrounded by experienced technicians, designers and researchers.” Two colleagues in particular have had a strong influence on Schmid with their extensive knowledge: Professor Hug, a tinkerer par excellence, and the likewise tech-savvy Jörg Raabe, who is still head of NanoXAS today. PSI’s integrated child-care centre Kiwi was also a big help, especially after the birth of her second son in 2008: “In the morning I would drop the boys off at Kiwi on the edge of the forest before I drove to SLS on the other side of the Aare,” Schmid recalls. Working in the cavernous hall, she saw no daylight but felt at home surrounded by all that technology.

Schmid proudly recalls the festive opening ceremony for the facility in 2010, with a colourful spectacle, fog and fireworks: “A lot of important people were there, and a red ribbon was cut.”

Dare to do something new

Then she was drawn into industry, where her expert knowledge was also urgently needed. This was the case with the COMET Group, based in Flamatt in the canton of Fribourg, which designs custom X-ray tubes: for quality control of safety-critical parts such as aircraft turbines and tyres, or for the inspection of oil pipelines in Siberia at minus 50 degrees Celsius. As Head of Development, Schmid observed that “the development of new X-ray sources was difficult to plan, because the approach was very ‘experimental’ and took up to two years.” From PSI she knew another approach: to simulate and model in advance all equipment that was to be built from scratch. So she hired a new staff member and acquired the proper software. “In 90 percent of the cases it worked, and we were finished after three months,” Schmid says with a laugh.

After five years she switched to the Plasma Control Technologies department where, as the Head of Global Project and Process Management, she optimised procedures. She coordinated between colleagues in Silicon Valley, Korea and China, dealing with different time zones, mentalities and languages. But after ten years with COMET, Schmid felt it was time to look for a new challenge.

At the end of 2020 she found it, joining Selectron in Lyss, the specialist in train automation with core competences in control, network and communication technologies. In every modern train there are numerous modules that are used for monitoring and control: from braking systems to door openers to air conditioning. Everything is monitored and au-

tomatically controlled. “A really small computer is installed near the brake system, with sensors and actuators,” Schmid explains. “The yellow modules with safety-critical functions are certified and tested separately. The software must never hang or freeze. If it did, the train wouldn’t be able to brake any more!”

And once again, Schmid is ready to venture into something new. As the new Head of Product Management, she leads her team in evaluating ideas for new products, shepherding them through development, and taking responsibility for introducing new products and presenting them to customers. Here too, efficiency is the key to being able to get new products to market at the right time. “It frustrates me when things run inefficiently and people lose time unnecessarily because they’re using the wrong tools,” Schmid says. “I try to question every procedure and optimise it.” And that, evidently, is exactly what she’s capable of doing exceptionally well. Her multifaceted experience helps. Schmid stresses: “I have never become a specialist in any one area, but instead have always kept my eyes on the big picture.” From the professional working environment of PSI, too, she derived much that she can still draw from today. ♦



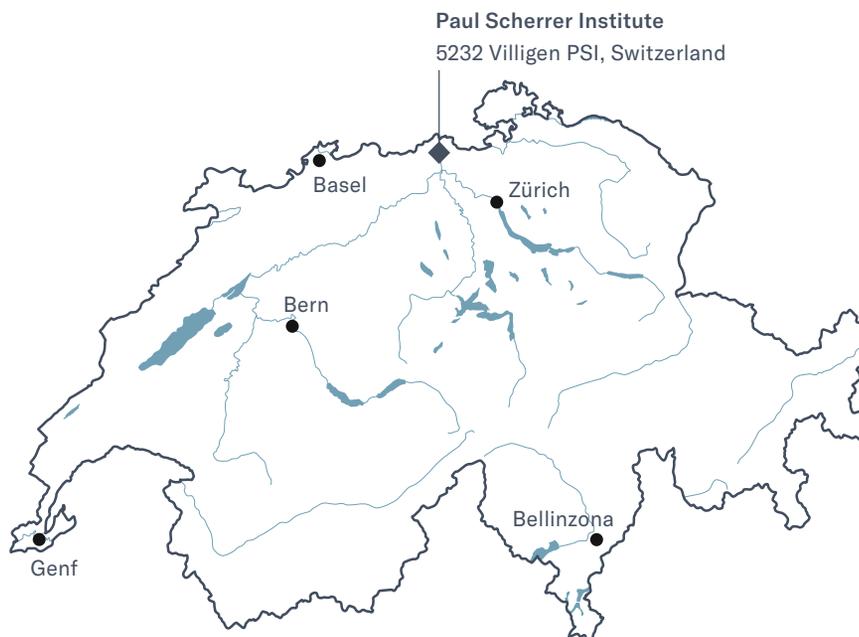


“I have always kept my eyes on the big picture.”

Iris Schmid, Head of Product Management at Selectron Systems AG

From our base in Aargau
we conduct research for Switzerland
as part of a global collaboration.





5

large research facilities that are unique in Switzerland

800

scientific articles a year based on the experiments performed at PSI's large research facilities

5,000

visits every year from scientists from across the globe who perform experiments at our large research facilities

5232 is Switzerland's prime address for experiments on large research facilities. The Paul Scherrer Institute PSI even has its own postcode, a distinction that seems justified for an institute that extends over 342,000 square metres, has its own bridge across the River Aare, and has around 2,100 employees – more people than in most of the surrounding villages.

PSI is situated on both banks of the River Aare in the canton of Aargau, in the municipal areas of Villigen and Würenlingen. Its main areas of research are in the natural sciences and engineering. Funded by the federal government, it belongs to the domain of the Swiss Federal Institute of Technology (ETH Domain), which also includes ETH Zurich, EPFL Lausanne, and the research institutes Eawag (Swiss Federal Institute of Aquatic Science and Technology), Empa (Swiss Federal Laboratories for Materials Science and Technology) and WSL (Swiss Federal Institute for Forest, Snow, and Landscape Research).

Complex large research facilities

Switzerland's federal government has given PSI the mandate to develop, build, and operate large, complex research fa-

cilities. These are the only such facilities within Switzerland, and some are the only ones in the world.

Running experiments at our large research facilities enables many scientists from the most diverse disciplines to gain fundamental insights for their work. The construction and operation of these kinds of facilities involve so much time, effort, and cost that comparable measurement equipment is not available to academic and industrial research groups at their own institutions. That is why we keep our facilities open to all researchers worldwide.

To obtain a time slot to use the experimental stations, however, both Swiss and foreign scientists first have to apply to PSI. Selection committees comprising experts from all over the world assess the scientific quality of these applications and recommend to PSI which candidates should be given measurement time. Even though there are around 40 measuring stations where experiments can be carried out at the same time, there is never enough capacity for all of the proposals submitted – around one-half to two thirds have to be rejected.

Around 1,900 experiments are performed every year at PSI's large research facilities. Time slots are free of charge

for all researchers working in academia. In a special process, users from private industry can buy time to carry out proprietary research and use the PSI facilities for their own applied research. For this, PSI offers special research and development services.

PSI operates five large research facilities in total where the internal processes of materials, biomolecules, and technical devices can be explored on the nanometre scale. Here scientists use different beams to “illuminate” the samples they want to investigate in their experiments. The beams available for this range from particles (neutrons or muons) to intense X-ray light from a synchrotron or X-ray laser source. The different types of beams allow a wide variety of material properties to be studied at PSI. The high complexity and cost of the facilities is due to the massive size of the accelerators needed to generate the different beams.

Three main areas of research

However, PSI not only acts as a service provider for researchers, but also carries out an ambitious research programme of its own. The findings produced by PSI scientists help us to understand the world better, and also lay the foundation for developing new types of equipment and medical treatments.

At the same time, our own research is an important prerequisite for the success of our user service programme for the large research facilities. Only researchers personally involved in current scientific developments in the fields external researchers are working in can support them in their investigations and further refine the facilities to ensure they continue to meet the needs of cutting-edge research in the future.

PSI has three main areas of research. In the area of Matter and Materials, scientists study the internal structure of different materials. These results contribute towards a better understanding of processes occurring in nature and provide starting points in the development of new materials for technical and medical applications.

In the Energy and Environment area, activities focus on the development of

new technologies to facilitate the creation of a sustainable and secure supply of energy, as well as an uncontaminated environment.

In the Human Health area, researchers search for the causes of illnesses and explore potential treatment methods. Their fundamental research activities also include the elucidation of generic processes in living organisms. In addition to research activities, PSI operates Switzerland’s sole facility for the treatment of specific malignant tumours using protons. This particularly sensitive procedure allows tumours to be destroyed in a targeted manner, leaving the surrounding tissue largely undamaged.

The brains behind the machines

The work at PSI’s large research facilities is challenging. Our researchers, engineers, and professionals are highly specialised experts. It is important for us to foster this expertise. So we want our employees to pass on their knowledge to the next generation, who will then put it to use in a variety of professional positions, not just at PSI. Around a quarter of our staff are therefore apprentices, doctoral students, or postdocs.

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Coming up in the next issue

The amount of data stored worldwide doubles roughly every two years. This data explosion, as some call it, affects the natural and engineering sciences as well as other areas. Computers that read out, store, and archive experimental data have made completely new scientific methods possible. Computer-aided simulations and modeling have brought about a revolution in research. In addition, since data storage is a relevant cost factor, many experiments – especially at large research facilities such as those at PSI – now require intelligent data reduction and compression. Thus it is not surprising to find researchers not only using computers, but also working constantly to improve them. One current goal that PSI and other institutions are pursuing: an experimental quantum computer that can, for certain applications, outshine classical computers.

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