Gold Therapy

The pharmaceutical industry is always in search of new drugs to treat diseases. However, despite the huge diversity of inorganic compounds and materials, the potential offered by inorganic chemistry is largely ignored. Promising results being produced by the TUM research group led by Angela Casini could be about to change that. Her research is laying the groundwork for novel therapies and new drug delivery strategies.

Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Heilen mit Gold

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Fast alle bis dato zugelassenen Arzneistoffe beruhen auf organischen Substanzen. Anorganische Verbindungen kommen heute nur bei wenigen medizinischen Anwendungen zum Einsatz. Das will Prof. Angela Casini mit ihrer Arbeitsgruppe für Medizinische und Bioanorganische Chemie an der TUM ändern. Sie sieht ein großes Potenzial in anorganischen Wirkstoffen, da Metallionen essenzielle Schlüsselrollen in biologischen Systemen einnehmen. So gelang es ihrem Team, mit metallorganischen Goldkomplexen winzige Wasserkanäle in Zellmembranen – sogenannte Aquaporine – selektiv und irreversibel zu hemmen. Ein erster Schritt für einen neuen Ansatz in der Krebstherapie.
Sogenannte supramolekulare metallbasierte Strukturen sind ein weiteres Forschungsfeld der anorganischen Chemie mit Potenzial für verbesserte zielgerichtete Therapien und einen optimierten Wirkstofftransport. Neuartige supramolekulare metallbasierte Käfigkomplexe sollen dabei Arzneistoffe oder Radiopharmaka für bildgebende Verfahren einkapseln und zu vorgegebenen Wirkorten transportieren. Wie molekulare trojanische Pferde im Körper eines Patienten könnten sie etwa die Aufnahme von Medikamenten in Krebszellen erhöhen. Durch erfolgreiche Wirksamkeitsstudien konnte Casinis Arbeitsgruppe bereits eine große Hürde überwinden und den Transport einer von Käfigkomplexen eingekapselten radioaktiven Verbindung durch die Blut-Hirn-Schranke in das Gehirn von lebenden Mäusen bewerkstelligen. Parallel ist die Gruppe stets auf der Suche nach neuen Materialien und therapeutischen Wirkstoffen für die regenerative Medizin. □

Link

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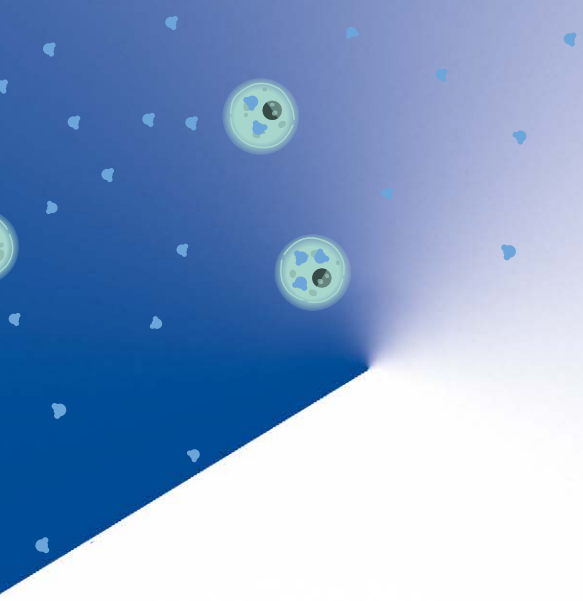
Picture credit: Magdalena Jooss

An organometallic complex containing a charged gold ion blocks the water flow through an aquaporin. Casini's group was the first to develop a gold-based inhibitor acting selectively on tumor cells.

Aquaporins form small channels in the cell membranes. Forming hourglass pores, they enable water and other substances to flow into the cells. Aquaporins play an important role in a number of diseases.

Graphics: ediundsepp (source: TUM/Casini)



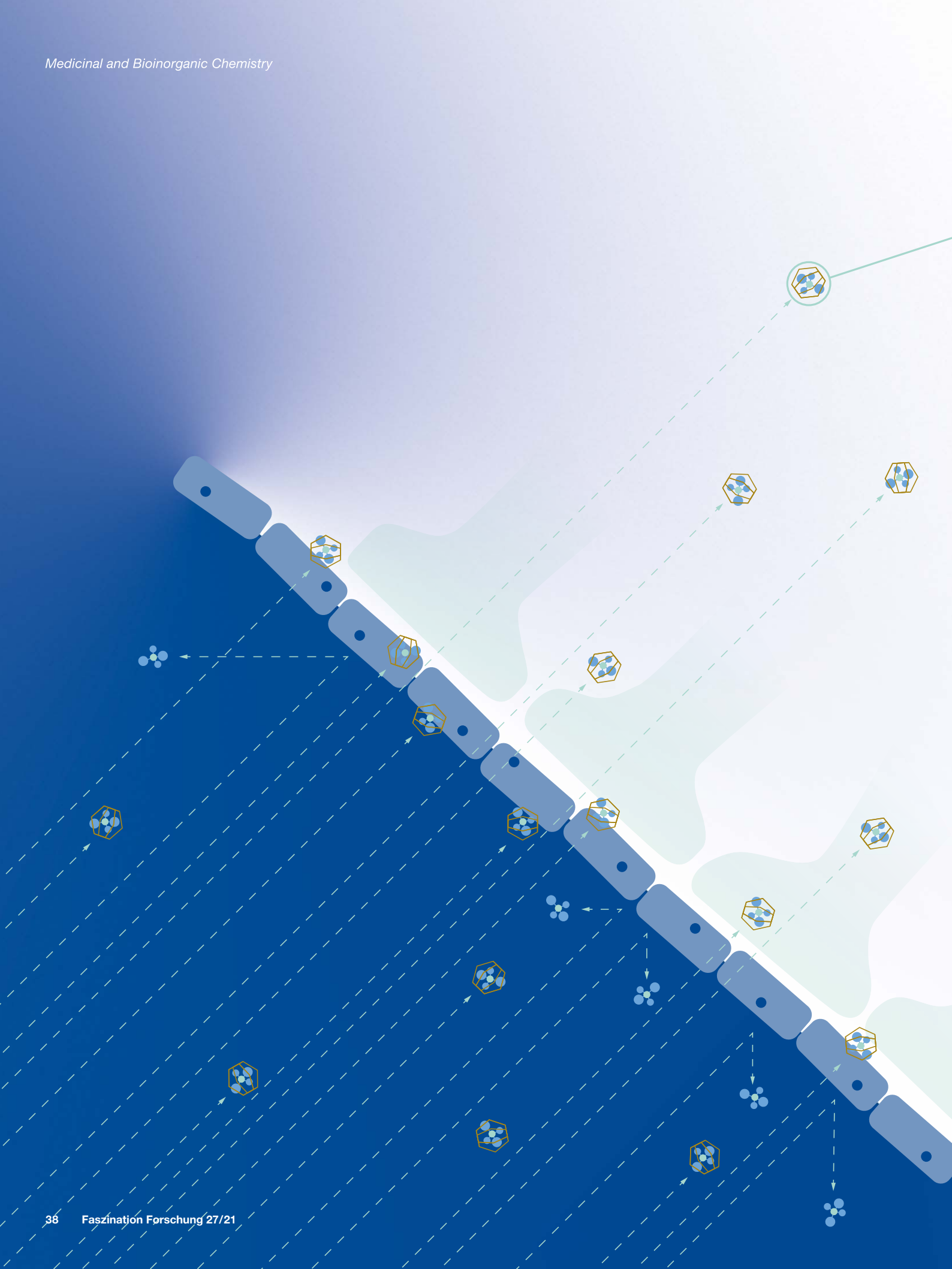
Prof. Angela Casini is using gold to stop water. But it is not raging waters that the Italian professor has in her sights; it is actually the water that flows through tiny channels in the cells that make up our bodies. In the process, her Medicinal and Bioinorganic Chemistry group at TUM is pioneering a completely new approach to fighting cancer and other diseases. Small water channels in tumor cell membranes play an essential, but largely overlooked, role in helping cancer spread around the body. Organometallic complexes, consisting of organic molecular groups clustered around a charged gold ion, are able to block the flow of water through these channels and, the hope is, neutralize tumor cells.

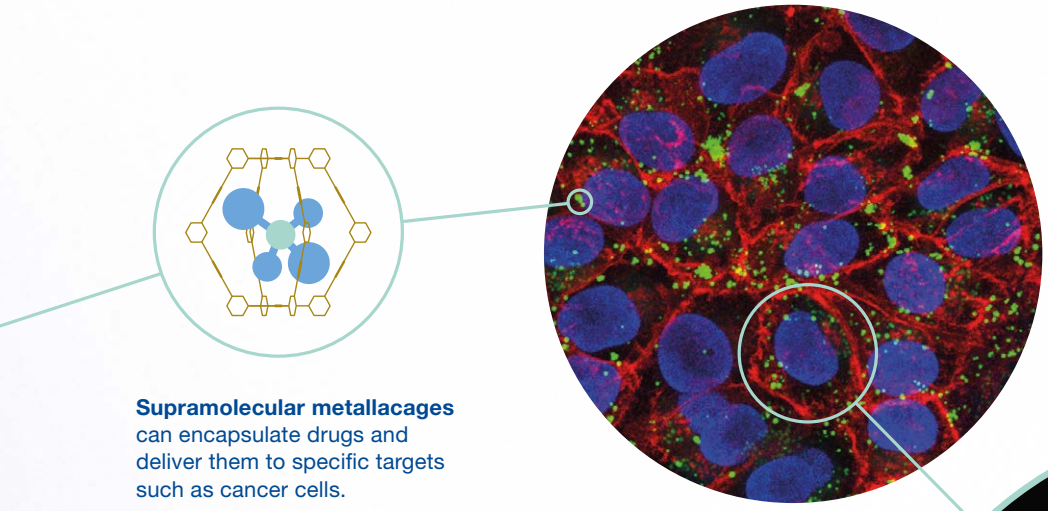
"Metal ions play a key role in biological systems," explains Casini. Having the exact dosage is, however, extremely important. A metal ion concentration that is too high can be harmful, but so can too low a concentration. Casini is therefore aiming for the "golden" middle ground. And her work is coming to fruition: "We were the first group to develop a selective gold-based inhibitor for these channels," says Casini. The membrane channels she is blocking are known as aquaporins. They are complex transmembrane proteins in which the amino acids are arranged in a series of helices to form a narrow hourglass channel. These proteins are built into the cell membrane, where they form small pores which narrow to a diameter as little as three tenths of a nanometer. They perform the essential task of maintaining the cell's osmotic balance. Up to three billion water molecules can flow through an aquaporin channel per second – many times more than would diffuse through the semi-permeable membrane which surrounds the cell alone.

Small water channels through the cell membrane

Aquaporins were discovered by US physician and molecular biologist Peter Agre – a discovery for which he was awarded the 2003 Nobel Prize in Chemistry. About 30 years ago, he realized that a previously identified protein performed an important role as a water channel through the cell membrane. Since then, aquaporins have been identified in a wide array of different cells and organisms ranging from bacteria to plants, animals and humans. Water molecules are not the only substrates that pass through aquaporins; there are also variants, called isoforms, which additionally transport small molecules such as glycerol, hydrogen peroxide, and urea. Aquaporins have been implicated in a number of diseases, including cancer and obesity. Nonetheless, they serve important purposes in a wide variety of organisms. In plants, they support water transport through stems and leaves. In humans they facilitate rapid diffusion of water in cells of the salivary glands, kidney and the crystalline lens of the eye, among other tissues. However, they also facilitate tumor cell mobility and have been identified in more than 20 different tumor types. Tumor cells use these highly efficient water channels to spread rapidly through the body and form fatal metastases.

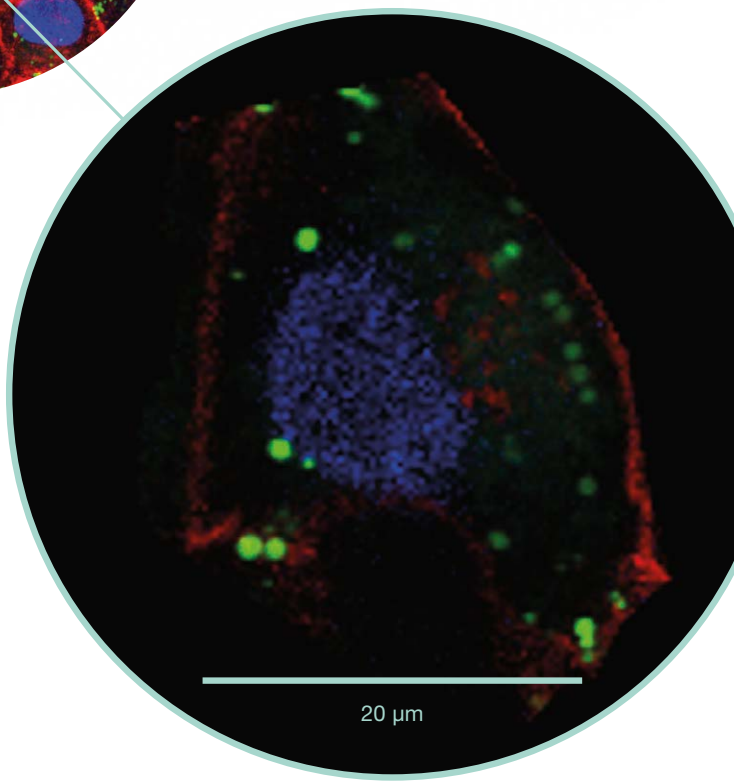
And this is where the work of Angela Casini, along with several international collaborators from the fields of biochemistry, biology, and physiology, comes in. "Selectively blocking tumor cell aquaporin channels could potentially offer a new approach to cancer therapy," says Casini. She has recently succeeded in using organometallic gold complexes to selectively and irreversibly inhibit cancer-associated aquaporins. This could be used to ▷





Supramolecular metallacages can encapsulate drugs and deliver them to specific targets such as cancer cells.

Fluorescent microscopy image of fluorescent metallacages (green) entering human cancer cells (red membrane, blue nucleus).



reduce tumor cell mobility, which could in principle form the basis for a future therapy aimed at stopping tumors from spreading within the body. Casini has not yet optimized these gold inhibitors to maximize their effect on tumor cells, but it is not unreasonable to hope that she might one day identify organometallic complexes able to act more or less exclusively on tumor cell aquaporins.

As promising as this work is, Casini's ideas and experiments extend much further. "Inorganic chemistry has a huge untapped potential for medicine," says Casini. Right now, the vast majority of drugs are organic compounds, i.e., compounds based on the element carbon. Inorganic substances occupy at best a small niche. Examples include the alkali metal lithium, used to treat depression, and radioactive isotopes of rhenium, yttrium, and zirconium, which are employed in nuclear medicine for imaging and therapy. "Medicinal inorganic chemistry will play a big role in future drug development for personalized medicine and will enable major advances in predictive medicine, i.e., predicting disease risk," asserts Casini confidently.

"Trojan horses" deliver drugs to their targets

Similarly, Casini is also very excited by the potential of supramolecular inorganic chemistry. The field was established by the French scientist Jean-Marie Lehn – work for which he was awarded the 1987 Nobel Prize in Chemistry. He discovered that individual molecules can assemble into complex supramolecular structures. Supramolecular chemistry could potentially be used to develop novel systems for targeted drug delivery to specific sites within the body. Casini's research group has already developed supramolecular metallacages able to encapsulate drugs or radioactive agents for imaging procedures. By acting as a kind of molecular "Trojan horse", these cages could be used to boost drug uptake by cancer cells.

Casini has performed initial experiments which prove that this approach is feasible. These involved functionalizing her metal cages with molecular targeting groups, designed by the TUM research group headed by Prof. Horst Kessler. Initial *in vitro* experiments showed increased uptake of encapsulated cisplatin – a cytotoxic drug containing a bound platinum atom in the center – by cancer cells. These metal cages have also been used *in vivo* in mice to transport an encapsulated radioactive compound (pertechnetate) across the blood-brain barrier into the brain. This overcomes a major hurdle to administering drugs into the central nervous system. Because metal-based supramolecular structures permit a wide range of variations and can be adapted for specific tasks, Casini expects these complex chemical systems to prove useful for many other biomedical applications in the future. ▷

Graphics: edlundsepp (source: TUM/Casini); Picture credits: TUM/Casini

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TUM Innovation Network for Artificial Intelligence Powered Multifunctional Materials Design (ARTEMIS)

Part of the TUM Excellence Initiative, TUM Innovation Networks are intended to nurture innovative research fields straddling multiple disciplines. The interdisciplinary teams are made up of seven to ten principal investigators and up to ten PhD students and postdocs. Each network is granted around €3 million in funding over a four-year period.

ARTEMIS, led by Prof. Casini and Prof. Gagliardi, brings together a team of TUM chemists, physicists, bioengineers and computer scientists. They will use machine learning techniques to generate new materials and give new impetus to two research fields prominent at TUM: energy and medicine.

A transdisciplinary Innovation Network to develop new materials

In the search for other supramolecular inorganic materials, Casini and her colleague Alessio Gagliardi have recently set up and now coordinate the Artificial Intelligence Powered Multifunctional Materials Design network ARTEMIS. The network will focus on using artificial intelligence to develop novel materials for energy research and regenerative medicine. All new metal-containing supramolecules will be studied by Casini's research group to determine their suitability for use as new multifunctional materials in regenerative medicine. To this end, the group will use biophysical and analytical techniques as well as pharmacological methods. In addition, they will harness atomistic computer simulations to help predict interactions between metallic active substances and target molecules in the body.

Angela Casini hopes that all these approaches will help to raise awareness within the pharmaceutical industry of the potential offered by inorganic chemistry. "Right now, there is a lack of knowledge concerning the possible use of metals to develop new drugs," she says. "We need to disseminate this knowledge more widely, starting by training a new generation of chemists who are familiar with interdisciplinary studies." One step towards achieving this goal could be the renowned Gordon Research Conference "Metals in Medicine" due to be held in summer 2022, which Casini, as one of the conference chairs, is organizing. Inorganic chemistry provides a fantastic set of tools for biomedical applications. "Failing to take advantage of the variety offered by the periodic table would be such a waste," says Casini. ■ *Jan Oliver Löfken*

Picture credit: Magdalena Jooss

Prof. Angela Casini

obtained her PhD at the University of Florence in 2004. Following a one-year postdoc at the University of Pisa, Casini attained the role of Principal Investigator at the Swiss Federal Institute of Technology in Lausanne. The post was funded by the Swiss National Science Foundation (SNSF). In 2011, she joined the University of Groningen in the Netherlands as an assistant professor for four years. During that time, she also conducted research as a visiting professor in Italy and France. Between 2015 and 2019, she held the Chair of Medicinal and Bioinorganic Chemistry at Cardiff University in the UK. Since 2019, she has headed the Medicinal and Bioinorganic Chemistry research group under the distinguished Liesel Beckmann Professorship at TUM.

Casini has received numerous awards for her pioneering work in the field of bioinorganic chemistry, including the European Medal for Biological Inorganic Chemistry, the Burghausen Diamond of Chemistry Award, and the renowned American Chemical Society Inorganic Lectureship Award. Here, she recently initiated the Artificial Intelligence Powered Multifunctional Materials Design network (ARTEMIS). Together with other researchers at TUM, she is coordinating the ARTEMIS network, which aims to use artificial intelligence to identify new materials for energy research and regenerative medicine.