KEY TOPIC

WONDERS OF THE CYTOSKELETON

The magazine of the Paul Scherrer Institute

03 / 2023

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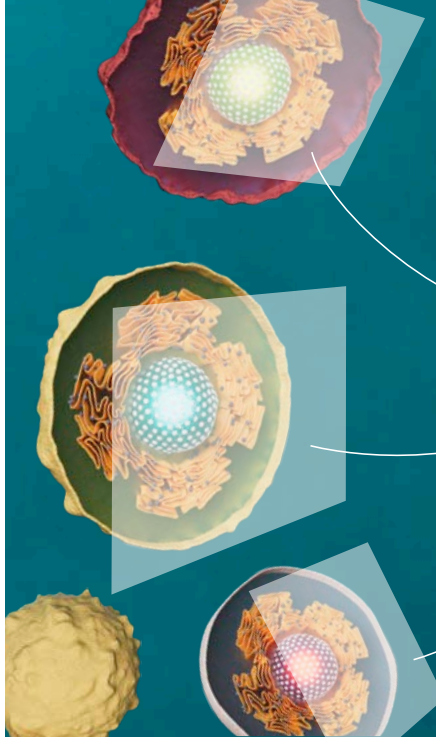
WONDERS OF THE CYTOSKELETON



BACKGROUND

More than just a support structure

The cytoskeleton fulfils very different functions within our cells. It proves to be much more dynamic than the term skeleton might suggest. Research into it promises, among other things, new possibilities for therapies against cancer and many other diseases.

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INFOGRAPHIC

The cytoskeleton

Whether acting as mechanical stabiliser, transport network or a crucial factor in cell division: microtubules, one of three essential building blocks of the cytoskeleton, take part in many central life processes. That's why they are central to cytoskeleton research at PSI.

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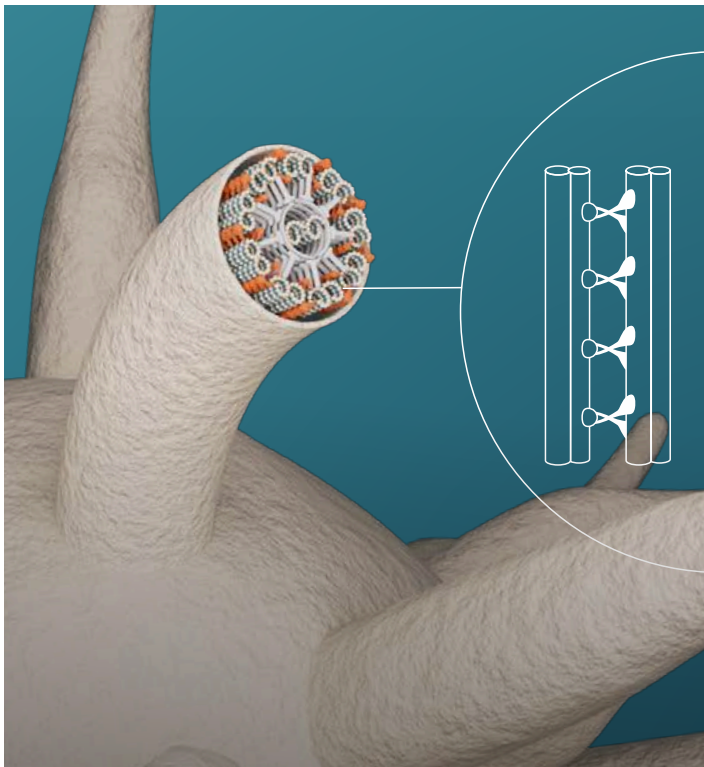

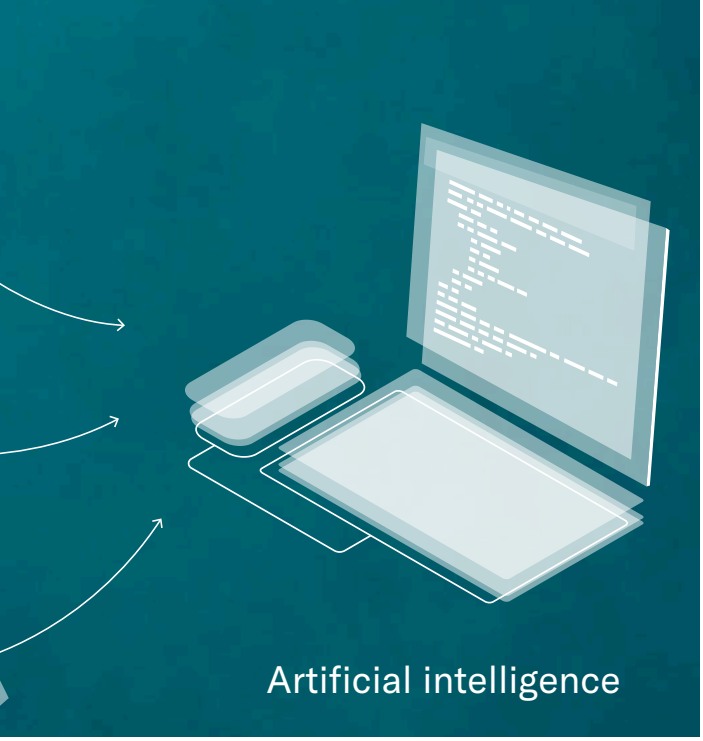

REPORT

Grasping diseases by the roots

Artificial intelligence is aiding researchers in their search for new approaches to drug development. Their painstaking search for clues seeks to alleviate or cure diseases in which the cytoskeleton plays an important role.

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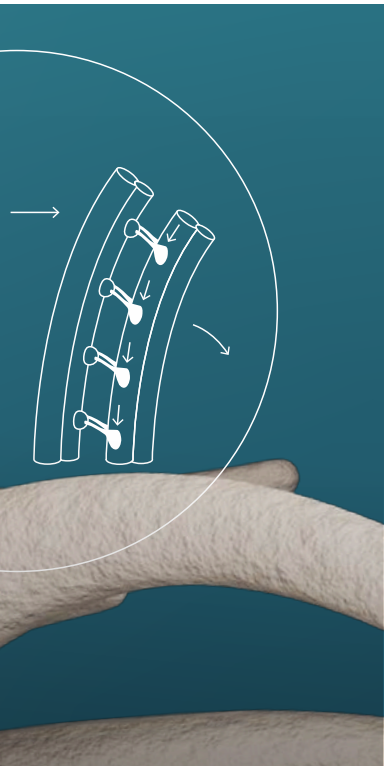

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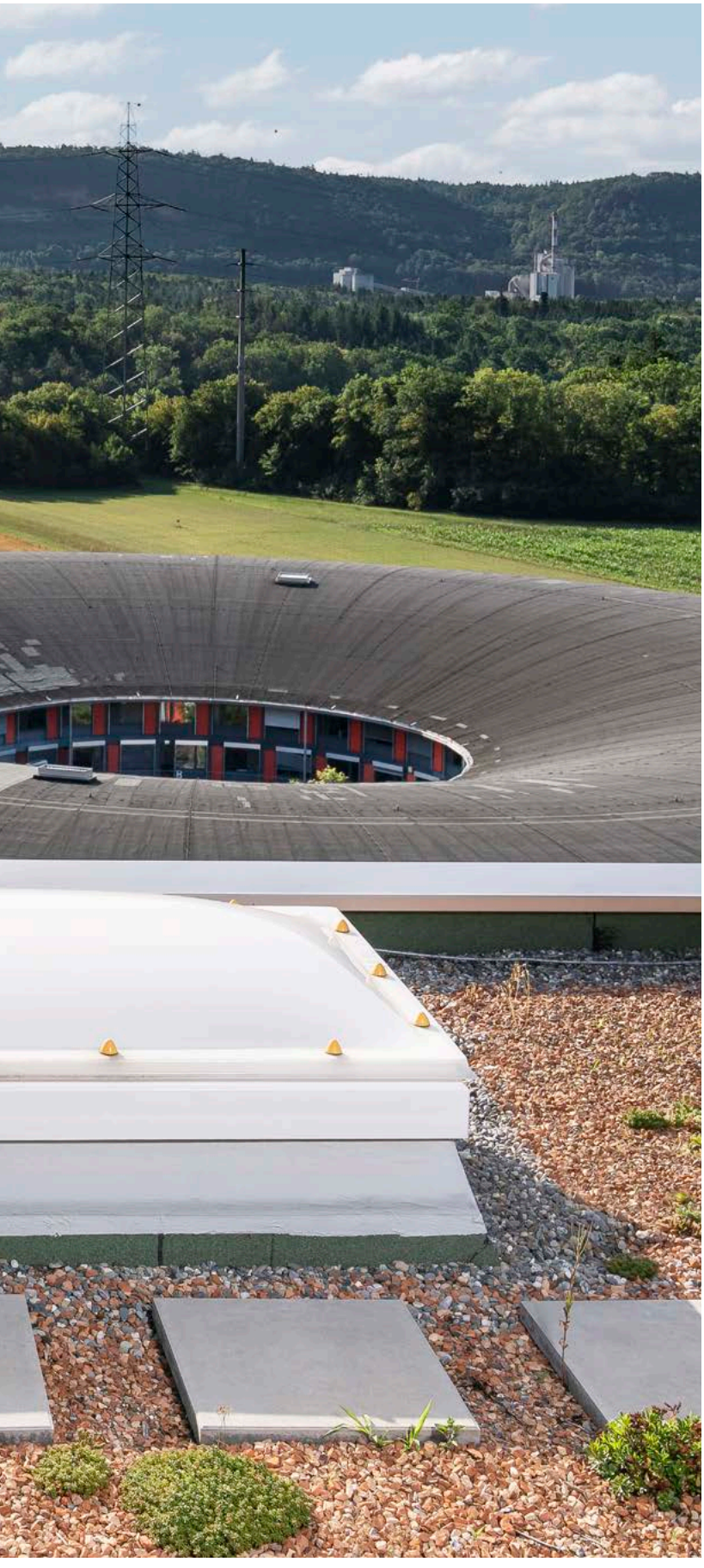
Christian Rüegg, PSI Director



New knowledge for new therapies

Invisible to the naked eye but crucially important: the cytoskeleton is a wonderful example of life's complexities. Among other things, its dynamic network of proteins shapes the interior of the cells. Contrary to what its name suggests, it is much more than just a support structure. It enables both the locomotion of individual cells and targeted transport inside the cell. Besides that, it plays a role in an absolutely fundamental life process, cell division. Without it, neither the growth nor the reproduction of organisms would be possible.

Research on the cytoskeleton not only furthers basic understanding of cellular processes, but has also led to medical advances. For example: PSI researchers have succeeded in identifying completely new docking sites on the cytoskeleton that medicinal agents can bind onto. This knowledge, in turn, can be used to show how new active ingredients should be structured to have the best possible influence on processes involving the cytoskeleton.

For both drug discovery and other research concerning the cytoskeleton, new data processing or artificial intelligence capabilities are now also being used every day to benefit from the enormous amounts of data generated by experiments at our research facilities. Bound up with the new knowledge we gain in this way is the dream of counteracting diseases such as cancer and neurodegenerative disorders, since the cytoskeleton plays an important role in their development and progression.

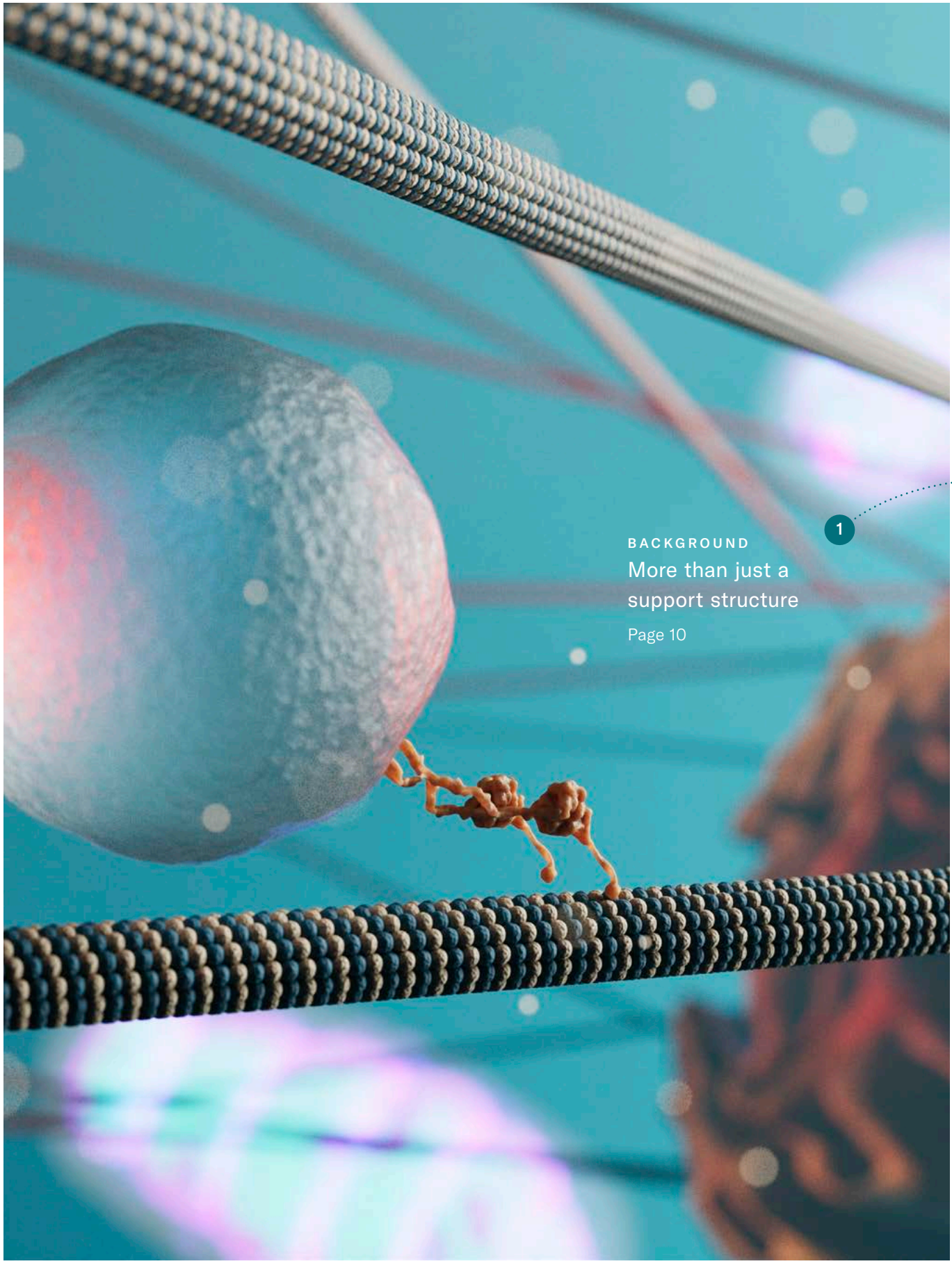
The basic requirement for us to succeed in gaining knowledge for new therapies is always the research at the large research facilities of PSI, such as the Swiss Light Source SLS, behind me, where we are permanently developing new methods and the best instruments. Research on the cytoskeleton is a perfect example of how fundamental research, which requires perseverance, can lead to applications with tangible benefits. This important step for our health and prosperity happens every day if we continue to invest in research and innovation and thus in the future.

Cleaning up

No one knows exactly when a person first used something more than water to wash. What's for sure, however, is that soap has been used for personal hygiene, in addition to water, for many thousands of years. The first evidence of this is found in writings more than 4,000 years old. Since then, the method for making soap has not fundamentally changed. One crucial process is called salting out. Chemically speaking, soaps are nothing more than salts of organic acids, specifically fatty acids. As their name suggests, they are essential components of fats. To obtain them, fats are heated – hence the term soap boiling – and spiked with chemicals, mainly lye. Then salt is added, for example ordinary cooking salt, which consists of the elements sodium and chlorine. Together with the sodium, the fatty acids are salted out and float on top of the solution, which contains the other remaining substances from the manufacturing process, as a so-called soap core. This soap core can now be easily separated – and you can lather up.

Airy and tiny

Salting out also plays a role in an area of our life that could not be farther from a bubble bath. In complex studies, PSI researchers are trying to analyse what processes are taking place in the atmosphere – to understand, among other things, their effects on weather and climate phenomena. This includes research on aerosols: tiny liquid or solid suspended particles with a size of between 0.1 and 10 micrometres. Liquid aerosols occur naturally, especially above the oceans, and can contain substances that resemble fatty acids. Among these are some that enable certain elements, such as bromine, to collect on the surface of droplets. The more bromine present at the droplet interface, the better it can react with ozone in the atmosphere. Ozone in the upper layers of our atmosphere in turn creates a protective shield against harmful UV radiation from the sun. When present in the lower layers, it can damage the lungs through the air we breathe. Sea salt in the droplets can cause the fatty acid-like substances to salt out, and ultimately this indirectly alters the concentration of bromine on the surface of the droplets. The investigation of these processes, for example with the help of the Swiss Light Source SLS, has only just begun, but is already highlighting the enormous complexity of what goes on in our atmosphere.



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BACKGROUND

More than just a support structure

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KEY TOPIC

Wonders of the cytoskeleton

The cells of the human body are held together by a network of protein filaments. The way this network functions and its potential for medicine have received too little attention in the past. Now, with the extremely precise large research facilities at PSI and new examination methods, researchers are tracking down its secrets.

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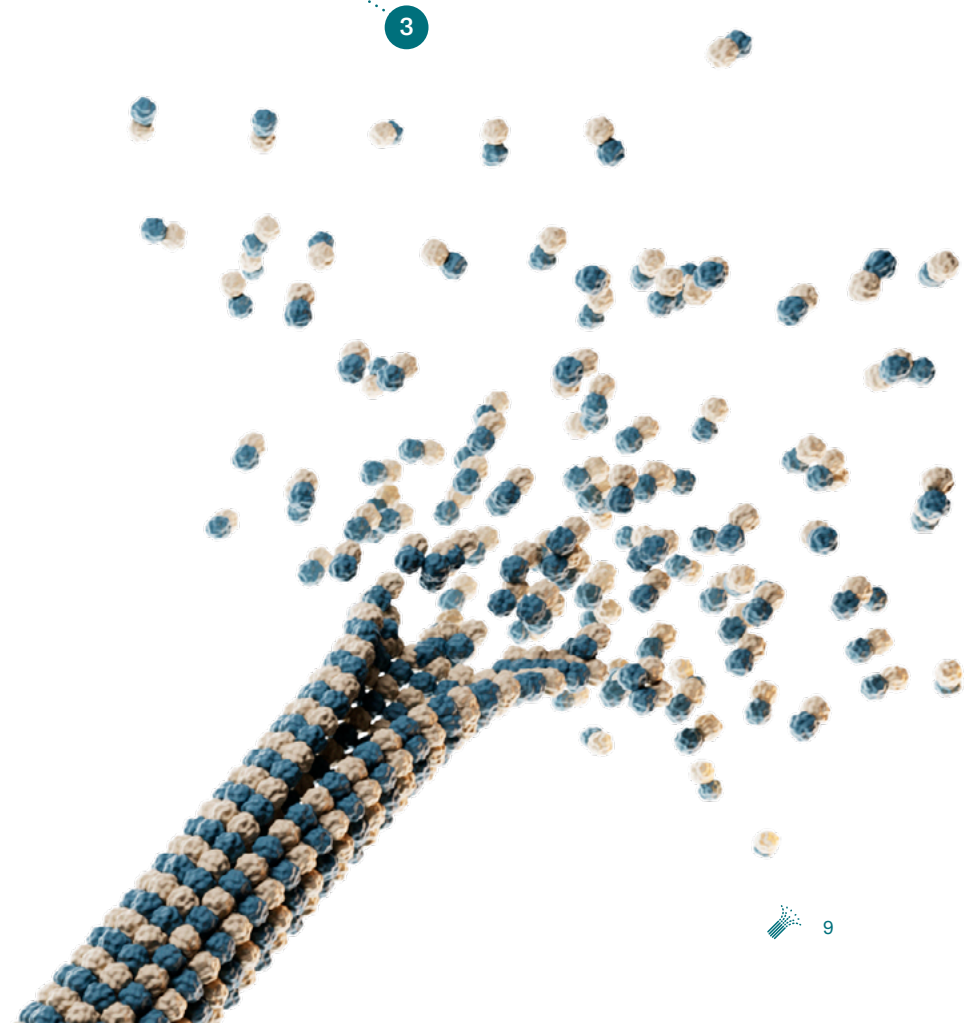


Assembly and disassembly

Microtubules are made up of multiple long filaments that dynamically assemble and disassemble themselves in the interior of cells. The individual filaments, in turn, are composed of pairs of alpha and beta tubulins (here, blue and white).

More than just a support structure

Each cell in the human body contains a network of extremely fine filaments: the cytoskeleton. Contrary to what the name suggests, the cytoskeleton is far more than just a support structure, and performs many vital functions. This makes it a promising area for research in biology and medicine, providing numerous starting points for novel therapies.

Author: Jan Berndorff

Every living thing consists of at least one cell, the basic unit of all life. Most plants and animals are made up of a multitude of cells – around 30 trillion in the case of humans, for example. Even the single cell is an enormously complex structure. An analogy is sometimes used to make it easier to understand how the cell works: the conceptual model of a city state. The cell nucleus, which contains most of the genetic material – that is, the blueprints for the cell's essential building blocks – forms the government district, where the rules are set that determine how the whole entity functions. Ribosomes are like factories that build everything needed in the city, according to the building plans stored in the control centre – the genes – including tens of thousands of types of different proteins. These proteins, as well as nutrients, signalling molecules and other substances delivered from outside the cell, are transported in so-called vesicles, small droplets, from one place to another – like parcels handled by the postal service. The transporters are so-called motor proteins. They carry the parcels to their destinations – the various facilities across the city.

Besides the government district of the cell nucleus, there are also the mitochondria. Like power plants, they produce the fuel adenosine triphosphate (ATP) from the incoming nutrients, thus providing the energy that keeps everything running. There is a mail order company that prepares goods from the factories for transport – called the Golgi apparatus. Control stations on the city wall (cell membrane) and the gates (membrane channels and transporters) perform entry control for external goods. The police (peroximones) arrest and take away unwanted intruders, often in cooperation with the rubbish collectors (lysosomes) that dispose of waste material.

The basic prerequisites for the functioning of the cell are the previously mentioned goods transport and information exchange. Both take place mostly on the streets of the city, which connect everything in an expansive network. Parts of the so-called cytoskeleton correspond to this road network in the cell. Among other things, this is responsible for the transport of cell components along defined routes and consists of three main components: microtubules, actin filaments and intermediary filaments (see infographic, page 16). Microtubules are like main roads where most of the exchange of biomolecules and other "goods" takes place. They also play an essential role in the proliferation of cells through cell division. For this reason, researchers at PSI have specialised in unveiling the secrets of these microtubules.

Michel Steinmetz (left) and Andrea Prota, close colleagues in the PSI Laboratory for Biomolecular Research, are investigating where on the microtubules new active agents could dock to fight severe diseases.

Investigating molecular processes

"Such dynamic structures and processes are highly complex and therefore can only be clarified with great difficulty at high resolution," says Michel Steinmetz, head of the Laboratory for Biomolecular Research at PSI. "So far we understand only a fraction of all the molecular processes in our body, since the crucial biology happens on a tiny scale that has so far largely eluded our technical possibilities for comprehensive investigations."

But this could change in the near future. Modern high-resolution imaging methods such as cryo-electron microscopy and X-ray crystallography made possible by the large research facilities such as those at PSI, put researchers in a position to precisely observe cell structures and their dynamic interactions with other biomolecules and substances – in atomic detail and exact to the nanosecond. This not only deepens our understanding of the organism and the molecular processes that take place within it, but also opens the door to the development of new medicines and treatments for patients with abnormal cell functions. Diseases such as cancer, Covid-19, malaria and Alzheimer's could become easier to treat.

Vital dynamics

Microtubules consist mainly of two types of tubulins – proteins that in turn are made up of around 450 chained amino acids: alpha and beta tubulins. The two proteins form pairs and link together into thin tubes. Each of these is no more than 25 nanometres wide; a normal human hair is around 2,000 times thicker.

The network of microtubules is very dynamic, as if the streets were constantly being shortened, extended or rebuilt. Guided by various binding partners and enzymatic mechanisms, the tubulins grow and die just as plants do over the years. In time-lapse mode, however: the microtubules grow from a so-called microtubule organisation centre – their root, essentially, which is located in the cell nucleus – and proceed in a certain direction by constantly docking with new tubulins. But whole rows of them also continuously fall back again, only to regrow in a different direction if possible. Often the microtubule dissolves completely after just a few minutes. If it hits a target structure and becomes a component of a solid new road, it stabilises itself and lasts longer. "This dynamism of the cytoskeleton is uniquely important for the most diverse processes in the body," Michel Steinmetz says. For example in mitosis and meiosis – cell division, which is critical for the organism's growth and reproduction. The cytoskeleton forms the so-called spindle apparatus and pulls apart the chromosomes, the carriers of the genetic material. In this way the DNA from the mother cell is evenly distributed between the two daughter cells. In addition, the cytoskeleton performs important functions in wound healing, the differentiation of stem cells and the networking of neurons in the brain.

Important approaches for medicine

On this dynamic road network, various motor proteins act as transporters. Dyneins, for example, take on the transport of vesicles, as well as cell organelles and other particles from the outer areas, to the centre of the cell and thus can also introduce pathogens. They take up their cargo piggyback by molecular coupling and carry it along the microtubule road as if on legs – at a rate of more than 100 steps per second. Given the length of their stride, which

amounts to roughly three micrometres. In some nerve cells, whose axons can be more than a metre long, transport can take up to 12 days.

Now if viruses or parasites manage to circumvent the cell membrane's intake controls, they too take this taxi in the direction of the cell nucleus. If just one of these invaders goes unnoticed by the cell's own immune system, made up of peroxisomes and lysosomes, it can smuggle in its own genetic material. Then the cell produces viruses in addition to the body's own proteins, and the infection takes hold.

Understanding this system down to the smallest detail in terms of structural biology – the dynamics of the microtubules, the movement of the motor proteins, the coupling and uncoupling processes of the body's own proteins with foreign substances – has now become possible with modern imaging methods. "With facilities such as the Swiss Light Source SLS and the X-ray free-electron laser SwissFEL, PSI has a strong presence in this field," Steinmetz says. And it has already scored several successes.

Finding puzzle pieces that fit

Researchers at the Laboratory for Biomolecular Research have more precisely described 27 docking sites for active substances on tubulin, 11 of which were completely unknown before. These can be thought of as indentations in the amino acid chains – which themselves are tangled together like a ball of yarn – into which some molecular compounds fit more or less perfectly, like pieces of a jigsaw puzzle. These sites are also known as binding pockets. The researchers carried out a crystallographic fragment screening. They immersed 800 tubulin crystals individually into a solution consisting of 800 different molecular fragments that are commercially available as standard active ingredients.In this way they were able to identify 56 fragments that nestled in the binding pockets, at least temporarily. "So these would be potential building blocks for a new active agent because they bind to the tubulin," explains Andrea Prota, a scientist in the Laboratory for Biomolecular Research.

For example, there are substances that disrupt the dynamics of tubulin and thus arrest cell division. The commonly used cancer drug Taxol® curbs the proliferation of tumours and can even make them shrink. However, Taxol® is originally a natural compound derived from the bark and needles of the Pacific yew tree. Since this tree species grows in a limited geographic range and because its Taxol®-content is low, the substance needs to be produced synthetically for widespread use. This in turn is very difficult because of the enormous size of the natural molecule. On top of that, Taxol® provokes undesirable side-effects. "Structural biology now allows us to replace such substances with smaller, tailor-made molecules that only have the necessary properties to bind to the tubulin," Prota says. "They also have a new mechanism of action, are easier to handle and with a bit of luck hopefully exhibit fewer side-effects."

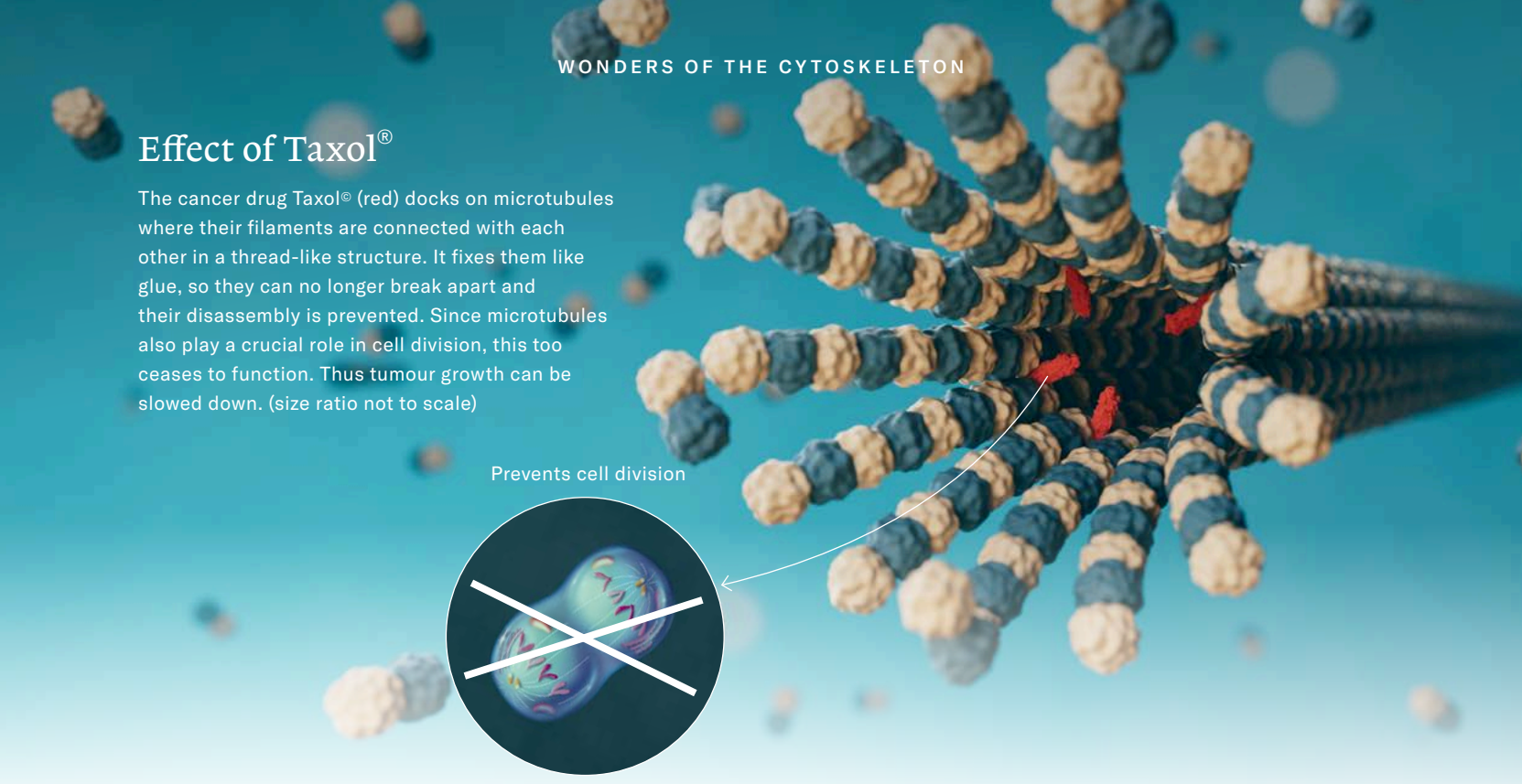
Once a fitting fragment has been found, its residence time on the tubulin needs to be increased. The longer an active agent stays bound – sooner or later even molecules that fit will be released again – the more effective it can be. The better a substance fills the binding pocket, the longer it should remain in it. So now the researchers search for other fragments to supplement the first one in order to produce a combination that fills the binding pocket optimally. To do this, they feed the measured characteristics of the discovered binding pocket and the first fragment into the computer and calculate which combination of fragments offers the optimal fit. It's like a jigsaw puzzle for which the computer knows all the pieces in detail and can suggest the right ones.

This is how the experts at PSI and IIT, the Instituto Italiano di Technologia in Genoa, developed the active agent Todalam. They measured one of the discovered binding pockets with atomic precision using SLS and then, in the computer, combined three fitting fragments into a single molecule that perfectly filled the pocket – as subsequent measurements confirmed. In cell cultures, the researchers then proved that Todalam, like Taxol©, actually does disrupt the dynamics of microtubules in cells and thus stops their proliferation. "Our studies showed for the first time that it is possible to develop tailor-made small molecules, assembled from fragments, which inhibit microtubules," Steinmetz

Natacha Gaillard and Ashwani Sharma have discovered that so-called parabulins can be used to prevent parasites from hijacking human cells. Parabulins dock on the parasites' tubulins and block them.

Effect of Taxol®

The cancer drug Taxol© (red) docks on microtubules where their filaments are connected with each other in a thread-like structure. It fixes them like glue, so they can no longer break apart and their disassembly is prevented. Since microtubules also play a crucial role in cell division, this too ceases to function. Thus tumour growth can be slowed down. (size ratio not to scale)



says. “In addition, Todalam is easy to recreate chemically and to produce in large quantities. Now it is important to show if it can be used to develop a novel cancer drug.”

In a new study published at the start of this year, a research group led by Jörg Standfuss produced a film, using the SwissFEL, created virtually in ultra-high temporal and spatial resolution. The film shows how a drug – in this case the cancer drug combretastatin A-4, currently being tested in clinical trials – detaches from the binding pocket and how both the active ingredient molecule and the pocket deform in the process. “A deeper understanding of these processes, which we have now managed to visualise for the first time, improves our possibilities of customising new active ingredients in a way that increases the attachment time and efficacy,” explains Standfuss, who works at PSI’s Laboratory of Biomolecular Research.

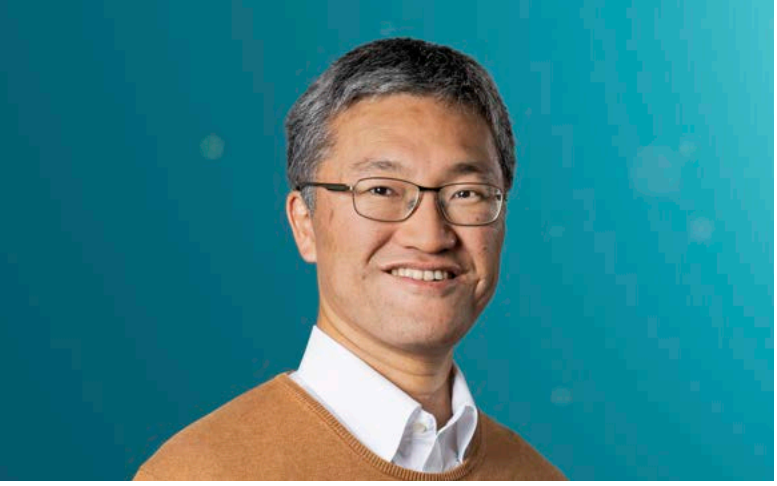
A targeted effect is required

One difficulty remains, however: how to design new active agents in such a way that they only target and block diseased cells, not healthy cells – since this is largely what provokes undesirable side-effects.

Research is already farther advanced in the effort to defend against single-celled parasites trying to infect the body. Here too, researchers at the Laboratory for Biomolecular Research are applying the principle of using tubulin dynamics to stop the hostile cells and prevent them from dividing.

Compared with fighting proliferating cancer cells, the advantage is that the tubulins of the parasites are constructed somewhat differently from those in humans. This could already be seen in their amino acid sequences and was confirmed through high-resolution imaging. PSI researchers Natacha Gaillard and Ashwani Sharma have analysed tubulins from the cells of the inconspicuous ciliated animal *Tetrahymena thermophila*. They are more or less identical to the tubulins of the malaria pathogen of the genus *Plasmodium* and the toxoplasmosis pathogen *Toxoplasma gondii*. On the atomic level, the researchers identified clear structural differences between these tubulins and those of humans. Then, by screening a database of active agents, they identified five candidates for substances that could bind to this form of tubulin in a targeted manner. In tests, one proved to be a hit. Gaillard and Sharma dubbed this compound Parabulin.

Cooperation partners at the University of California in the USA tested Parabulin in cultures of human cells that were infected with *Toxoplasma gondii*. And in fact, the parasite could no longer multiply, while the human cells were as good as unaffected. “The Parabulin was able to prevent the invasion of the cell by toxoplasmodia as well as their proliferation within the cell,” Gaillard reports. This would probably work with other parasites, and that



Takashi Ishikawa's research focuses mainly on cilia and flagella. The movements of these cell extensions, which are important for many life functions, are controlled by the motor proteins of the microtubules. Exactly how, Ishikawa is trying to find out.

is currently being tested. "For that, though, it seems clear that different Parabulin variants must be customised through structural biology."

To continue down this path, Gaillard and Sharma have applied for a patent and founded the start-up ASTRA Therapeutics to develop species-specific Parabulins for targeted treatment of malaria, toxoplasmosis and other diseases caused by parasites.

Meanwhile at PSI, Gaillard and Sharma are working to advance fundamental research on this topic: "The more precisely we know the processes through which parasites misuse the cytoskeleton and its functions for their purposes, the more accurately we can target treatments," Gaillard says. For example, they want to find out which protein a parasite uses to dock, as well as where and how, on the microtubule. Then, binding could perhaps be blocked on the side of the parasite or the host, or maybe they could be prevented from finding each other.

Propellers and conveyor belts made of microtubules

Researchers associated with Takashi Ishikawa, a group leader in PSI's Laboratory for Nanoscale Biology, are on the trail of other severe diseases and new therapies. They are studying cilia and flagella. These are thread-like appendages found on many cells, which likewise are made up of microtubules and thus, in a way, represent extensions of the cytoskeleton; they too fulfil many kinds of functions in the body.

We know them, for example, from the sperm, which is propelled by a flagellum like a fishtail when it is looking for a way to the egg. Some protozoa, such as the green alga *Chlamydomonas*, have two flagella that they use for locomotion. The mucous membranes in the human throat and nose are covered with carpets of such threads. In such cases they are called cilia, "but they are not really different from flagella in detail," Ishikawa says. They move rhythmically back and forth and transport inhaled pollutants bound in the mucus, like a conveyor belt, away from the lungs and towards the trachea and throat. The harmful substances are swallowed and disposed of in the stomach. Inside the nose, olfactory cells also transport scent molecules in this way. Brain cells transport brain fluids in the same way. Cilia even play an important role in the development of embryos: here their movement serves as a kind of gyroscope that is crucial for the differentiation of the organs and their asymmetric distribution in the body. For example, the gyroscopic motion can sometimes run in the opposite direction. In patients affected by this, the organs are arranged in reverse; for example, the heart beats on the right. This is known as *situs inversus*.

There are countless diseases associated with defective functioning of cilia. For example, it can render both men and women infertile: men, because the sperm don't move forwards properly; women, because the eggs in the fallopian tube are likewise transported by cilia insufficiently. Brain damage and various lung diseases are also among the so-called ciliopathies. Primary cilia dyskinesia (PCD), which afflicts around half a million people worldwide, not only affects the airways but in half of the cases is also accompanied by *situs inversus*.

It all comes down to protein defects. More than 400 genes are involved in the movement of cilia – that many have been discovered so far. "But exactly how the proteins control this is still unknown," Ishikawa says. He would like to change that.

Mysterious bending

Cilia consist of a tubular framework of microtubules: two individual microtubules in the centre are surrounded by nine doublets, each made up of two microtubules fused together. Radial proteins hold it all together – just as the spokes of a bicycle wheel connect the hub with the rim and tyre. Between the outer microtubules, along the entire length, are dynein proteins – those motor proteins that travel on the microtubules. Investigations at PSI have now shown that with ATP, the fuel adenosine triphosphate, as their energy source, they cause the individual doublets to push back and forth lengthwise – similar to hands rubbing against each other. "However, we have yet to discover exactly how this gliding movement causes the cilia to bend," Ishikawa says.

In a new study using cryo-electron microscopy, his team showed that after the dynein protein complex has cleaved the ATP, it looks different than it did before. There is a molecular rearrangement of

its building blocks, the amino acids. “We suspect this is the driving force behind it,” Ishikawa says. But his team has only observed one small part of the entire ciliary apparatus. “We still need to examine many other parts to identify connections and to characterise the overall mechanism.” Presumably, the structural changes in the dynein differ along the cilia, so that they influence each other in a certain mechanism and cause the movement.

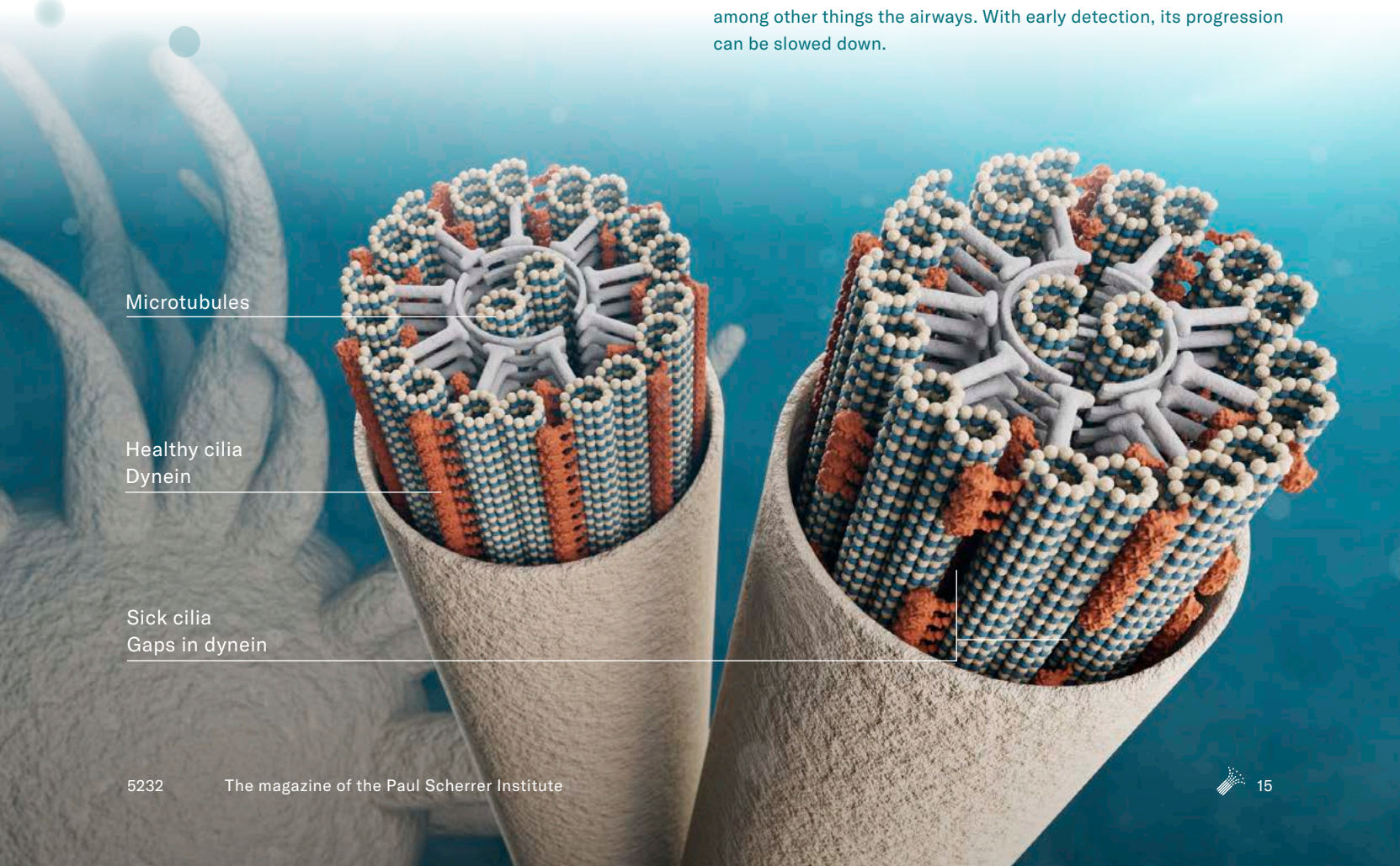
It will take years before the picture is complete. But the studies already offer a concrete benefit today: the PSI researchers are cooperating with the Inselspital of the University of Bern, which is providing tissue samples from PCD patients. Ultrahigh-resolution images of their cilia show that there are often large gaps in the dynein covering of the filaments, and in some the dynein is even completely absent. At present, it can be several years between the first symptoms of PCD and the point when a patient experiences acute respiratory problems, goes to the doctor and receives the diagnosis. This means valuable time is lost for potential early intervention. “This could be shortened significantly through routine visual inspection of the cilia,” Ishikawa says.

New means for targeted corrections

These examples show that research into the molecular processes in our body using the new imaging methods promises great progress. At the same time, it is humbling. “When we see how delicately linked, dynamic and finely balanced all these processes are, we researchers are in awe,” says Michael Steinmetz. “What biology is now revealing to us, piece by piece, is difficult for us to comprehend in all its complexity – a true wonder. All the same, the new methods available to us here at PSI enable us to understand a bit more about it – and possibly to make more targeted corrections in the event that something goes wrong in the system.” ◆

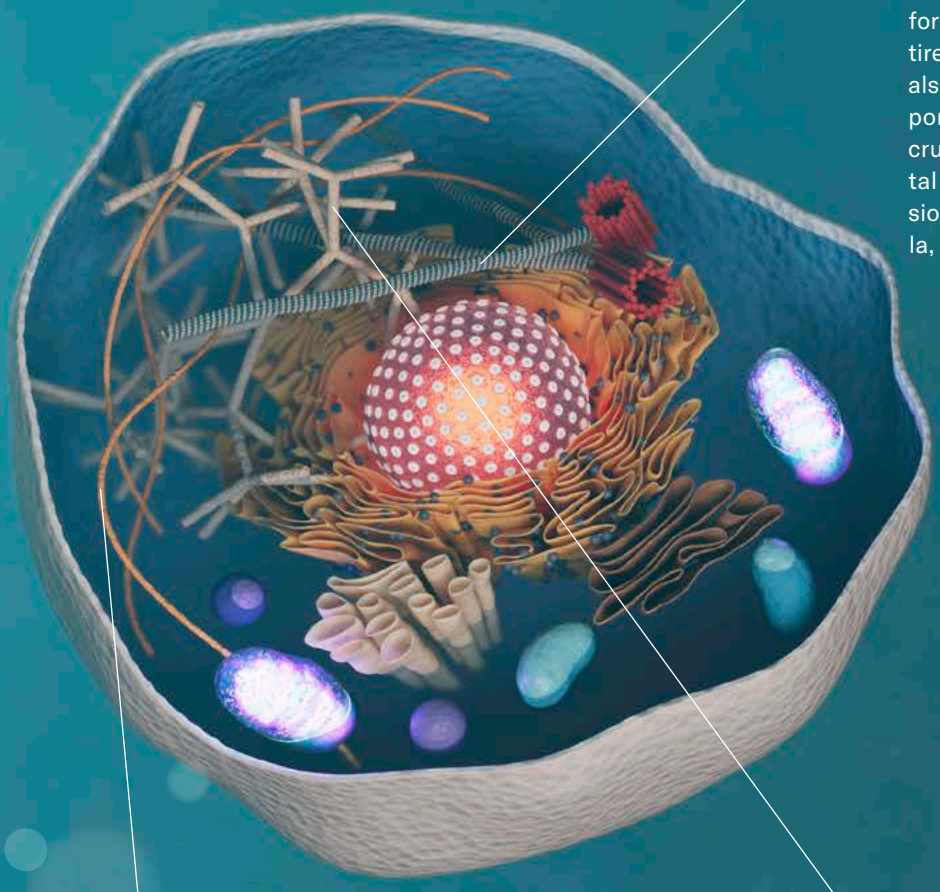
Cilia disorders

As a result of genetic defects, it can happen that the microtubules of cilia are not continuously furnished with motor proteins, so-called dyneins (red), as they normally would be. Such gaps – as seen in the cilia to the right – are the cause of primary ciliary dyskinesia, a multiple disease in which cilia movement is restricted, affecting among other things the airways. With early detection, its progression can be slowed down.



The cytoskeleton

Contrary to what its name suggests, the cytoskeleton is much more than just a support structure. It does in fact make a crucial contribution to the stability of cells and is partly responsible for giving them their shape. Beyond that, however, it takes on many other extremely important functions in the life cycle of every individual cell. It is made up of three basic elements: microtubules, actin filaments and intermediate filaments.



Microtubules

They are at the centre of cytoskeleton research at PSI. Their functions within the cell are diverse (see also graphic, right). They are composed of two similar building blocks, alpha- and beta-tubulin. These form tubular filaments that run throughout the entire cell and thus contribute to its stability. The cell also uses this network as a roadway for the transport of vesicles. In addition, microtubules play a crucial role in cell division. They are also fundamental building blocks for cilia, which, as cell extensions, can move liquids outside the cell or, as flagella, can enable the mobility of individual cells.

Actin filaments

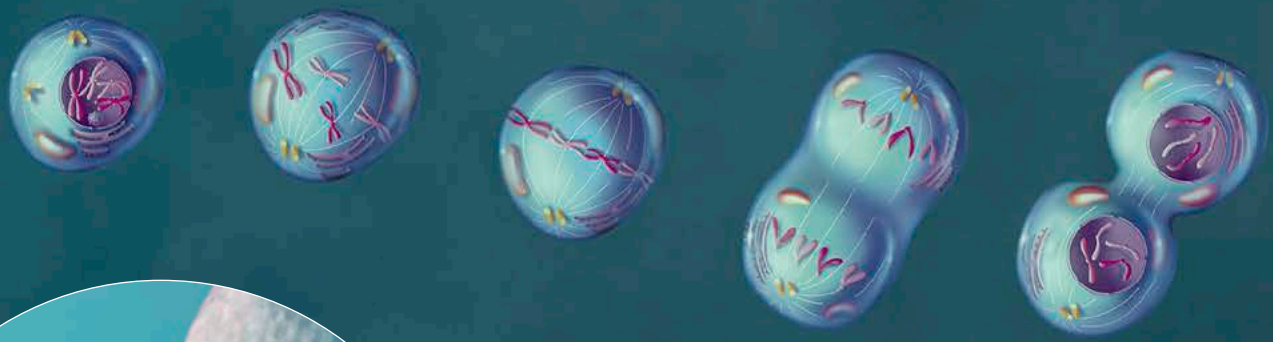
These thread-like structures are mainly composed of the protein actin. Like the microtubules, they assume functions in the mechanical stabilisation of the cell, in the transport of substances within the cell and in cell movements.

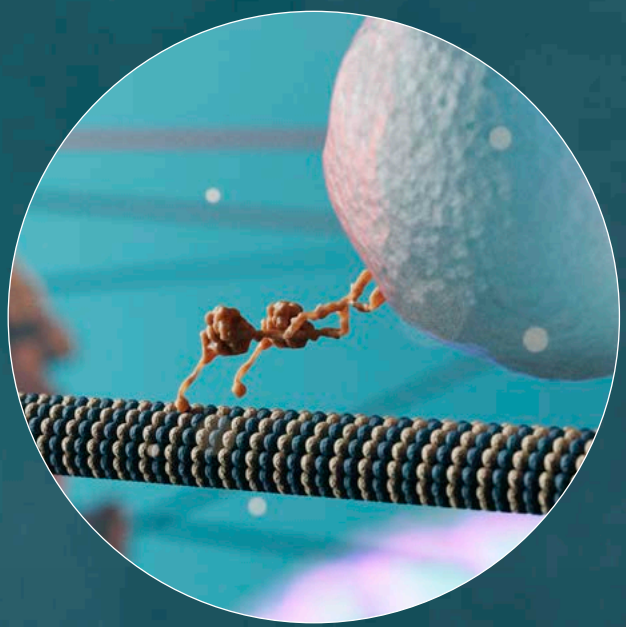
Intermediate filaments

This third major component of the cytoskeleton serves mainly as a mechanical support structure. The term intermediate derives from the fact that their diameter is roughly between that of the microtubules, at around twenty-four nanometres, and the actin filaments, at around seven nanometres.

Mitosis / Meiosis

Mitosis and meiosis are crucial processes in reproduction, and each concerns the division of genetic material. Mitosis (see graphic, below) takes place during cell division, which occurs for example in the growth of multicellular organisms. First, the genetic material within the cell nucleus is completely duplicated. Then the cell nucleus divides in such a way that each daughter cell receives a complete copy of the genetic material. Microtubules pull the chromosomes, the carriers of genetic information, to one of two poles, the so-called centrosomes. Meiosis, on the other hand, involves the production of reproductive cells, in humans, the egg cells and sperm. Each of these carries only half a genome. The microtubules ensure the appropriate division of the chromosomes.



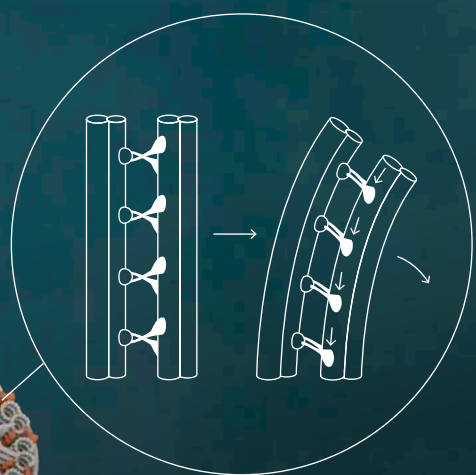


Transport

Since microtubules run throughout the entire cell, they are also suitable as roadways. Movement proteins, for example dyneins (shown here), can run in any given direction along these routes. They either move in the direction of the cell nucleus – that is, towards the interior of the cell – or in the direction of the cell membrane – towards the exterior of the cell. Vesicles, which can be thought of as tiny transport bubbles, ride piggyback on dyneins. Thus, depending on their direction of movement, some dyneins transport their load into the centre of the cell or to the cell periphery.

Cilia / Flagella

Cilia and flagella are extensions of the cell's outer membrane. Microtubules are a crucial component in both. When cells grow in assemblages, the cilia serves to move fluids – for example in the airways or in the brain. As flagella, they propel individual cells like a kind of outboard motor. The swinging motion is due to the fact that dyneins push individual microtubule strands against each other in such a way that one side stretches and the other contracts.



Grasping diseases by the roots

Modern supercomputers and artificial intelligence are helping to decipher the causes of diseases. That could help improve diagnostics and therapies.

Author: Jan Berndorff

Anyone using large research facilities such as the Swiss Light Source SLS and the X-ray free-electron laser SwissFEL to investigate molecular structures has to process vast amounts of data. The measurement of a single protein produces 250 terabytes. Stored on blank DVDs, this would make a stack as high as the Leaning Tower of Pisa.

Research on the cytoskeleton involves measuring a whole series of proteins, protein complexes and other biomolecules, taking and comparing pictures of their structures and observing molecular interactions. To make progress and maintain an overview, modern forms of data analysis, including those using artificial intelligence, have become indispensable. For example, G.V. Shivashankar, head of the PSI Laboratory for Nanoscale Biology and professor of Mechano-Genomics at ETH Zurich, uses these methods in his research.

He is investigating, among other things, an important property of the cytoskeleton: its rigidity. As humans age, this multifunctional support structure of the cell becomes less flexible and dynamic, making it easier for pathogens to do their harmful work. In less dynamic cells, they are better able to intervene in the cell's signal pathways and have an easier time multiplying. "This may be the reason why older people are more likely to become seriously ill from a Covid-19 infection," the researcher says.

The cytoskeleton has a major influence on the shape of the cell nucleus and on how well the genetic material is packed into it. Spread out and put together, the molecular chains of the DNA would be more than a metre long, but they are so tightly and cleverly wound into a ball that they fit into the tiny, ten-micrometre cell nucleus. If the cytoskeleton becomes more rigid, this packaging no longer functions optimally and the individual genes can no longer be read as effectively to produce proteins the body needs, for example for metabolism or signal transmission.

And this is where modern imaging could bring a breakthrough: "We already know a few hundred active agents that target the signalling pathways of the cell," says Shivashankar. "It is just unclear what combination and dose is best to counteract the rigidity of the cells and the corresponding restricted signal transmission." His team wants to find out, by adding the active agents to cultures of infected cells in the Petri dish and then observing, in high resolution, what happens. "We need a screening of all known drug candidates. And PSI has the necessary infrastructure to carry out something like this – SLS in particular is very well suited for this task."

The roots of many diseases

There is one reason this research is especially important: it is now assumed that an abnormal packaging of the genetic material in the cell nucleus plays a major role in cancer as well as in neurodegenerative diseases such as Alzheimer's. Shivashankar's lab is working on a process that routinely makes images of cell nuclei to determine, by examining various characteristics, how the DNA is packed. This allows predictions to be made as to which genes cannot be read, resulting in particular diseases. That would be much simpler and less expensive than sequencing the genes on an individual basis to achieve the same result.

The challenge here is that the characteristics which need to be analysed and compared are extremely diverse. Without powerful computers and algorithms that can compare hundreds of characteristics on thousands of images, this could not be accomplished. Artificial intelligence reliably detects subtle differences in the type of DNA packaging and recognises correlations with cell malfunctions. So Shivashankar's team is cooperating with experts in machine learning – a group led by statistician Caroline Uhler, professor at the Massachusetts

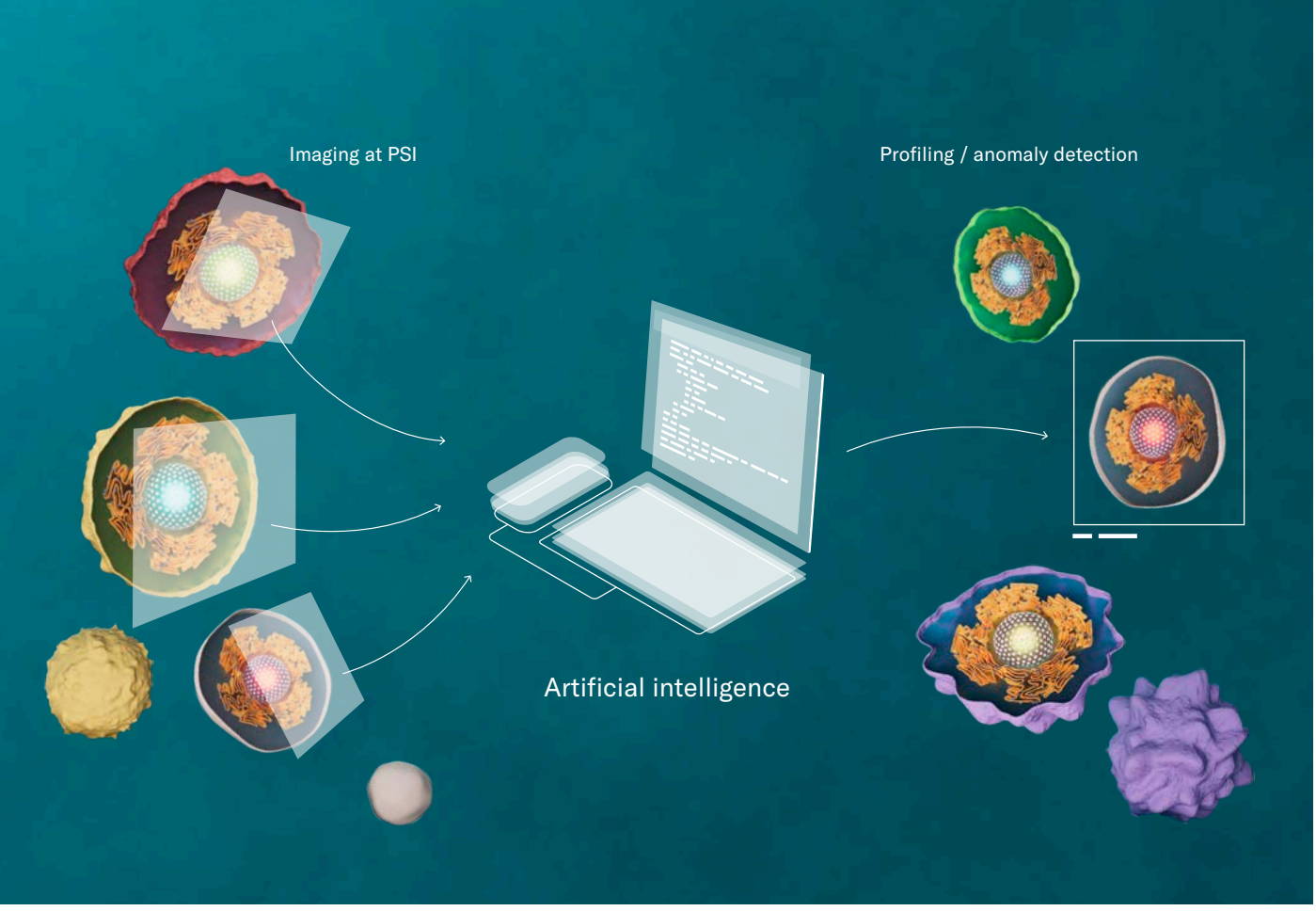
Institute of Technology in the USA. “The advantage of using machine learning is that it can help us identify novel features which may not be directly interpretable by humans but automatically give a strong indication of cell health or disease,” Uhler says.

Powerful computers are indispensable

Advances in machine learning are having an enormous impact in all areas where there is explosive growth in the volume of data. And one reason the amount of data is so large is that the researchers really would like to look at each cell individually to identify diseases. “Even cells of the same type can have very different structures and thus behave differently,” says G.V. Shivashankar. “It’s like trying to examine and understand each individual grain of sand on the beach.” Fed ever more examples, the computer learns over time which cell structure leads to which behaviour and recognises patterns.

Ultimately it might be possible to make statements – solely on the basis of high-resolution imaging of a cell nucleus as a kind of biomarker – about how well a cell is functioning, what diseases the person concerned might suffer from, and what type of therapy holds the most promise for success, making early, targeted interventions possible. In any case, the method would be an enormous boost for diagnostics. “To exploit the enormous potential of machine learning for biological discovery and

G.V. Shivashankar, head of the PSI Laboratory for Nanoscale Biology, is exploiting the potential of artificial intelligence to discover patterns and abnormalities in the way DNA is packaged in the cell nucleus. It is possible that high-resolution images of the cell nucleus can be used as biomarkers for diseases.

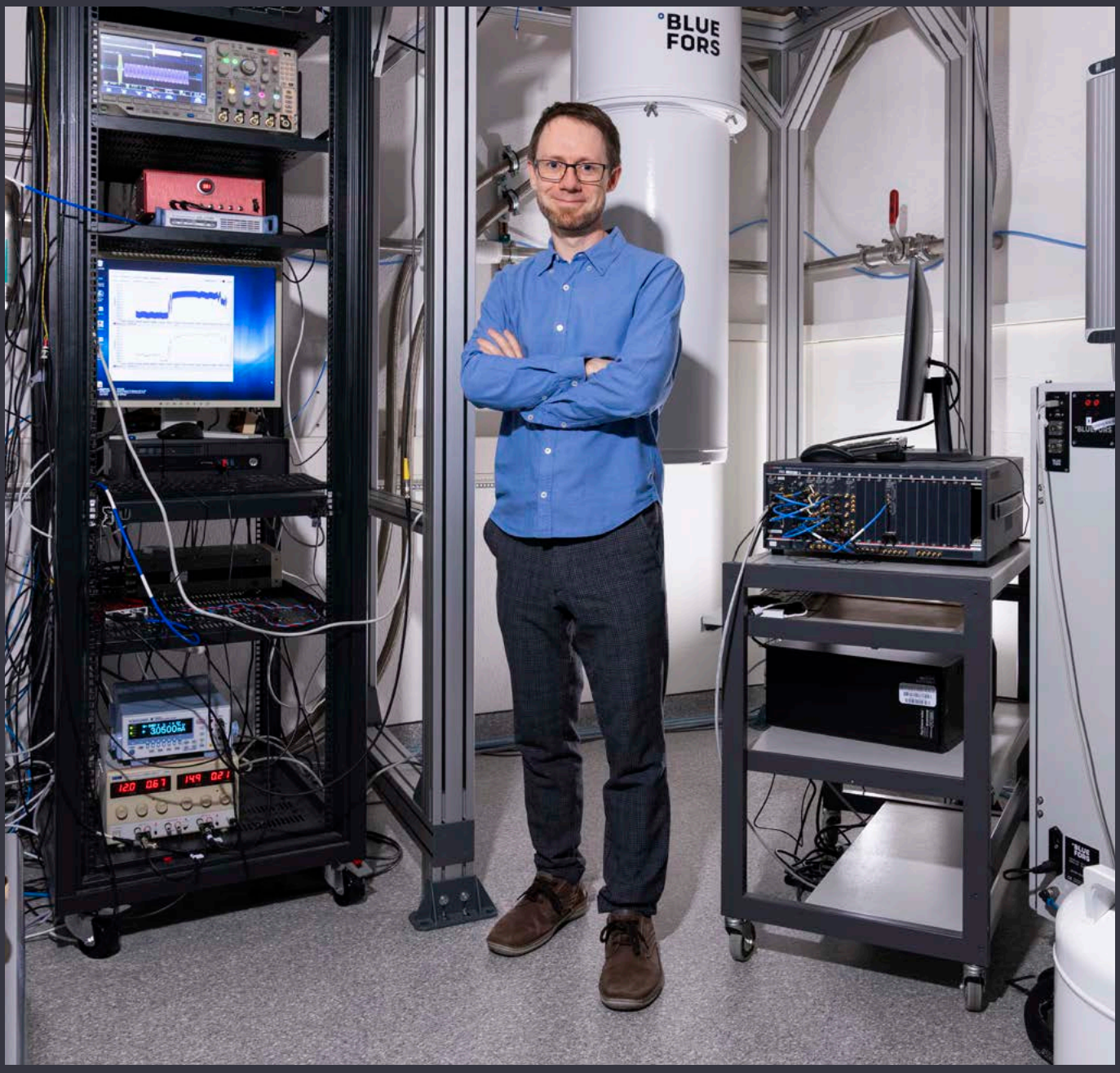


PSI researchers take pictures of cell nuclei using modern high-resolution imaging techniques, employ learning algorithms to comb through these data, and thus can more reliably identify anomalies that require medical intervention.

medical diagnostics, however, it is crucially important to carefully evaluate the identified cytoskeletal and nuclear biomarkers in the clinical environment," Uhler says.

With the Centre for Proton Therapy at PSI, Shivashankar's group is also investigating whether high-resolution images of blood cells, the cytoskeleton and the cell nucleus could provide indications of therapeutic efficacy. "We compare images from before, during and after treatment of cancer patients and check for correlations between the changes we see and the progress of the therapy," Shivashankar says. Here too, it is important to reliably and quickly recognise possible irregularities within an enormous amount of image data. "Anyone still working on such tasks nowadays without machine learning," Shivashankar says, "is missing out." ◆

> "Even cells of the same type can have very different structures and thus behave differently."
>
> G.V. Shivashankar,
> head of the PSI Laboratory for Nanoscale Biology



Quantum error correction

Physicist Alexander Grimm heads the Bosonic Quantum Information Group in the Laboratory for Nano and Quantum Technologies. His research centres on quantum bits, the basic information units of a quantum computer. They are volatile by nature, and that can lead to erroneous results in calculation. A specialist in quantum measurement and control, low-temperature technology and the design of superconducting circuits, he develops new ways to store and manipulate quantum information, with the aim of eliminating existing sources of errors. In 2022, his achievements were honoured with the Nicholas Kurti Science Prize.

Barbara Horvath wants to use thin nanowires to alter the optical and electrical properties of glass.

Smart glass and music from SLS

Every year the PSI Founder Fellowship Programme supports new ideas for innovative applications with up to 150,000 Swiss francs. Whether smart glass or music restoration at the synchrotron – the resulting spin-offs are as diverse as the research at PSI.

Text: Benjamin A. Senn

Glass is no modern invention – in fact, archaeological finds show that this material has been manufactured and used by humans for more than 5,000 years. Glass is not only used as a vessel for fine wines – optical lenses are also ground from glass to make the smallest or most distant objects visible. Our communications flow through glass fibres in optical cables. Windows keep out the wind and rain while letting light pass through. The translucent material finds application in numerous areas of our civilisation. Yet glass is not just glass – we adapt it to our needs and reinvent it more or less constantly.

Barbara Horvath works with glass. The materials scientist, a candidate for the PSI Founder Fellowship, has been working to establish her spin-off Inveel since August of this year. Using tiny nanowires, the young entrepreneur wants to print electrodes on glass, for example to change its optical and electrical properties.

Smart glass

"One possible application for our technology is so-called switchable glass – also called smart glass," Horvath explains. "That is a special material that can turn opaque, transparent dark or coloured, automatically or at the touch of a button." This capability is enabled by a thin nanostructured coating sandwiched between two panes of glass. When electrical charges are applied to this layer, it becomes optically active and can change its colour as a result. This not only puts privacy at your fingertips, but can also be used to regulate the temperature in buildings.

The invention itself is not new. Such glass is already in use for windows in modern office buildings and aircraft, for example. However, producing them is very complex and thus costly. "To be able to apply the weak electrical charges to the switchable glass, thin wires must be accommodated – so thin that they will not impair visibility," Horvath explains.

During her work at PSI, Horvath and her group leader Helmut Schift developed a method for the production of such fine conductor tracks. "Our method makes it possible to produce wires with a diameter of around one hundred nanometres," the scientist explains. It functions much like a printer: nanoparticles are applied as liquid droplets and fuse together to form linear structures. This allows large areas to be printed with extremely fine, parallel conductors. Using conductive materials such as silver and gold, a wide variety of surfaces can be furnished with invisible electronics quickly and inexpensively.

Switchable glass is just one possible application. The nanowires could also be used to change the direction of polarisation of incident light in the glass so that only certain wavelengths penetrate. This could be used, for example, for temperature control in greenhouses or for laser protection in eyeglasses. "In the laboratory, we have shown that the technology works in principle," Horvath adds. "The Founder Fellowship has now made it possible for us to take the next step towards practical applications."

Researchers today – entrepreneurs tomorrow

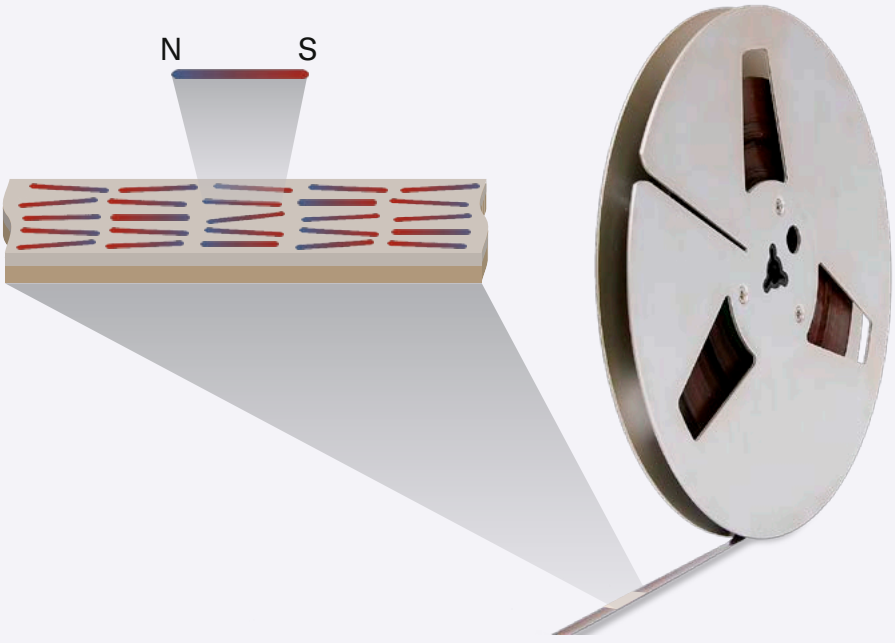
Just like Barbara Horvath, researchers from all areas of PSI submit proposals to this coveted programme every year. "It's often a long way from a promising research result to a marketable and innovative product," explains Angelo Sozzi from PSI's Technology Transfer – together with his team, he coordinates the Founder Fellowship, offers courses and coaching, and supports the entrepreneurs in their ambitious undertakings.

"When researchers decide to pursue such a career path, the initial focus is on deepening the business idea, preparing the market and creating a business plan," adds the entrepreneurship coach. "In business, in contrast to fundamental research, the further development of technology is directly subject to commercial interests." Each winner receives a one-time sum of 150,000 Swiss francs – money that the winners are responsible for apportioning themselves, as with an investment. The fellowship also allows researchers to maintain access to PSI for up to 18 months. During this time it is important to find a market and establish a viable business plan.

Particularly important for the commercialisation of innovative technologies are the use of the PSI infrastructure and the exchange with other researchers on the PSI campus. Access to large research facilities and specialised laboratory equipment would otherwise be unaffordable or completely unavailable. In this way, Barbara Horvath can continue to work in her familiar environment and benefit from the exchange with her colleagues. In the case of Sebastian Gliga, likewise a PSI Founder Fellow, having his own lab far away from PSI would have been impossible. For his business idea, the physicist uses the Swiss Light Source SLS – he wants to use it to digitise the recordings on old music tapes.

Music from the synchrotron

At this point magnetic tapes have almost completely disappeared from our lives and enjoy only a nostalgic niche existence. In the archives of recording studios, radio and TV broadcasters, museums and private collections, however, there are still vast quantities of these analogue data carriers.



Magnetic tapes are made up of a layer of tiny magnetic particles – like little compass needles that can be oriented to store information. To make recordings on old and unreadable tapes audible again, Sebastian Gliga uses synchrotron light from the Swiss Light Source SLS.

Sebastian Gliga adds: “Only a fraction of all these recordings have been digitised so far.” It’s not just about our cultural heritage; in the age of digital music platforms such as Spotify and the business of music licensing, real treasures are slumbering in these archives, and sometimes no effort is spared to restore and digitise forgotten tapes by well-known artists in the highest quality.

But why do you need a synchrotron for this? “Recording tapes are not made for eternity,” Gliga explains. “The material disintegrates and can no longer be played back – with the X-rays from the synchrotron, however, such recordings can be restored without contact.”

Recording tapes store information in a layer of tiny magnetic particles – like tiny compass needles that point either south or north. When sound is recorded on the tape, their alignment changes – the tape becomes magnetised, and the audio information is now physically stored in the alignment pattern. To replay this pattern, the tape is moved past a read head. Since the magnetic field is constantly changing due to the pattern, an electrical signal is generated, which in turn can be amplified and converted into an acoustic signal.

To make music on damaged tapes audible again, Gliga does not rely on the magnetic field, but rather on the individual compass needles that generate this field. “The magnetisation states of these tiny particles, whose size is less than a tenth of the diameter of a human hair, can be read out almost individually in the synchrotron and converted into a high-quality audio signal.”

Giliga is collaborating with the Swiss National Sound Archives and the Montreux Jazz Digital Project – launched in 2010 by EPFL and the Claude Nobs Foundation to digitise, preserve and enhance the audiovisual collection of the Montreux Jazz Festival – to develop his method further. “We want to create the ultimate copy – the best quality for the best music,” the physicist adds with a smile. ◆

Latest PSI research news

1 Exploring Jupiter's moons

The European Space Agency has launched the JUICE (Jupiter Icy Moons Explorer) mission. Its aims include the exploration of three of the largest moons of the planet Jupiter – Ganymede, Callisto and Europa. Researchers suspect that gigantic oceans lie beneath the thick layers of ice that cover these satellites, possibly hosting extraterrestrial life. Besides fundamental questions about the formation of planetary systems, the mission also wants to find out if Jupiter's icy moons offer the necessary conditions for the emergence and long-term existence of life as we know it. On board the space probe is a high-tech detector called RADEM (Radiation-hard Electron Monitor), developed at PSI. The measurement technology built into the apparatus, which is about the size of a conventional car battery, should provide information about the complex radiation conditions and highly dynamic magnetic environment of the Jupiter system.

Further information:
https://psi.ch/en/node/56710

Around **8** years until the mission reaches the Jupiter system.

Around **780** million kilometres is the distance to the sun.

Roughly **3** kilograms is the weight of the entire measurement apparatus developed at PSI.

2 New process for even more compact computer chips

A group at PSI, in collaboration with researchers at University College London, has made an important advance towards further miniaturisation of computer chips. The researchers proved that photolithography – the standard exposure process used in the mass production of chips – also works even if no photosensitive layer has been applied to the silicon. With the new process – using extreme UV light, among other things – the researchers managed to create conductor tracks just 75 nanometres wide. For comparison: that's around 930 times thinner than a human hair. These are the smallest structures ever written with photons without a photosensitive layer.

Further information:
https://psi.ch/en/node/57573

3 Joint initiative for the climate

Zero greenhouse gas emissions by 2050: Switzerland can only achieve this ambitious goal if science, business, politics and society work towards it together. With the Swiss Centre of Excellence on Net-Zero Emissions (SCENE), the six institutions of the ETH Domain are teaming up to support the decarbonisation of the country, with PSI as the leading house. It combines the expertise of more than 30 research laboratories and provides a platform for interdisciplinary collaboration across institutional boundaries within the ETH Domain. All institutions of the ETH Domain are involved in the joint initiative: PSI as the leading house, Empa, WSL, Eawag, ETH Zurich and EPFL. The ETH Board is providing half the project funding, with the six participating institutions contributing the other half – the total budget over the three-year project period is 17.2 million Swiss francs.

Further information:
https://psi.ch/en/node/57201

4 Fighting tumours down to the last cancer cell

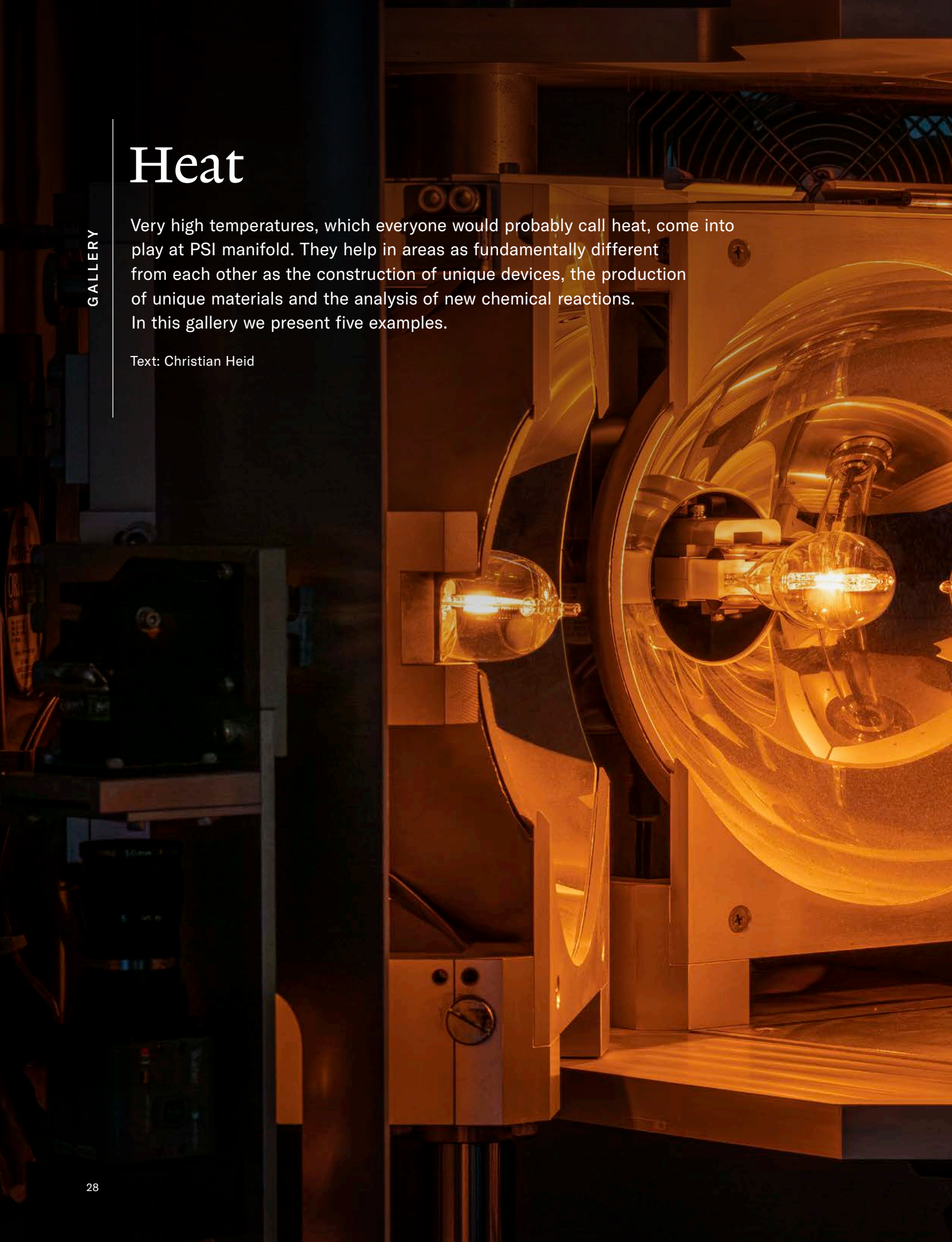
Around one-third of patients with metastatic prostate cancer do not respond adequately to existing drugs, because individual cancer cells can survive and form new metastases. A drug developed by PSI researchers could increase the chance of survival for such patients in the future. It contains the radioactive isotope terbium-161, which emits electrons with low energy and thus with a range of only a few micrometres. Brought to the cancer cell by a carrier molecule, they release all their energy in a cell or clump of cells, so their destructive power is much more precisely targeted. The tumour cell is damaged, can no longer divide and ultimately dies, preventing metastases from forming. Preclinical trials with mice at PSI have already shown that this approach promises to be successful. Within the framework of the PROGNOSTICS project, in cooperation with the University Hospital of Basel and ETH Zurich, the new drug is now to be tested for the first time on humans.

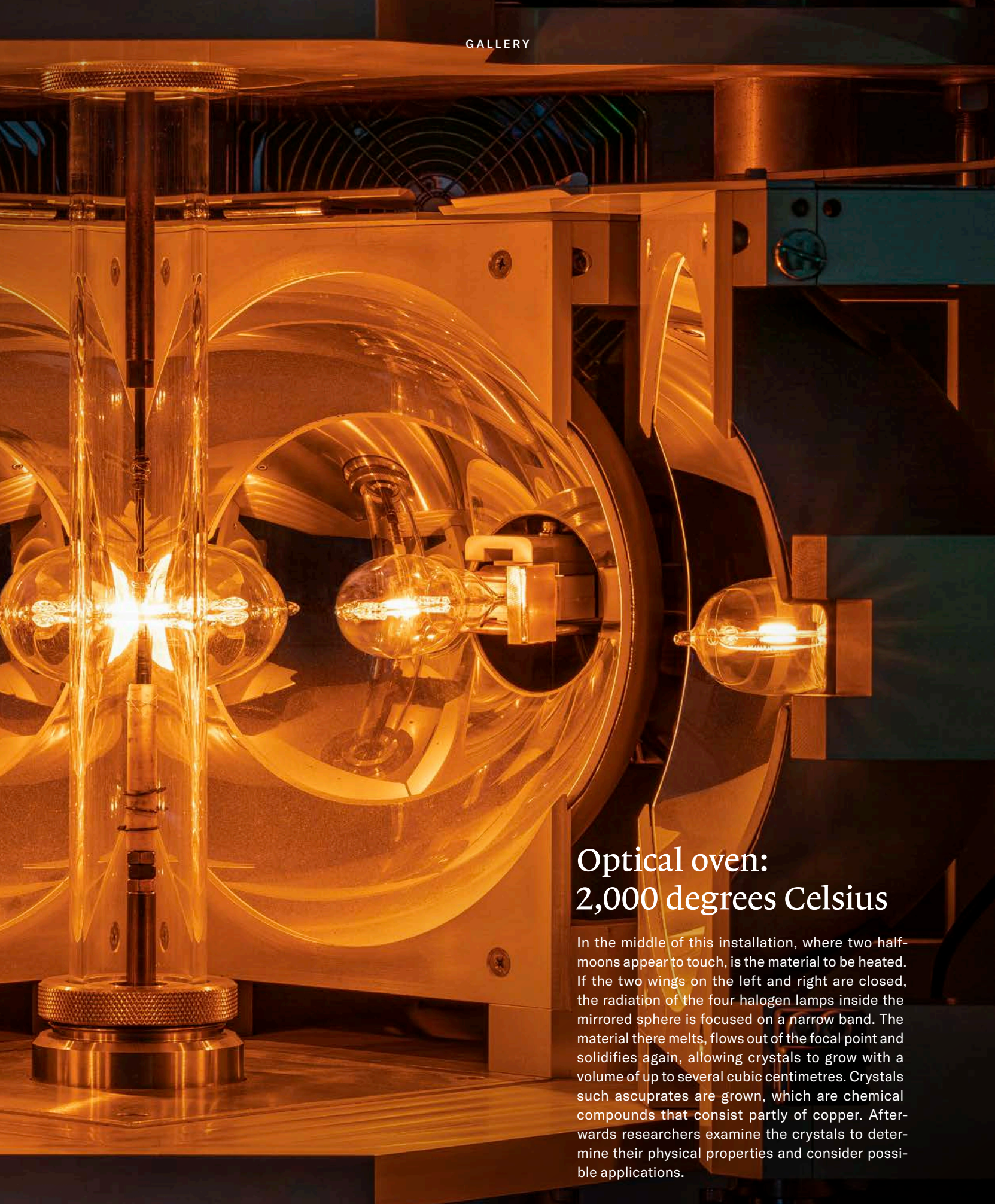
Further information:
https://psi.ch/en/node/58029

Heat

Very high temperatures, which everyone would probably call heat, come into play at PSI manifold. They help in areas as fundamentally different from each other as the construction of unique devices, the production of unique materials and the analysis of new chemical reactions. In this gallery we present five examples.

Text: Christian Heid





Optical oven: 2,000 degrees Celsius

In the middle of this installation, where two half-moons appear to touch, is the material to be heated. If the two wings on the left and right are closed, the radiation of the four halogen lamps inside the mirrored sphere is focused on a narrow band. The material there melts, flows out of the focal point and solidifies again, allowing crystals to grow with a volume of up to several cubic centimetres. Crystals such ascuprates are grown, which are chemical compounds that consist partly of copper. Afterwards researchers examine the crystals to determine their physical properties and consider possible applications.

Electric arc furnace: 3,000 degrees Celsius

Clearly visible in the greenish-blue light behind the porthole is the vertical black rod of the tungsten cathode, at the end of which the arc begins, throwing a carpet of light downwards to a copper crucible on which the metal sample lies. In a matter of seconds, high-purity metallic compounds of materials are produced in this oven. Does the newly made metal compound now have the desired properties? Analyses at PSI's large research facilities will reveal the answer.

Induction soldering: 850 degrees Celsius

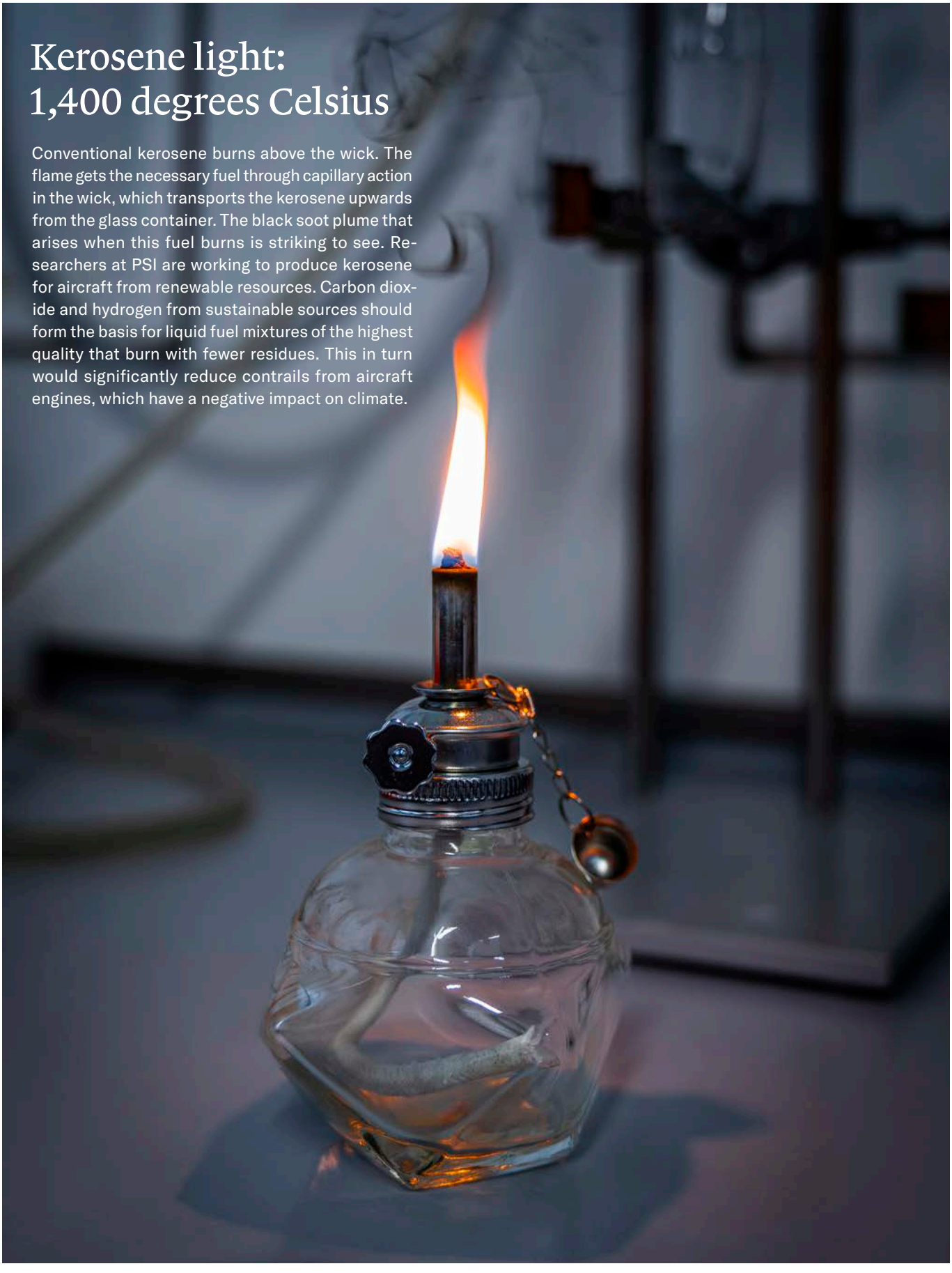
Without contact, a two-wind standard inductor causes a screw thread to anneal and creates a connection with the underlying flange. To achieve this, the inductor's high-frequency alternating current generates an electromagnetic field. The field induces a current in the screw thread and internal resistance in the metal of the screw thread leads to heating. The advantage of this soldering method lies in the exclusive and uniform heating of the metal. Induction soldering is often used for the construction of low-temperature systems such as those required for cooling in PSI's large research facilities.

Minireactor: 1,000 degrees Celsius

Glowing in a vacuum on the other side of the viewing window – surrounded by a tangle of sample holder, water cooling and cables – is silicon carbide, a ceramic composed of silicon and carbon. This reactor is heated by an electrical voltage while various gas mixtures flow through it. It's the chemical reactions now taking place that are of scientific interest. They are recorded by detectors using ultraviolet light at the large research facility Swiss Light Source SLS. Subsequently, different reactive environments and their dynamics can be described. The goals can range from optimising the reaction mechanisms of industrial catalytic processes to gaining a better understanding of the chemistry of interstellar processes.

Kerosene light: 1,400 degrees Celsius

Conventional kerosene burns above the wick. The flame gets the necessary fuel through capillary action in the wick, which transports the kerosene upwards from the glass container. The black soot plume that arises when this fuel burns is striking to see. Researchers at PSI are working to produce kerosene for aircraft from renewable resources. Carbon dioxide and hydrogen from sustainable sources should form the basis for liquid fuel mixtures of the highest quality that burn with fewer residues. This in turn would significantly reduce contrails from aircraft engines, which have a negative impact on climate.



Getting back to cycles

Claudia von Scala gained her PhD at the Paul Scherrer Institute in the 1990s. Today she works at the industrial company Sulzer, where she is responsible for sustainability.

Text: Andreas Lorenz-Meyer

Polymers form the basic framework for every plastic, whatever the item: buckets, suitcases, foils, carpets, sockets or plastic bottles. The term polymer comes from the Greek words for “many” and “part.” That captures the meaning pretty exactly, since polymers are made up of many similar building blocks, so-called monomers, whose basic structure consists of a carbon string. Anyone who talks with chemical engineer Claudia von Scala comes to realise the world is full of polymers – and these are by no means limited to plastics, but start with humans. “We too are carbon-based, just in a different way,” says the 53-year-old. “We’re also largely made up of polymers.” Examples include proteins and the genetic material DNA. And in everyday life, too, we are almost constantly dealing with polymers, for example when cooking. “Take caramel, for instance,” von Scala says. “When sugar is heated in a pot, the carbohydrates in it join together to form polymers.”

When von Scala talks about chemistry, her enthusiasm for the subject is immediately apparent. She works on the 17th floor of the Sulzer headquarters building in Winterthur. Sulzer is an industrial company steeped in tradition, starting as a foundry in 1834 and thriving today as a manufacturer of products based on fluid engineering, such as pumps and systems for separating or removing solids. Claudia von Scala works as technology manager for sustainable solutions in the area of chemical technology. Her task is to develop chemical processes for making sustainable products, such as sustainable plastics. So polymers and monomers are part of the basic equipment for von Scala’s work.

She grew up in São Paulo, the largest city in Brazil. Since her maternal grandfather was Swiss, she attended the Swiss school there, the Escola Suíço-Brasileira de São Paulo. Her chemistry teacher, who had previously worked at ETH Zurich, recognised her talent for substances and their reactions and advised her to continue her education in Switzerland after graduation. She took his advice: in 1989, having just turned 19, she boarded a plane, crossed the Atlantic and began studying chemical engineering at ETH Zurich. Why this subject and not chemistry? “Because I wanted to go right back to Brazil after my studies. There is much more manufacturing than research there. So my job prospects would have been better as a chemical engineer.” Also, the multidisciplinary approach of chemical engineering appealed to her. “You need to understand not only chemistry, but also mechanical engineering, structural analysis and industrial processes.”

In spite of her plans for returning to South America, von Scala stayed in Switzerland. “After a while, I had built myself a life here and found friends.” And she had met her future husband, who was also Brazilian and studying chemical engineering. In addition, her doctoral thesis was yet to be done. After completing her master’s degree in 1994, she asked herself where she should do her doctoral work. She would have liked to go to the French-speaking part of Switzerland, but EPFL in Lausanne had filled all available doctoral positions with its own students. When the opportunity for a doctoral position at the Paul Scherrer Institute presented itself, she jumped at the chance immediately. “I had a project and three years’ time. I had to make something out of it.” She already possessed the theoretical knowledge, and now it was time to master the practical side. With a small reactor, she started a series of experiments. The task was to gasify waste wood with the addition of a small amount of oxygen and use the resulting gas to synthesise methanol. Not so easy, since the molecules are invisible. “So you can’t see how and why molecules react. To understand what happens during the experiments, you need analytical methods, which I learned from scratch at PSI.”

Von Scala completed her doctorate in 1997 and subsequently found a job at Sulzer. Married since 2001, she has three sons who are now 16, 18 and


PLA
PET

“We need to learn to close the cycle again.
That’s how nature, the whole planet, works.”

Claudia von Scala, chemical engineer

20 years old. She holds three passports: Swiss, Brazilian, and – through her father – Austrian. Von Scala has now been living here for 34 years – long enough to be able to clearly explain the differences between her old and new homes. “They are two extremes. In Brazil, people like to live for today, want to enjoy the moment and don’t think much about the future. That’s because the future there is unpredictable,” von Scala explains. “Here in Switzerland, in contrast, many people often think about tomorrow and are busy with plans for the future. Neither is perfect – and I try to find the middle way: enjoy the moment, but don’t forget about tomorrow.”

That’s a good fit with her present job, where sustainability is her responsibility. Sustainability means ensuring sufficient natural resources will still be available tomorrow and that Earth’s climate will be tolerable. That brings us to von Scala’s current work: the development of sustainable products. With respect to plastics, two aspects need to be considered: How well can the plastic be recycled? And how biodegradable is it?

Time to take a closer look at the structure of plastic. Von Scala stands at a flip chart and draws a structural formula: all C’s, H’s, and O’s – carbon, hydrogen, and oxygen atoms – and lines that connect the atoms with each other. “This here is PET, polyethylene terephthalate.” This complicated word slips easily from her lips. PET, a fossil fuel-based plastic in the polyester family, is best known for making soft drink bottles. PET has practical properties: very stable, transparent, and impermeable to gas, so the carbon dioxide does not escape. And PET is easy to recycle – better, for example, than polypropylene (PP) and polyethylene (PE), the most common plastics. The recycling rate for PET bottles is therefore high in Switzerland, 77 percent for the year 2022.

Yet many countries around the world lack an appropriate recycling system, and they also have no plants capable of incinerating plastic to generate electricity or heat for industrial processes. Viewed globally, PET bottles are often neither recycled nor incinerated in a controlled manner. Instead, they end up in sealed landfills or, even worse, in the environment – and ultimately in the ocean, where they remain for hundreds of years, since PET is made from petroleum or natural gas and is not readily biodegradable.

But plastic need not be made from fossil fuels. Von Scala draws a second structural formula. “This here is PLA.” The abbreviation PLA stands for polylactide, a plant-based plastic made by fermenting corn or sugarcane into lactic acid and then assembling the lactic acid monomers into long chains. The technical term is polymerisation. The end product is PLA, a biopolymer with properties similar to those of fossil fuel-based PET. Von Scala has brought two such products: an anthracite-coloured PLA cup and a matching bowl. Both feel absolutely stable and are superficially indistinguishable from conventional plastic.

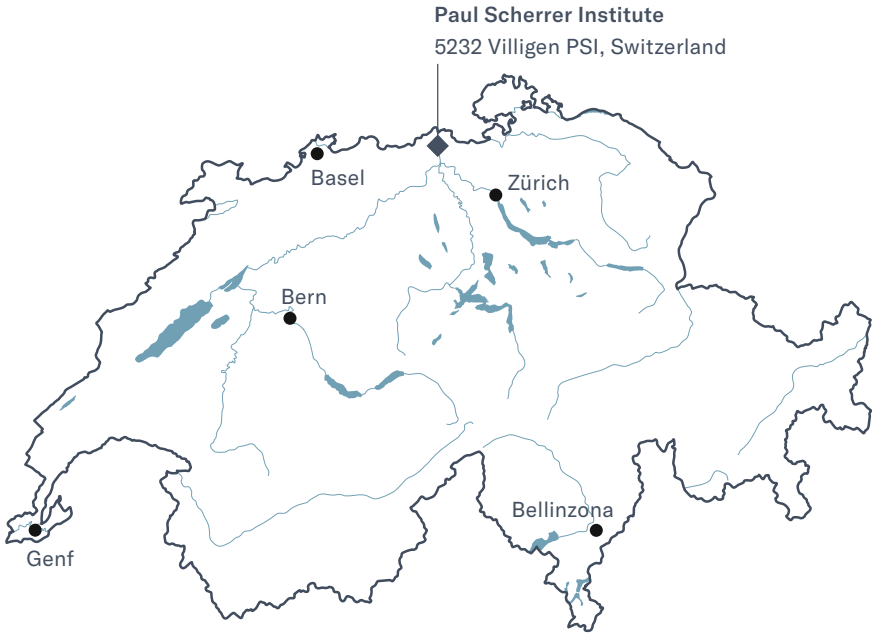
We also encounter plant-based plastic in supermarkets: the see-through covering on salad bowls can be made from biopolymers. But there’s a catch: our plastic waste problems won’t simply vanish into thin air, since PLA too is made to last a long time. Consequently, PLA doesn’t simply disappear. In nature, it takes years for it decompose. “It’s only when we put it into an industrial composting system and add the right microbes that it breaks down quickly,” von Scala explains.

So in plastic production there are always trade-offs that must be weighed against each other: quality and durability on the one hand, degradability on the other. Von Scala is working towards a balance between these two sides. As part of one project, she is targeting the basic building blocks of biopolymers, the monomers. In the case of PLA, the monomer is called lactide – and von Scala and her team are working to optimise the mixture. With the help of additives, it should be possible to control degradability and stability more effectively. “Unfortunately, chemistry doesn’t offer a switch we can install that would let us produce a reaction or decomposition at the push of a button.”

She has a second project where the focus is on recycling polystyrene, which is used to make insulating materials. Even though it is fossil fuel-based, polystyrene has a lot of potential in terms of recyclability. Von Scala wants to convert the polymer chains in the plastic back to monomers. The process this requires is called pyrolysis. “When something organic is heated, it burns. When it is heated without oxygen, the carbon chains simply break apart. For that to happen, a few catalysts are needed so they break nicely.” At first, however, these monomers are still mixed with other substances that come either from incomplete pyrolysis of the polystyrene or from other plastics. Von Scala is mainly concerned with the purification of this mixture. In the end you have pure styrene again, the monomer – and thus the basic building block for the production of new polymers. “Now the cycle is closed.”

That’s what it’s all about for von Scala: closing cycles, supporting a circular economy. “For a long time, we didn’t pay attention to this. We were thinking linearly, extracting all the carbon that has been lying underground for millions of years, and burning it in a short period of time. Now we have global warming, we need to learn to close the cycle again. That’s how nature, the whole planet, works.” ◆

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



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 2,200 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, ETH Lausanne (EPFL), 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). We conduct basic and applied research and thus work on sustainable solutions for central questions from society, science and business.

Complex large research facilities

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

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

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

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. 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.

Four 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.

Our own research is concentrated on four focus areas. In the area of Future Technologies, we investigate the diverse properties of materials. With the knowledge this yields, we create the foundations for new applications – whether in medicine, information technology, energy production and storage, or new industrial production methods.

The goal of our work in the focus area Energy and Climate is developing new technologies for a sustainable and safe energy supply, as well as for a clean environment. Also in this area, we are investigating interconnections within Earth's climate system.

In the focus area Health Innovation, researchers are looking for the causes of diseases as well as for potential therapeutic methods. In addition, we operate the only facility in Switzerland using protons for the treatment of specific cancer diseases. This special technique makes it possible to destroy tumours in a targeted way while leaving the surrounding health tissue largely undamaged.

In the area Fundamentals of Nature, researchers are seeking answers to fundamental questions about the basic structures of matter and the functional principles of nature. They investigate the structure and properties of elementary particles – the smallest building blocks of matter – or clarify fundamental processes in living organisms. The knowledge gained in this way opens up new approaches to solutions in science, medicine and technology.

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.

PUBLISHING DETAILS

5232 – The magazine of the Paul Scherrer Institute

is published three times a year.
Issue 3/2023 (September 2023)
ISSN 2674-1261

Publisher
Paul Scherrer Institut
Forschungsstrasse 111
5232 Villigen PSI, Switzerland
Telephone +41 56 310 21 11
www.psi.ch

Editorial team
Monika Gimmel, Martina Gröschl, Christian Heid, Sebastian Jutzi (Lead), Benjamin A. Senn, Dr. Mirjam van Daalen

Translation
Patrick Regan

Editor
Graeme High

Design and Art Direction
Studio HübnerBraun

Photos
Paul Scherrer Institute / Markus Fischer, except: pages 35–37: Jürg Waldmeier.

Illustrations and graphics
Paul Scherrer Institute / Monika Blétry, except: pages 6 / 7: Daniela Leitner; page 17 above: Alamy; page 25: Paul Scherrer Institute / Christoph Schütz; pages 26 / 27: ESA (European Space Agency); page 41: Studio HübnerBraun.

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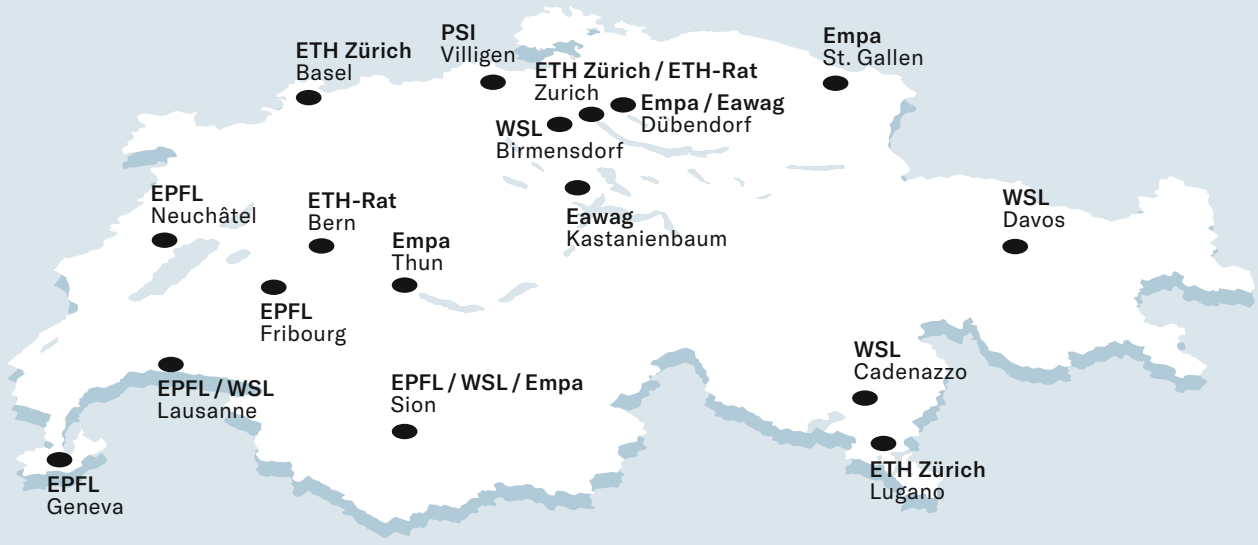
PSI and ETH Domain



Coming up in the next issue

PSI operates an ensemble of large research facilities that is unique worldwide, and is the largest research institute for natural and engineering sciences in Switzerland. This makes it an important part of an even bigger network of scientific and research institutions: the ETH Domain. Together with the two universities, the Swiss Federal Institute of Technology Lausanne EPFL and ETH Zurich, and the research institutes Empa, Eawag and WSL, PSI creates cutting-edge knowledge to master the diverse challenges we are facing. These include, for example, innovative materials – for sustainable processes and products or for quantum computers – as well as research on energy and the environment, and innovation in the field of medicine. We present outstanding examples of excellent research only made possible through collaboration across a strong community.

Paul Scherrer Institut
Forschungsstrasse 111, 5232 Villigen PSI, Switzerland
www.psi.ch | +41 56 310 21 11