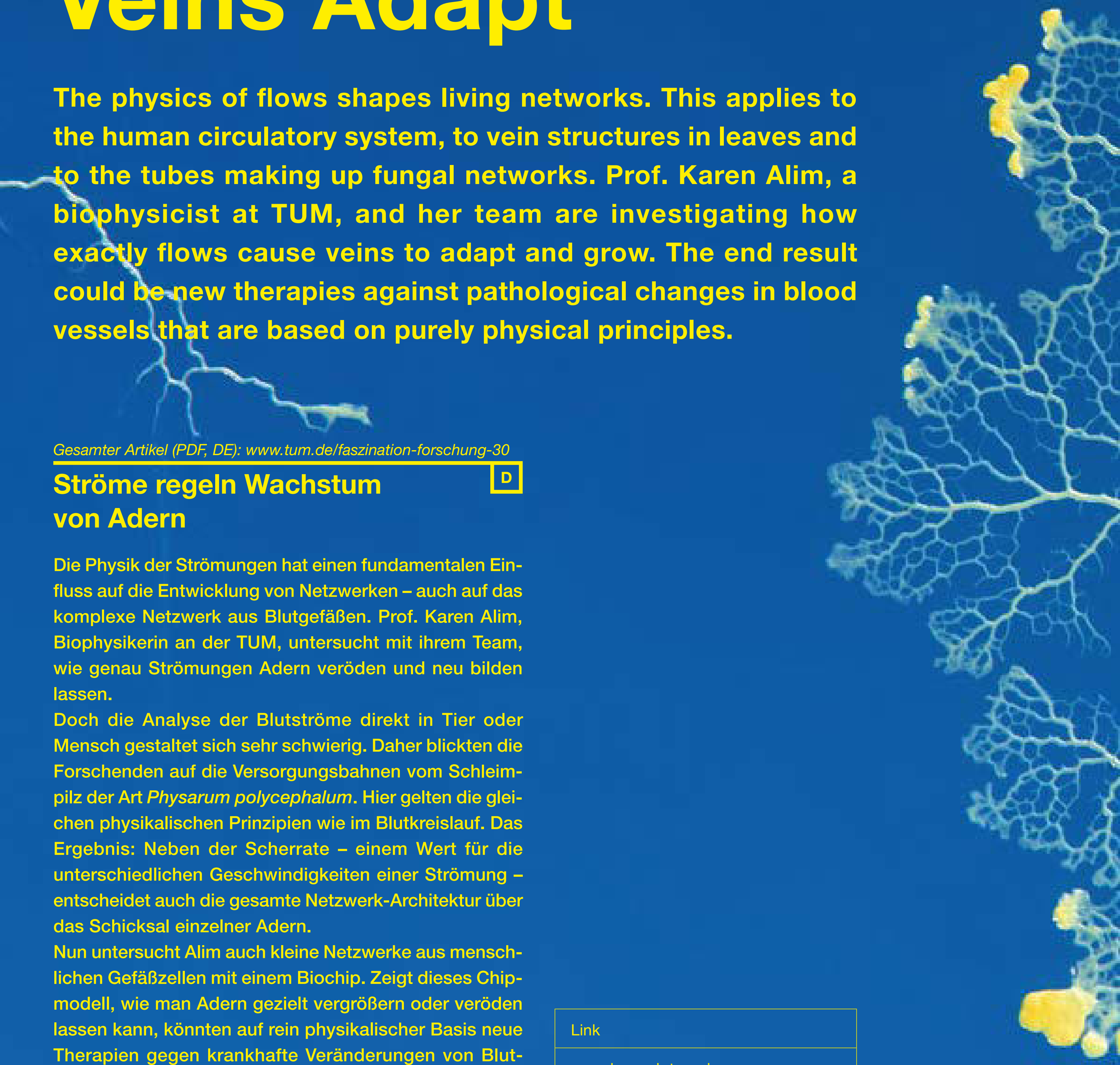
Flows Govern how **Veins Adapt**

The physics of flows shapes living networks. This applies to the human circulatory system, to vein structures in leaves and to the tubes making up fungal networks. Prof. Karen Alim, a biophysicist at TUM, and her team are investigating how exactly flows cause veins to adapt and grow. The end result could be new therapies against pathological changes in blood vessels that are based on purely physical principles.



Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-30

Ströme regeln Wachstum von Adern

D

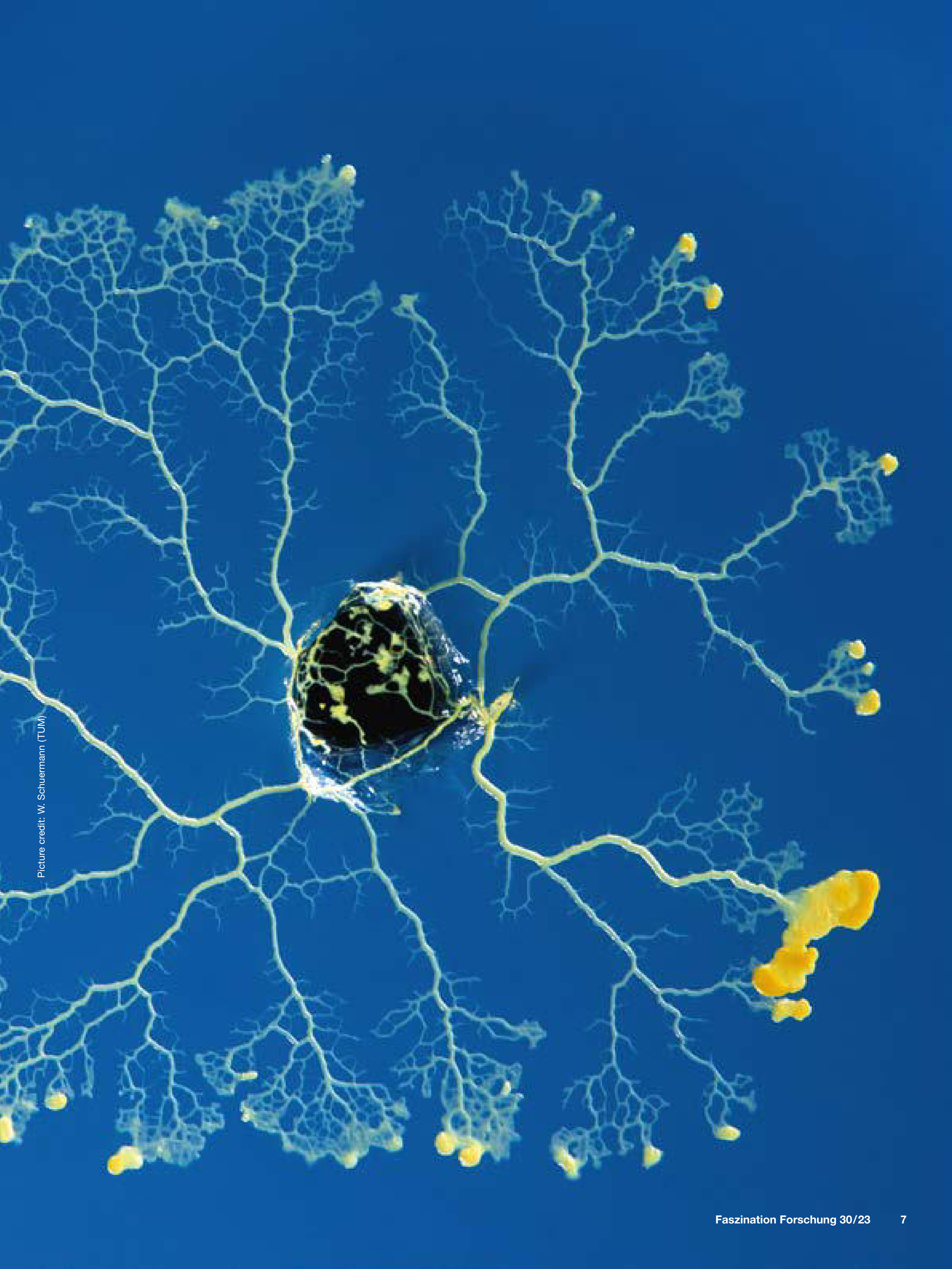
Die Physik der Strömungen hat einen fundamentalen Einfluss auf die Entwicklung von Netzwerken – auch auf das komplexe Netzwerk aus Blutgefäßen. Prof. Karen Alim, Biophysikerin an der TUM, untersucht mit ihrem Team, wie genau Strömungen Adern veröden und neu bilden lassen.

Doch die Analyse der Blutströme direkt in Tier oder Mensch gestaltet sich sehr schwierig. Daher blickten die Forschenden auf die Versorgungsbahnen vom Schleimpilz der Art *Physarum polycephalum*. Hier gelten die gleichen physikalischen Prinzipien wie im Blutkreislauf. Das Ergebnis: Neben der Scherrate – einem Wert für die unterschiedlichen Geschwindigkeiten einer Strömung – entscheidet auch die gesamte Netzwerk-Architektur über das Schicksal einzelner Adern.

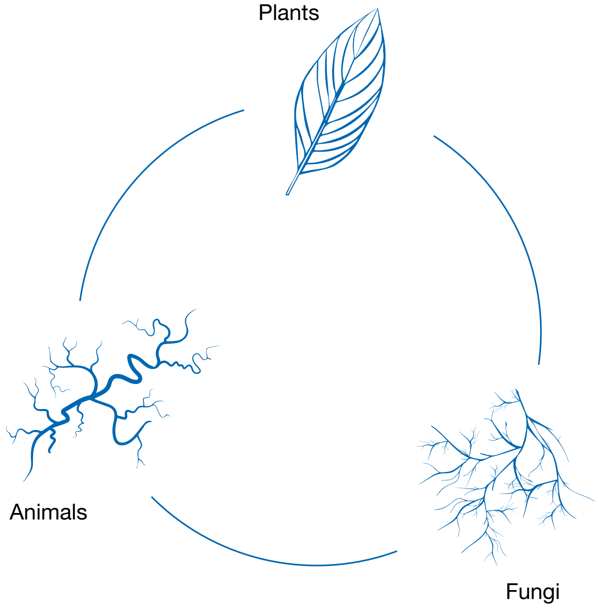
Nun untersucht Alim auch kleine Netzwerke aus menschlichen Gefäßzellen mit einem Biochip. Zeigt dieses Chipmodell, wie man Adern gezielt vergrößern oder veröden lassen kann, könnten auf rein physikalischer Basis neue Therapien gegen krankhafte Veränderungen von Blutgefäßen entstehen. □

Link

www.bpm.ph.tum.de



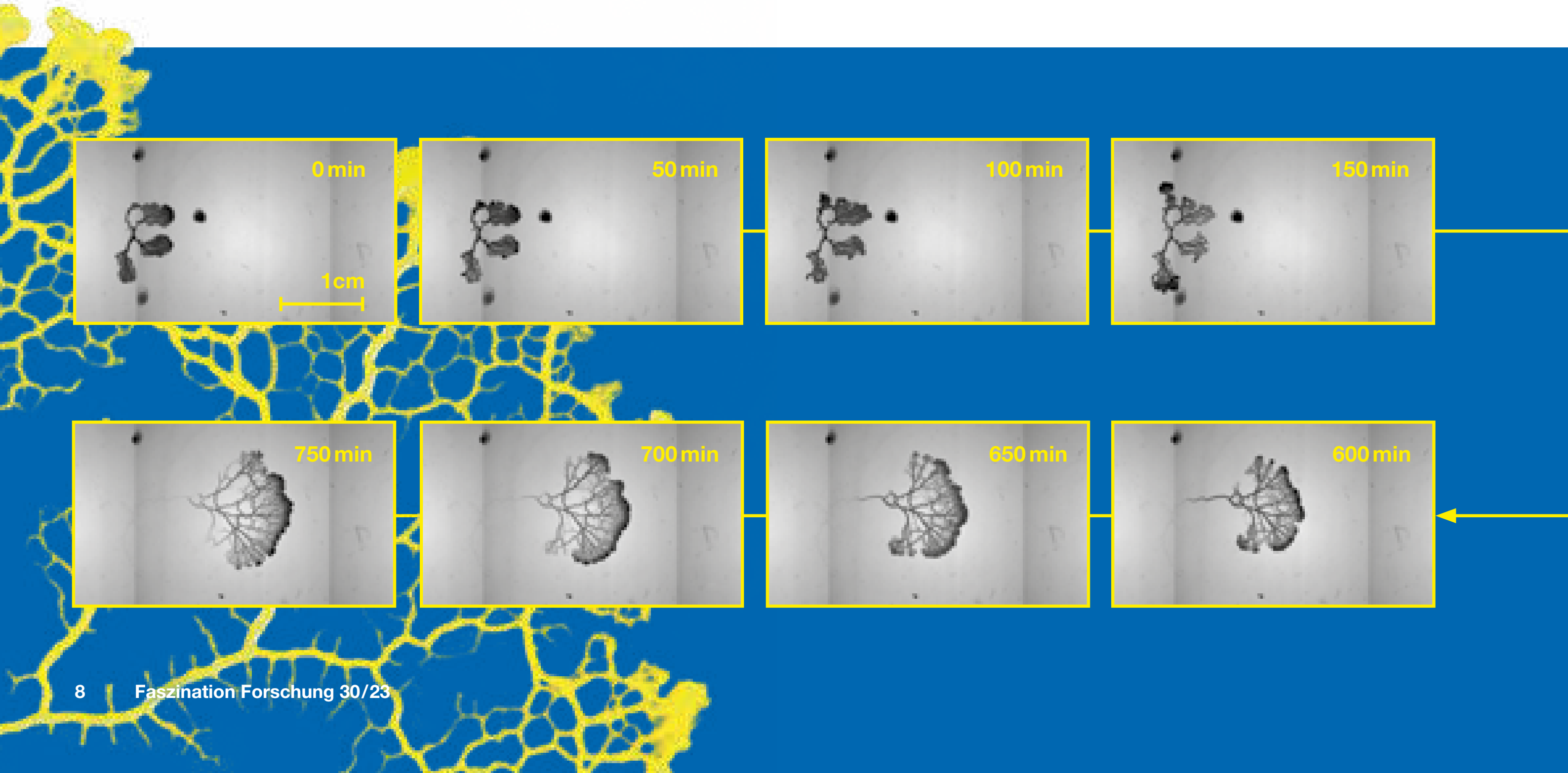
Picture credit: W. Schuermann (TUM)

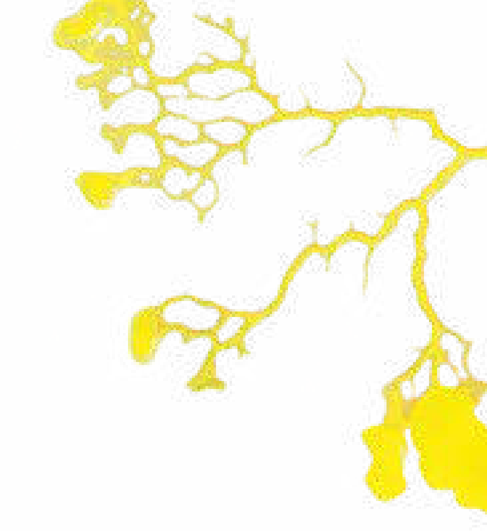


Living tubular networks are a fundamental building block of life. They form the vessels pervading us as well as transport veins in leaves. They also exist in pure form as the body plan of fungi and slime molds.

Every day, the human heart beats around 100,000 times – fairly slowly when we're sitting down and very fast when we're running. Although this hollow muscular organ weighs only 300 grams, it pumps up to 7,000 liters of blood through centimeter-wide arteries to ultra-fine capillaries measuring just micrometers across. This complex network of veins and arteries is constantly reorganizing itself, with some blood vessels vanishing and new ones forming. It is precisely this continuous process of growth and decay that TUM biophysicist Karen Alim and her team are working to understand in more detail. Ultimately, a blood vessel's fate is determined not solely by behavior, environment, nutrients and toxins. The physics of flows also plays a fundamental role in the organization of these networks.

"A network reorganizes itself as soon as blood flows through it," says Alim. In living systems and physical systems, there is always a drive to achieve the maximum possible benefit – in this case, an optimal circulatory system – with the least possible effort. However, scientists are still in the dark about many of the finer details of the relationship between blood circulation and blood vessel dynamics. This means that physicists need not look to the vastness of space or peer into the smallest quantum structures to make new discoveries. Even close at hand, in our own bodies, there are still unexplained processes whose cause and effect can be deciphered using the language of physics. "We have an opportunity to play Newton here," says Karen Alim, referring to the field of biological physics she loves so much. "In my youth, for example, I was fascinated by the lotus effect. It inspired me to examine more closely the multifaceted techniques and mechanisms at work in nature."





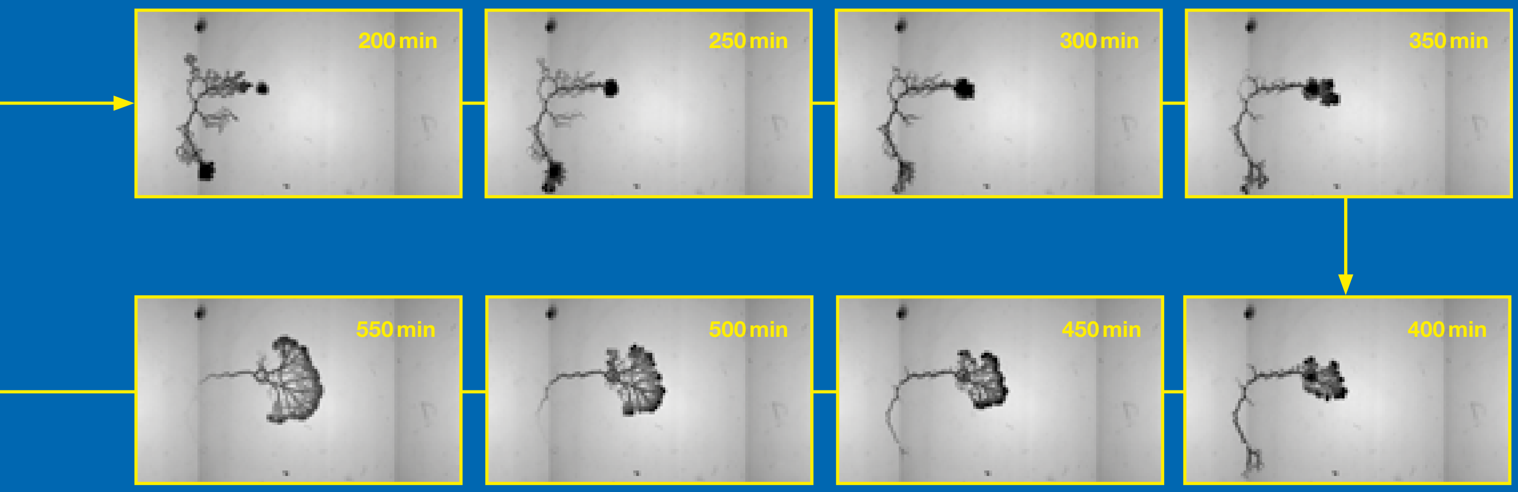
It all lies in the physics

Just as legend has it that a falling apple inspired in Isaac Newton the idea to describe gravity, so observation and experimentation today remain the foundation of models and generally accepted theories. Yet these fundamental methods are extremely difficult to implement when it comes to analyzing blood flows in detail, whether in humans or in animals. “However, similar networks form in many organisms – from animals to plants to fungi,” says Alim. She is well aware of the significant differences in their biology. “That means it’s not their genetic code but rather physics that explains the dynamics within the networks, from the human circulatory system to vein structures in leaves to the supply pathways through a fungal network.”

The general validity of physical principles is what presented Karen Alim’s interdisciplinary team of around 12 researchers with an ideal organism for their experiments: a slime mold of the species *Physarum polycephalum*. This single-celled organism – genetically classified as between animals and plants – builds an ever-changing network of supply lines. In its cytoplasm, nutrients and signaling substances flow through a flat, two-dimensional network of tubes, or veins, measuring just micrometers wide. The TUM scientists pressed the slime mold between a glass slide and a wafer-thin cover. “It grows quite happily there and we can observe and measure the flows using a microscope,” says Alim. ▷

> *“We have an opportunity to play Newton here.”*
>
> Karen Alim

Picture credit: K. Alim (TUM), Graphics: ediundsepp (source: TUM)

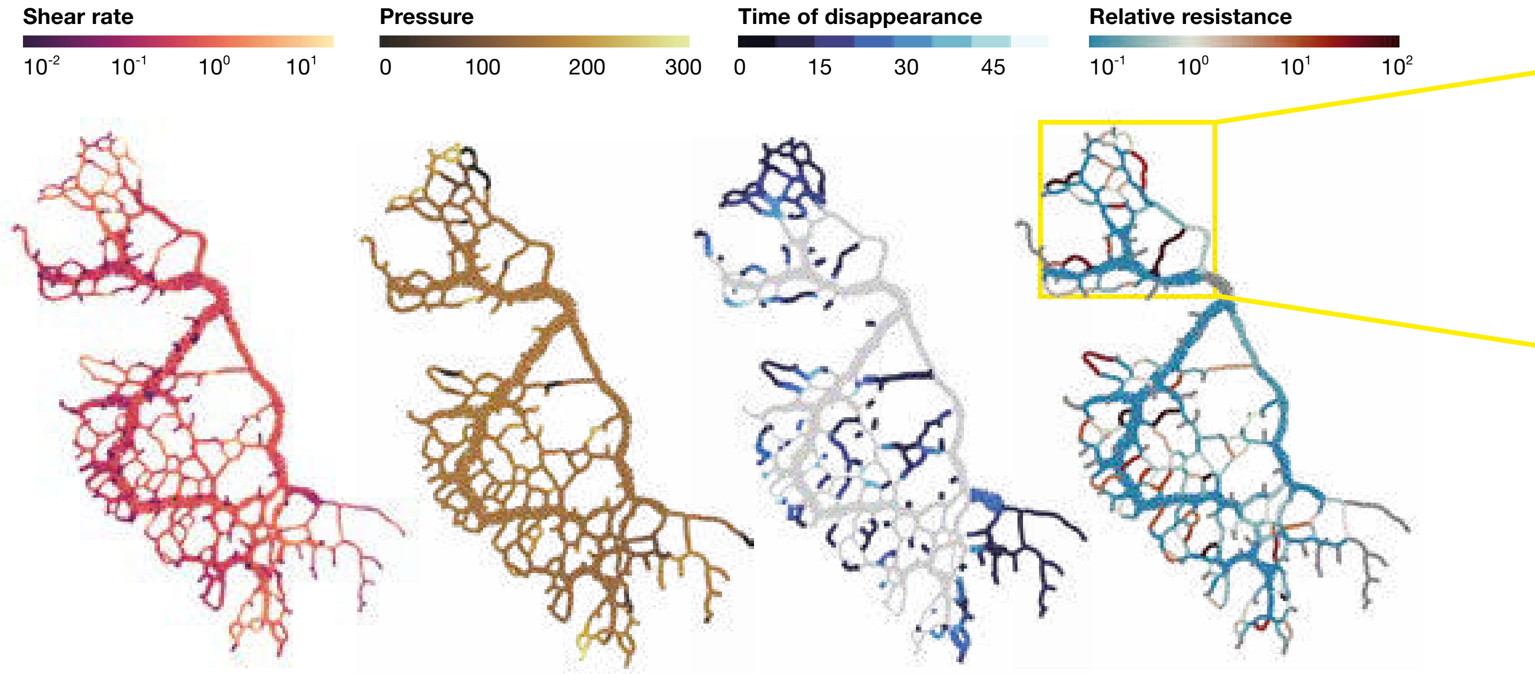


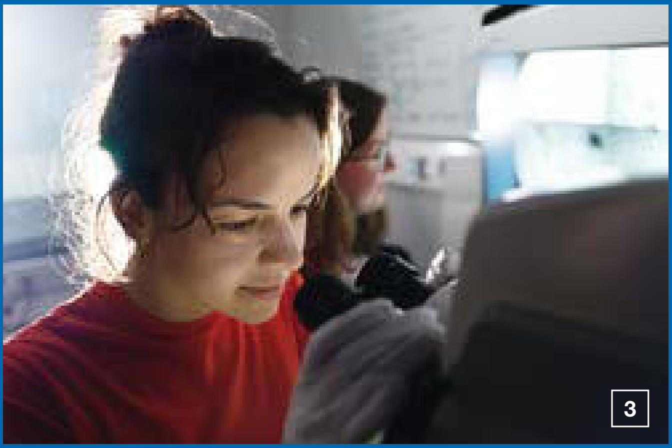
To her surprise, the slime mold did not behave at all as expected. “Initially, we thought that shear rate alone was responsible for the growth of veins in slime mold,” says Alim. In simple terms, shear rate describes the different speeds of a flow through a tube. At the edges, the fluid is subject to frictional forces that slow it down, while the fluid in the center is undisturbed and moves more quickly. A low shear rate with weak shear forces should therefore cause a slime mold vein to shrink until it eventually vanishes, while high shear rates should promote vein growth – or at least, that was the assumption until now. Alim’s measurements, however, did not line up with this

Graphics: ediundsepp (source: TUM); Picture credit: Stefan Woidig

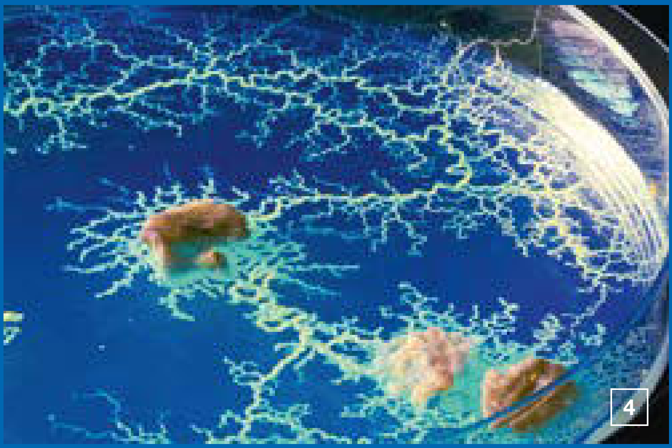
△

Alim’s laboratory cultures the slime molds in liquid. 1 For an experiment, the scientists take a small amount and centrifuge it. 2 From this, they pick up the single-cell mold (plasmodia) and spread 3–4 drops on the Petri dish. 3 The growth of the mold is observed under the microscope. 4 The slime mold aligns its network according to food sources – in this case, oat flakes.





3



4

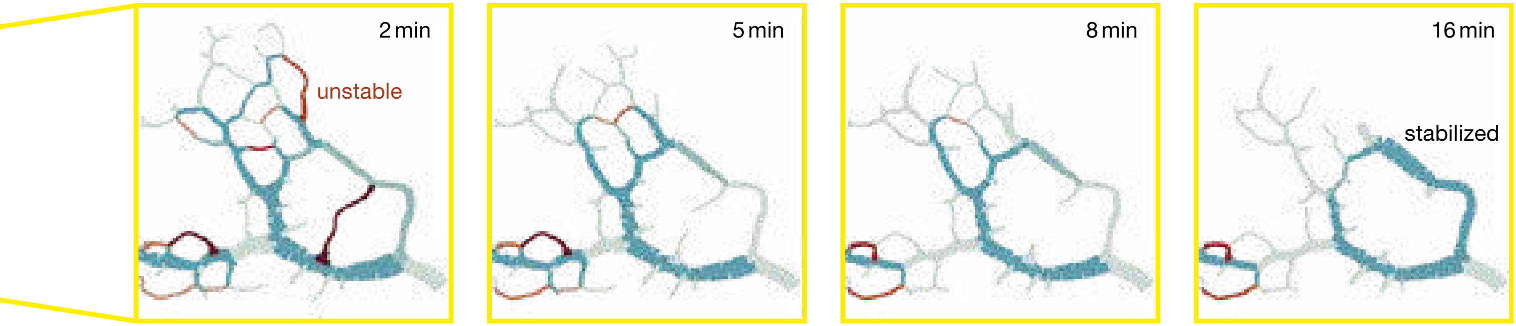
expectation. Despite having identical shear rates, only some of the measured veins shrank, while others remained unchanged. “This parameter alone – shear rates and shear forces – simply does not provide a sufficient explanation,” says Alim. There had to be another factor at play to explain the behavior of the veins in the network.

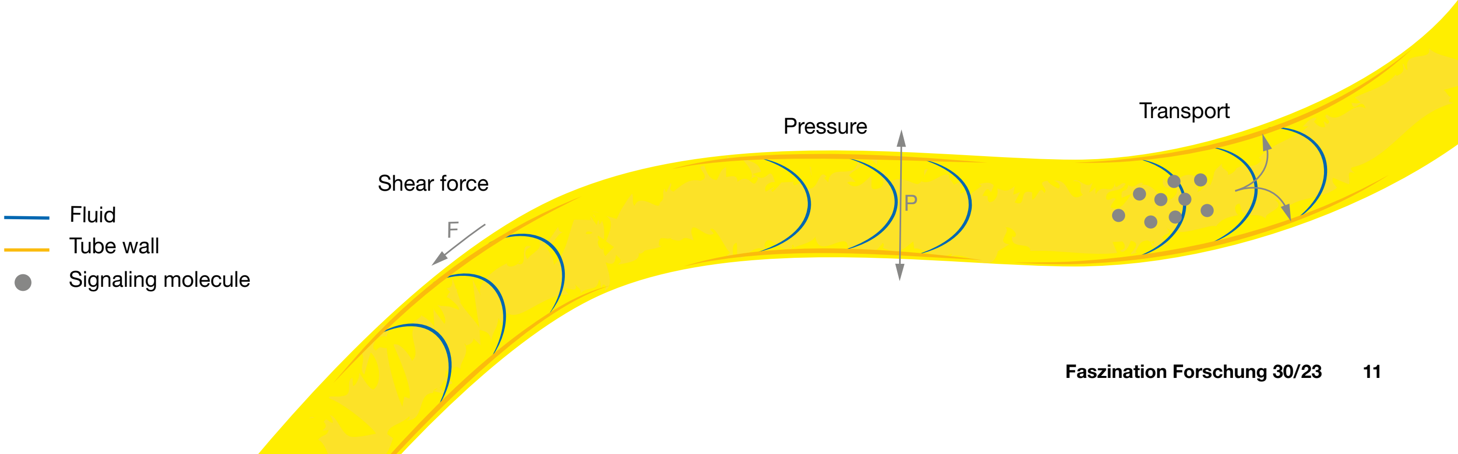
By conducting many more observations – always accompanied by modeling based on complex flow equations – Alim and her team examined the vein behavior in ever-greater detail. Rather than looking solely at individual veins, the scientists considered the network as a whole. This wider focus ultimately delivered the solution. ▷

▽

Shear force, but also pressures and concentration gradients, determine whether veins grow or shrink. But the network architecture, i.e. the condition of neighboring veins, also has an effect. Thus, growing or shrinking veins also influence the network surrounding them.

Time series of network reorganization





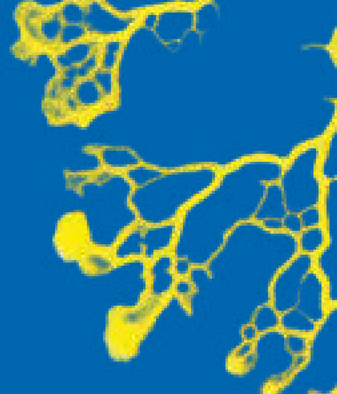
Karen Alim and her PhD student study the growth of a slime mold in the optical microscope.

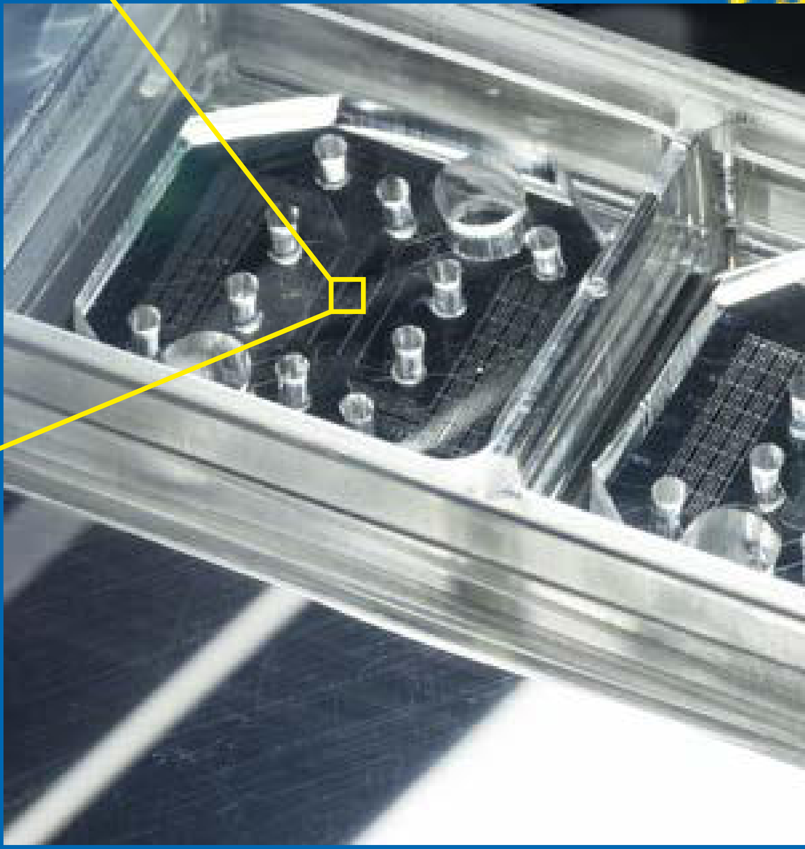
> *“The entire network architecture [...] has an impact on each individual vein.”*
>
> Karen Alim

Picture credit: Stefan Woidig

“The entire network architecture, with all its adjacent larger and smaller pathways, has an impact on each individual vein,” explains Alim. This means, for example, that a small vein would vanish if there was a larger vein nearby. However, if a small vein was surrounded by only other small veins, they would all be maintained. The network’s responses were not immediate and always involved a delay of several minutes. It was this delay that made it so difficult to identify the influence of the network architecture on a single vein. “There is a good explanation for this delay: the cells need some time to react,” says Alim.

The shear rate of flows and the overall network architecture are therefore the decisive factors in the growth or shrinkage of individual veins. Alim is convinced that the same also applies to the blood vessels in humans and animals. In more complex organisms, however, it likely takes considerably longer for networks to reorganize, potentially several hours. With this in mind, Alim is ▷





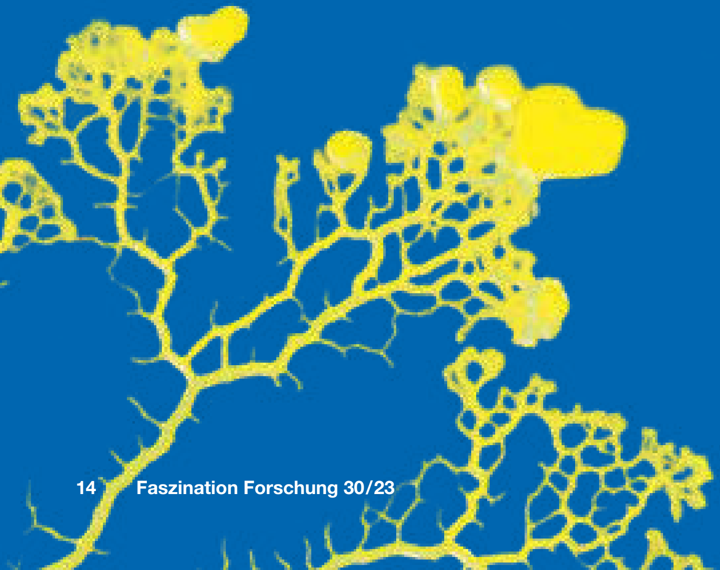
Experiments to program the growth of blood vessel networks (above) with the help of a biochip (right). A medium containing cells that form human blood capillary systems is deposited into the chip cavity. The cells and their network in the chip can be fed and controlled by perfusion flows.

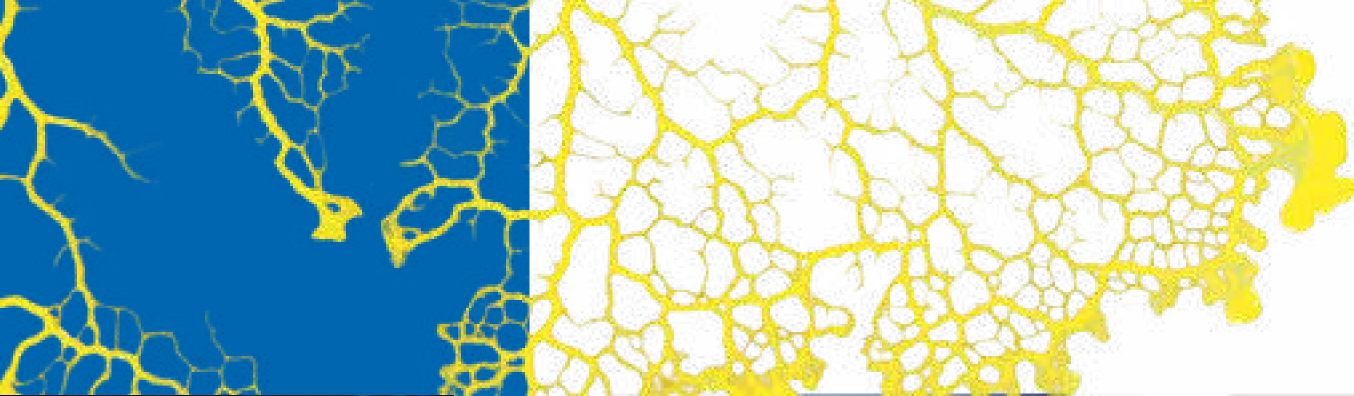
currently planning further experiments using a form of biochip as an observation device. On the surface of the chip, human vascular cells build small networks – like rudimentary artificial circulatory systems. Observing what happens and modeling it could help to explain the behavior of blood vessels. “We hope such chip models will effectively enable us to learn how we could program blood vessels, in other words, deliberately increase or shrink them,” says Alim.

“If we knew the conditions under which blood vessels grow and shrink, there would be plenty of potential applications,” says Alim. In the not-too-distant future, these insights could be used to develop new treatments for pathological changes, including blocked blood vessels. By the same token, these techniques could be applied to deliberately weaken newly formed blood vessels supplying nutrients to a dangerous tumor. “That would be wonderful confirmation that medical progress can be achieved not only in the field of biology, or in chemistry where researchers are looking for new active ingredients, but also through physics,” says Alim. ■

Jan Oliver Löfken

Picture credit: Stefan Woldig





Prof. Karen Alim

has been fascinated by biophysics since she was a child. She studied physics at the University of Karlsruhe, LMU Munich and the University of Manchester. Following her doctorate in theoretical physics (at LMU), she took up a postdoctoral research position at Harvard University before being appointed head of the Biological Physics and Morphogenesis research group at the Max Planck Institute for Dynamics and Self-Organization in Göttingen. In 2019, Alim accepted a professorship in biophysics at TUM and, thanks to a Starting Grant from the European Research Council (2020), has since furthered her research into flows in biological circuits, from fungal networks to the human circulatory system. She is also Vice Dean for Diversity and Talent Management at TUM School of Natural Sciences.