

SPEKTRUM

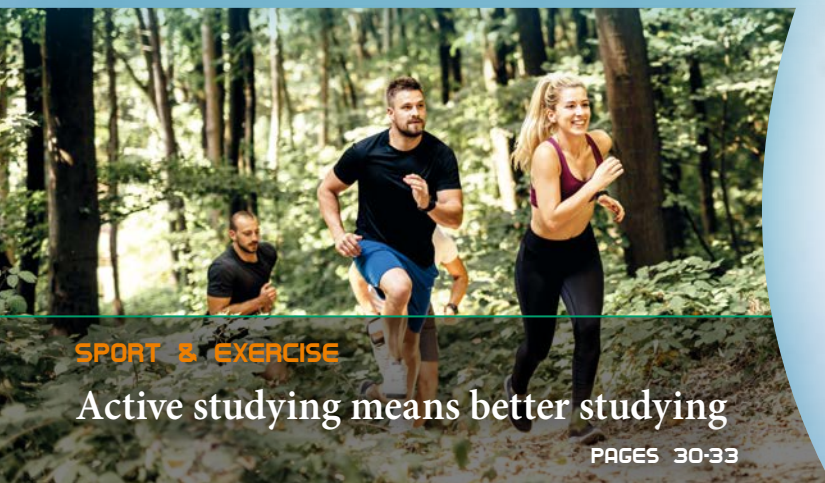
The Science Magazine of the University of Bayreuth ■ Volume 16 ■ Issue 2 ■ November 2020



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FOCUS
Life Sciences

Dear Readers,



■ Prof. Dr. Stefan Leible, President of the University of Bayreuth.

When the University of Bayreuth took up its research and teaching responsibilities 45 years ago, the term "life sciences" was far from being as established in science, politics, or in the media in the way it is today. It refers to the networking of different disciplines indispensable in solving fundamental questions, including both the "classic" natural sciences and, for example, nutrition, sports, and health sciences. The credo "innovation through interdisciplinarity" has characterized the University of Bayreuth since its foundation. This issue of SPEKTRUM sets out to show you selected examples of the diversity of disciplines and research fields that work together on our campus in the ecosystem that is the life sciences.

New findings in the life sciences often have great potential for future application. Yet they do not necessarily have their origins in a defined research agenda that aims to find solutions to concrete problems from the outset. In many cases, they are the result of intensive research work over many years, aiming to get to the bottom of complex and seemingly mysterious phenomena of life with creativity and a spirit of discovery – and then reveal surprising starting

points for technological applications or even for the establishment of start-ups.

As a matter of principle, our campus offers an inspirational environment for projects that consciously take a risk in trying something new. Despite the limitations imposed by Covid-19, we are striving to maintain and strengthen this prerequisite for high-quality university research and teaching. Not least of all, new digital formats, which have meanwhile triggered an unexpected dynamic, are contributing to this. In the months ahead, we will continue to face the daily challenges of dealing with the pandemic responsibly and with innovative ideas.

Yours faithfully,



Prof. Dr. Stefan Leible
President of the University of Bayreuth

Further SPEKTRUM issues

On the homepage of the University of Bayreuth you will find previous issues of SPEKTRUM on the following topics:

- 1/2020: Hydrogen
- 2/2019: Africa
- 1/2019: Batteries
- 2/2018: War
- 1/2018: Planet Earth
- 2/2017: Sustainability
- 1/2017: Governance
- 2/2016: Molecular Bioscience
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- www.uni-bayreuth.de/de/universitaet/presse/spektrum

The coronavirus pandemic has brought challenges in health protection that have come to influence critically the planning and everyday organisation of studies, teaching, and research, for the first time in the history of our university. When the decision was made, on the occasion of the 2020 annual academic celebration, to dedicate this issue of SPEKTRUM to the life sciences, the recent increase in the number of infections could not yet be foreseen. Now, however, this issue will give you a timely overview of the diversity of scientific disciplines and research topics being pursued on our campus, which – directly or indirectly – all have something to do with the fulfilment of those wishes and life plans we refer to with the ubiquitous salutation "Stay healthy!"

In the field of life sciences, the University of Bayreuth is currently expanding its range of courses in a way that is unique in Germany. At the University's Kulmbach site, our new Faculty of Life Sciences: Food, Nutrition & Health has launched master's programmes for "Food & Health Sciences", "Food Quality & Safety", and "Global Food, Nutrition & Health". Meanwhile, Sport Science has recently been expanded to include the interdisciplinary field of sports technology. In addition, the University of Bayreuth

is a partner of MedizinCampus Oberfranken, which is set to establish a novel interdisciplinary profile for medical education. And the research topics in our tried and tested interdisciplinary courses of study always reveal surprising tangents leading to innovation in the health sciences and biomedicine.

In high-quality, internationally networked degree programmes that focus on current research issues, we aim to continue encouraging and empowering students on our campus to competently and confidently participate in shaping new developments in the life sciences.

Yours faithfully,



*Prof. Dr. Martin Huber
Vice President for Teaching & Learning
at the University of Bayreuth*



■ Prof. Dr. Martin Huber is the Chair of Modern German Literature at the University of Bayreuth.

SPEKTRUM-Magazine of the University of Bayreuth

Circulation:

German edition: 1.500 copies

English edition: 500 copies

Published by:

University of Bayreuth
Press, Marketing &
Communications (PMK)
95440 Bayreuth

Phone 0049 - 921 55 - 53 56 / - 53 24
pressestelle@uni-bayreuth.de

Editorial management:

Christian Wißler (V.i.S.d.P.)

Translation:

Ralph Reindler

Printing:

bonitasprint gmbh, Würzburg

Layout and Design:

GAUBE media agentur, Bayreuth

Image source labelling:

sst: www.shutterstock.com



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All contributions are free for publication provided sources are cited and specimen copies forwarded.

■ Cover photos and illustration: sst, Photo upper right: James Wagstaff / Shutterstock.com.

■ Fig. left: The Campus of the University of Bayreuth (Photo: UBT).

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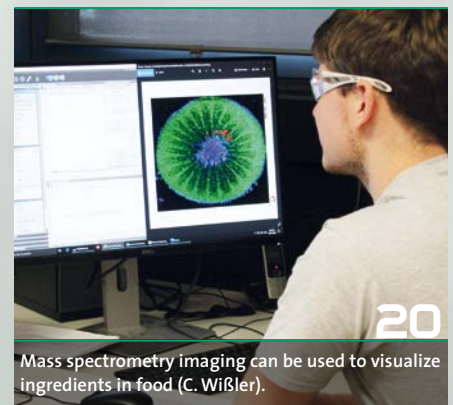
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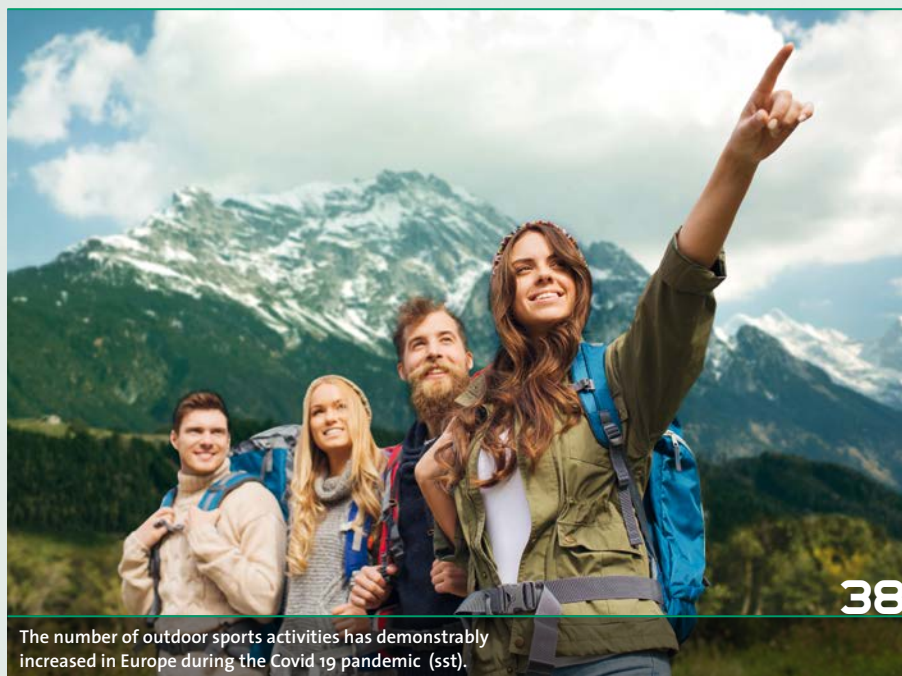


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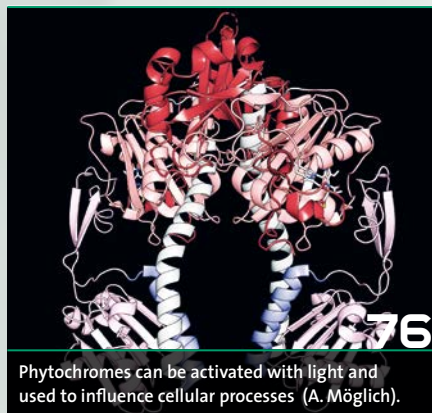


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FOOD & NUTRITION

■ Kai Purnhagen

Innovations in food law

Securing the future
of food supply



■ Food law today is no longer limited to the aspect of food safety, but is linked to numerous other areas of law (sst).

Food influences many aspects of our daily life. From breakfast to dinner, food forms the context of many key moments in our daily routine. Many in our Western world take this for granted and overlook a fact that should worry us. Over 20,000 people still die of hunger every day. Around 65 percent of all deaths worldwide are caused by noncommunicable diseases, which are largely due to malnutrition. This goes hand in hand with the need to increase productivity in food production in order to meet the growing demand for the high-quality food of sufficient nutritional value and energy. At the same time, climate change is expected to reduce the amount of land available for agricultural use worldwide. In addition, more land must be taken out of agricultural use to make room for afforestation and an increase in biodiversity.

In addition to these public welfare concerns, other pressing questions have arisen. They concern public and individual health, especially with regard to nutritional issues, and the adaptation of food law to a changing institutional environment with liberalized markets and integrated transnational value chains.

New networking of food law

These challenges influence also food law. Initially, food law – narrowly defined as an area of law that regulates the production, trade, and handling of food – focused on food safety, mainly at national level. Within this narrow view of food law, international aspects are only relevant insofar as they relate to the import and export of food. However, this view is now perceived as too narrow. A broader



■ Fig. 1: Not taken for granted everywhere in the world: nutritious meals (sst).

range of legal considerations are now part of food law. Data protection law becomes relevant when data on dietary behaviour is collected in order to better design effective legislation. Technology law provides the legal framework for the evaluation of new cultivation methods and food innovations. Environmental law provides the legal framework for the use of pesticides, consumer law includes regulations that affect individual nutritional behaviour, and competition law and other private law orchestrate global supply chains. Increasingly, we are recognizing that regulations at home have a global impact, often with a time lag.

This complexity makes it difficult to bring together all the parts of food law and to reveal the hidden



■ Fig. 2: Environmental law, which regulates the use of pesticides, also influences food law (sst).



■ Fig. 3: Increasingly, the same legal regulations apply to agricultural products as to foodstuffs. Here, organic potatoes and supermarket shelves with potato chips (sst).

legal connections that the inconspicuous concept of food law encompasses. The complexity of the food market also means that traditional distinctions are losing their significance. Agricultural products are increasingly subject to the same legal regulations as food, while environmental protection law and consumer law influence all areas of food law and are therefore difficult to separate from food law as "commercial law". Public and private law merge to form the regulatory law of the supply chain. Increasingly, food law refers to extra-legal facts by using concepts from the natural and social sciences. For example, genetically modified organisms are exempted from the obligation to obtain approval if the modification is the result of mutagenesis. As a result, it is necessary to communicate with neighbouring disciplines on the interpretation and application of the law, in order to achieve a congruent understanding between the legal and natural sciences as to the interpretation of these terms. In any case, the effects associated with the regula-

tion of the food market can only be determined by borrowing from the neighbouring sciences.

Food law under pressure: The need for innovation in an international context

All these developments increasingly demand legal innovations from food law. The conflicting necessities of food production – for example, the need to increase productivity while simultaneously reducing land use – must be reconciled. In some countries, the most urgent task is to reconcile consumer demand for a wide variety of high-quality food products available in sufficient quantities with necessary restrictions on the consumption of certain products - for example, when it is necessary to curb increasing diet-related diseases. In other countries, a primary goal is to ensure access to sufficient food and/or lucrative markets. Above all, this includes



■ Fig. 4: Globally different climatic conditions also determine access to food (sst).

ensuring access to technological innovations in order to ensure equitable and fair nutrition for all people despite the pressures of changing ecological and economic conditions.

These challenges require a rethinking of food and agricultural law in Europe. The current food law is essentially based on the idea that free circulation in the market, in principle, can only be restricted if there is a (potential) danger for certain protected goods. Large parts of food law are therefore risk or hazard-based in that they are designed to identify



■ Fig. 5: Genetically modified, Sharka-resistant plum variety (Photo: wikimedia commons / Scott Bauer, USDA ARS / PD).

actual or potential hazards and make them manageable. In doing so, the benefits that a certain product or process brings are regularly disregarded. Benefits, so the implicit assumption, are rewarded

on the market and therefore do not require special legal assessment. Food law overlooks the fact that benefits often outweigh risks. However, a careful weighing of benefits and risks is particularly relevant today, as food innovation is urgently needed to meet the above-mentioned challenges. If, for example, a technology such as genome editing, especially CRISPR Cas9, cannot be applied in Europe because, among other reasons, the law only assesses the potential dangers but not the benefits of the technology, one must ask oneself whether food law does not need to be reoriented in this respect.

"Increasingly, we are recognizing that regulations at home have a global impact, often with a time lag."

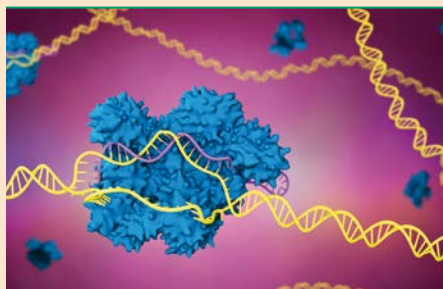
Agricultural law is still shaped by the requirements of the fight against hunger in the post-war period. Environmental problems and the shifting of European food production problems to other countries were not on the agenda. Today there is no longer a problem with food supply in Europe. Rather, questions of healthy nutrition and sustainable food production are coming to the fore. In our latitudes, for example, the question regularly arises as to how law must be designed to accompany these processes. Especially when evaluating political demands, the consequences of certain legal regulations must

RECOMMENDED READING

K. Purnhagen, J. Wesseler: EU Regulation of New Plant Breeding Technologies and Their Possible Economic Implications for the EU and Beyond. Applied Economic Perspectives and Policy (2020), DOI: 10.1002/aepp.13084.

Genome editing in the European Union

With genome editing, individual plant characteristics can be changed in a targeted manner. So-called "gene scissors" (CRISPR) are also used for this purpose – developed by Emmanuelle Charpentier and Jennifer A. Doudna, who were recently awarded the 2020 Nobel Prize in Chemistry for their research work on genome



editing. Compared to mutagenesis, genome editing is much more precise and produces far fewer unforeseen side effects. In the international scientific community, it is considered a safe and promising way to provide a growing world population with sufficient food.

Nevertheless, its application is regulated in European law far more strictly than conventional mutagenesis. In practice, this means that plants modified by genome editing may only be agriculturally produced and marketed within the EU if they have successfully undergone an approval procedure that is as expensive as it is time-con-

■ Fig. 6: 3D illustration of the CRISPR-Cas9 system of genome editing (sst).



■ Fig. 7 and 8: The 2020 Nobel Prize winners in chemistry: Left: Emmanuelle Charpentier (Photo: wikimedia commons / Bianca Fioretti, Hallbauer & Fioretti / CC-BY-SA-4.0), right: Jennifer A. Doudna (Photo: wikimedia commons / Duncan Hull / CC-BY-SA-4.0).

suming and unpredictable. These plants may not be used at all in certified organic products. Farmers in EU member states therefore have little chance of using new genetic engineering techniques to produce food, and thus of competing on the world market.

From farm to fork

"Farm to fork" is the name of the new strategy with which the EU Commission is seeking to combat climate change, promote biodiversity, and feed all Europeans in a sustainable way. In a non-binding declaration of intent, the EU Commission has thus announced a comprehensive package of measures. Among many measures, it includes some concrete goals: By the year 2030

- 25 percent of the total agricultural area is to be managed by certified organic farming,
- the use of chemical pesticides will be halved,
- soil nutrient loss is to be reduced by at least 50 percent,
- the use of fertilizers to be reduced by at least 20 percent, and
- the use of antibiotics in livestock breeding and aquaculture is to be halved by 50 percent.



■ Fig. 9: Currently the subject of controversial debate in the EU: the legally mandated increase in areas for organic farming (sst).

be taken into account. For example, we are forced to question whether it makes sense to increase the area of organic farming production in the EU to 25 percent in order to achieve sustainable food production. This was recently called for in the "Farm to Fork" strategy of the European Commission. The production methods of organic farming are strictly regulated in EU law. If all regulations are complied with, it is to be expected that, if organic production does increase to 25 percent across Europe, yields on these areas will fall by up to 50 percent compared to conventional farming. This is a consequence difficult to reconcile with the need to increase production. One solution would be to improve the performance of plants used in organic farming. However, EU law prohibits the use of agents that would be effective in this regard - such as genome editing. Here, too, legal innovations will be needed to resolve these conflicting goals.

Meanwhile, consumer food law is also under pressure to change. Based on a ruling of the European Court of Justice in the 1970s, consumer food law today is essentially food information law. Food law normatively assumes that responsible consumers are sufficiently protected by EU law merely if they

Food consumption – reason rarely decides

Several studies have shown that when people are under time pressure and hungry, they are far less motivated to absorb and process information. Numerous research studies in psychology and economics have come to the conclusion that a large part of consumer behaviour is not targeted and controlled, but is determined by habits and automatic tendencies. In such situations, our behaviour is essentially characterized by short-term stimuli and appeals in our environment, which can strongly influence our decisions in such situations.

The perception of food and our food intake is mainly influenced by factors that often have little to do with the food itself. For example, portion and unit size, texture, shape, and packaging images of food determine our decisions rather than the properties of the food itself. For example, it is assumed that people's preferences for unhealthy

foods are particularly strong when tempting foods such as snacks are made easily accessible to them. Many consumers also read much more into the information presented to them than the wording contains. For example, simply by labeling a food product with a quality label, consumers believe that it has better properties than other foods that do not have a label. This applies regardless of the information contained on the label. A label can, for example, provide information about compliance with environmental standards, but many consumers believe that it makes

the food healthier. Information can also have the opposite effect, causing consumers to act against the interests it is actually appealing to. If a food, for example, is advertised as low-calorie, many consumers therefore believe more of it can be eaten, which, in turn, can lead to obesity.

The Food Law research group cooperates with the Junior Professorship for Public Health Nutrition at the Kulmbach Campus in researching these processes and the ramifications to be derived from them.

■ Fig. 10: Only rarely information-driven: our eating habits in everyday life (sst).



are adequately informed (the so-called information paradigm in consumer protection law). In the meantime, however, it is accepted that information rarely provides a sufficient basis for decision-making. Far too often in life, we are distracted by other things and do not pay sufficient attention to the information, interpret it incorrectly, or simply cannot find it. It is also questionable whether decisions made by consumers even reflect the necessary changes in consumer behaviour mentioned above. Legal innovations are necessary, which on the one hand reflect the individual's freedom of decision, and on the other hand, the changes in consumer behaviour that are being strived for. A growing number of experts from politics and science therefore demand that consumer law should be oriented less towards the normative target group of average consumers and more towards the results of behavioural science research. Only on this way, so the assumption, can law be written which actually achieves its goals.

Prospects

Food law is facing great challenges. The legal framework must be designed in such a way that new technologies can develop their effectiveness. It must also be ensured that food law is appropriate to the changing climatic conditions of food production and the needs of health protection. Legal innovations are necessary to meet these challenges. In large parts, food law is still based on preconditions that have now been overtaken by reality. For example, behavioural science findings have called into question many of the premises underlying European competition law. In food law, this concerns the information paradigm already mentioned, which is the basis of consumer law. Yet progressive findings in the natural sciences are also being



■ Fig. 11: View of SIAL in Paris, an annual international food fair (Photo: wikimedia commons / SIAL Paris / CC-Zero).

inadequately or belatedly considered in law. There are simply not enough possibilities to effectively incorporate a fundamentally new level of knowledge into the law.

All this will be necessary to make food law and thus the framework for our daily life suitable for the coming decades. To conclude with an old wisdom from technology law: Innovations in the sciences can rarely be countered by traditional law, but should in most cases lead to legal innovations. There are many possibilities for this – starting with the fresh interpretation of existing law and ending with the creation of new law. The status quo will not do; the possible economic and ecological consequences are too serious for that.

AUTHOR



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■ Fig. 12: Kulmbach is home to the new Faculty of Life Sciences: Food, Nutrition & Health at the University of Bayreuth (Photo: wikimedia commons / CC-BY-SA-2.0-DE).



■ Jörg Schlüchtermann
Julia Reinig

Supply chains in the global food industry

On the coordination of inter-company flows of goods, information, and finance

■ South-South trade: Cocoa beans imported from the Ivory Coast are unloaded in the port of Ilheus, Brazil (Foto: Joa Souza / shutterstock.com).

The food industry is not only one of the largest industries in the world, it is also of vital importance for the daily supply of food to the world's population. Population growth, rising incomes, and increasing urbanisation are driving demand for food. At the same time, the food preferences of many people have shifted in recent decades. In particular, the demand for resource-intensive animal products and for processed food has increased considerably. For many people, food means individual indulgence and well-being. However, because hunger and obesity occur simultaneously in many places in the world, and because the production and transport of food plays a major role in today's ecological problems, coordinated cooperation between different scientific disciplines is needed to meet current and future challenges.

Food Supply Chain Management (Food-SCM) is a field of research in business management that deals with the coordination of inter-company flows of goods, information, and finance. The food production chain begins with the production of raw materials and extends through processing and trade to consumption. It is based on a network of different organisations, whose interaction should be designed as an integrated process. The objectives to be pursued are manifold: Consumers want the most convenient access possible to high-quality, safe, and affordable food, while the companies involved pursue long and short-term business objectives along the entire logistics chain. As a result of digitisation, there are fascinating new opportunities to make chains more efficient and effective at all levels, and in doing so, to curb food fraud.

Scope and structure of a supply chain for food: "From farm to fork"

A typical food supply chain basically comprises several stages involving different actors. The complexity of the chain depends to a large extent on the type and degree of processing of the products, and on the number and degree of networking of the actors

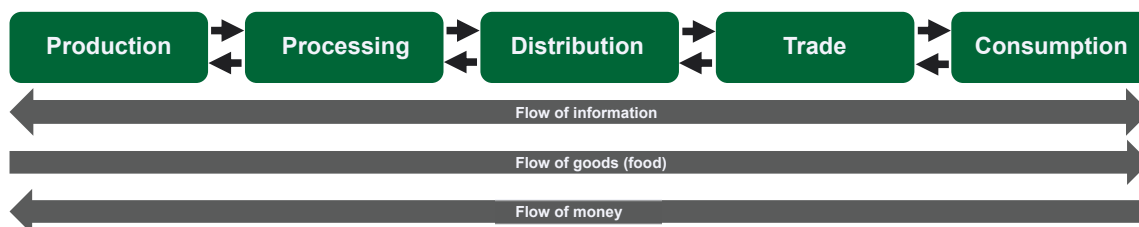
involved. Consequently, supply chains for common unprocessed fruits and vegetables are generally much simpler and shorter than those for meat or confectionery, for example. For these latter products, highly complex chains have formed in many cases, often crossing the borders of countries or continents. To illustrate this, the food supply chain can be simplified and presented in a few steps (Fig. 1).

- The producers form the first stage. These are usually agricultural enterprises that deliver raw, unprocessed food to the next stage and have a major influence on the availability of food. They are dependent on global raw material suppliers, but also on weather conditions and thus bear high levels of risk.
- The next stage is processing. Food producers transform the food supplied into products that are intended to meet consumer demands. These requirements, and the respective environmental conditions, are constantly changing. In order to adapt flexibly to this dynamic, producers need to work closely with actors at downstream stages of the supply chain, while being open to innovative developments and technologies.
- The next stages in the chain are distribution and retail. Logistics play a critical role here. The companies involved act as links between producers, processors and markets. They purchase large quantities from processors or producers and, through their infrastructure of warehouses and distribution centres, ensure that the necessary food is available at subsequent stages in the chain.
- Retail trade makes the diversity of products of the food sector accessible to the consumer. Due to the large number of retailers, this stage of the food chain is characterised by fierce competition. To differentiate themselves from their competitors and attract consumers, retailers strive to develop unique selling points.

RECOMMENDED READING

J. Eastham et al.: *Contemporary Issues in Food Supply Chain Management*. Oxford 2017.

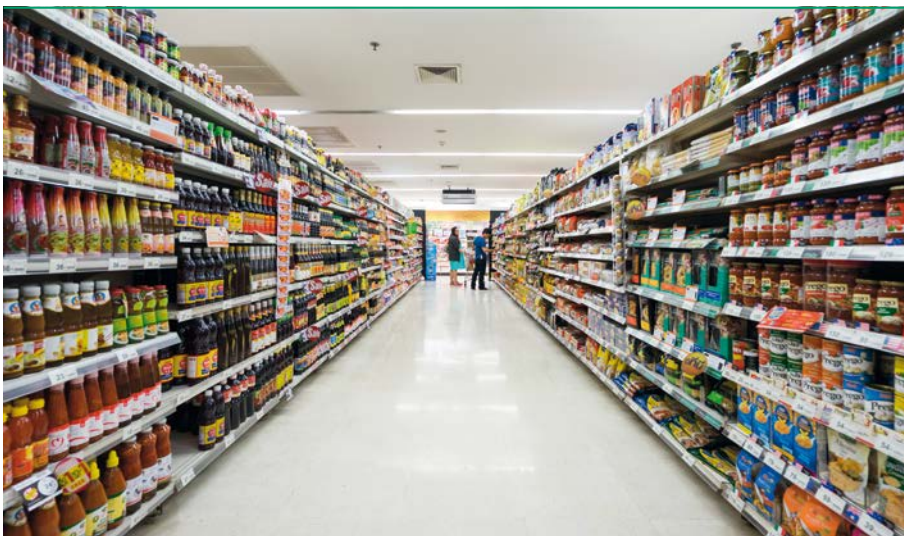
E. Iakovou et al.: *Supply Chain Management for Sustainable Food Networks*. Chichester West Sussex 2016.



■ Fig. 1: Structure of a simplified food supply chain (Illustration: Julia Reinig).

- The food supply chain ends with consumption. With their purchasing decisions, consumers determine the economic sustainability of the chain.

The size of companies along the chain varies widely. The majority of the actors involved are usually small or medium-sized enterprises (SMEs), but especially at the retail level, there are usually large players who seize the initiative for the whole chain thanks to their market power.



■ Fig. 2 (above): BigC-Supermarkt in Chiangmai/Thailand (Foto: 06photo / shutterstock.com).

■ Fig. 3 (bottom): The street market in Bolzano in South Tyrol/Italy is famous for its rich variety of fresh food (Foto: Happy Poppy / shutterstock.com).

Food supply chains differ from other supply chains because requirements such as food quality, freshness, and safety make the management of all areas at once difficult. In the case of perishable products, the complexity is particularly high due to their short shelf life. In this case, a cold chain or temperature-controlled supply chain is required to maintain quality and quantity. Temperature is one of the most important factors when it comes to extending or maintaining the shelf life of perishable foods. Cold chain management has therefore become an essential part of many food businesses. It is characterised by systematic temperature tracking and monitoring using new technologies, such as the "Internet of Things". The increase in international trade in perishable food, the growing consumer demand for high quality perishable food, and technological advances in cold storage and transport will make cold chain management even more important for global supply chains in future.

Seamless traceability

Since the coordination of food supply chains is usually carried out at a global level, an integrated view of efficiency and effectiveness is necessary. In order to guarantee the quality and safety of products, all resources along the food supply chain must be efficiently utilized. This requires documentation of the incoming quality of materials, storage conditions, processing methods, and outgoing quality at every stage of the chain. Moreover, the synchronisation and sharing of this information among all stakeholders along the chain is crucial. Only in this way is it possible to trace individual batches, to document the joint coordination and optimisation of processes, to provide product consistency and quality management, to ensure compliance with regulations and, finally, to justify customer safety and satisfaction. For consumers, food quality and compliance with all safety regulations are among the most important factors.

For this reason, the demands for a transparent global supply chain are increasing. Just one weak link in the supply chain, and an associated contaminant-

"As a result of digitisation, there are fascinating new opportunities to make chains more efficient and effective at all levels."



■ Fig. 4: RFID tag for traceability (sst).

ion, can have a great influence on the quality of the products, and lead to brand and image damage for suppliers. The well-known statement that a chain is only as strong as its weakest link applies. In addition, food safety within the supply chain is also of central importance because the physical well-being of consumers should and must never be compromised. New rules and regulations for companies are tightening this safety factor. Compliance with these rules, which are intended to ensure that contaminated products are eliminated, is therefore of central importance for food businesses. It is considered a driver for the development of innovative technologies. A key approach to food safety compliance is the complete traceability of products, from farm to fork.

Traceability systems have one common, overarching objective: They aim to link the physical flow of goods with the corresponding flow of information along the entire supply chain. They are therefore only efficient if they are set up at the level of the entire supply chain and not in a company-specific way. Various technologies are available for this purpose, including (semi-)automatic identification systems. A proven system is the standards of the International Global Standards One Association, GS1 for short, which form the basis of today's product identification procedures. The best-known instrument of traceability is the barcode placed on end products. Other instruments used for this purpose are the QR code (*Quick Response Code*) and RFID (*Radio Frequency Identification*) marking. In addition, there are various technical solutions that enable the comprehensive exchange of data between partners in the supply chain. These include ERP systems (*Enterprise Resource Planning Systems*), but also innovations such as block chain technology.

Economic, social, and environmental perspectives

The growth of the world's population, increasing environmental problems, and the ecological burden of food production and consumption mean that sustainability and efficiency issues are becoming increasingly important in the food industry. Among the issues being debated are extensions of the food chain and the impact of food waste. Initiatives to avoid food waste are proof that environmental aspects, resource conservation, and social justice are becoming increasingly relevant. In its latest available global estimates, the FAO (*Food and Agriculture Organization of the United Nations*) has calculated that one third of the food products produced worldwide are lost or wasted.¹ This has considerable economic, social, and ecological impacts.

How can we counteract this development? In today's competitive business environment, it is unlikely that focusing on individual links in the overall supply chain will bring about long-term success. Reducing food waste is a major responsibility for consumers, but also for businesses. The main causes include lack of preservation techniques, poor temperature and humidity conditions, and transport delays. As the variety of foods supplied continues to increase as a result of globalisation, the prevention of food waste will represent one of the biggest challenges for food supply chain management in the coming years.

Conclusion

The continuing growth of the food sector and the increasing awareness of consumers of the quality, safety, and freshness of food will add to the current challenges. This will also increase the importance of food supply chain management. Some of the problems mentioned above may be reduced by a return to local products. On the other hand, it should also be remembered that the growing global demand for food can only be met with higher productivity and efficiency along that chain. Tailor-made concepts are therefore needed for companies of all sizes and positions in the food supply chain. Some chains will become shorter and therefore more regional and transparent by themselves. In many other areas, however, it will be a question of exploiting economies of scale and, in particular, the opportunities offered by digitisation in order to achieve higher efficiency and quality.

AUTHORS



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¹ FAO (Food and Agriculture Organization of the United Nations): Global Food Losses and Food Waste – Extent, Causes and Prevention. Rome 2011.

■ Stefan Bindereif
Jan-Marcel Schubert
Gerhard Gebauer
Stephan Schwarzinger

Quality check for food of the gods

Modern food analysis
enables determination of
the origin of cocoa beans

■ *Cocoa tree with fruits in Thailand (sst).*

Whether as a bar, a truffle or a chocolate Father Christmas – Germans love their chocolate. Each of us enjoys an average of about eleven kilograms of the cocoa product per year. This puts us in first place in Europe in terms of per capita consumption.¹ The global demand for chocolate is growing steadily, and to meet it, ever larger quantities of cocoa beans must be produced. The cocoa trees cultivated for this purpose in West Africa, South America, and Asia bear the scientific name *Theobroma cacao* (Fig. 1). The first part of the name comes from ancient Greek and means "food of the gods" (theos = god, bromo = food).

The vast majority of cocoa trees are cultivated by small farming families using simple, traditional agricultural methods. One of the reasons for this is that the cocoa plantations have to meet very special growing conditions, which can only be found in tropical forests on the equator. About five years after a cocoa tree has been planted, many small flowers are formed along the trunk and branches, which are pollinated by insects. However, only a small proportion of them actually develop cacao fruits, which in turn can be harvested after about six months.²

In order to obtain these coveted cocoa beans, the farmers open the shell of the fruit with sharp machetes and remove the white flesh (pulp) together with the beans (Fig. 2). The beans develop their characteristic aroma during the subsequent fermentation process.³ They are first stored in covered boxes for about five days so that yeasts and bacteria can decompose the pulp. The last step is carried out in the tropical sun. It dries the cocoa beans spread



■ Fig. 2: Cocoa harvest: A farmer in Selva Zoque (Mexico) removes the sweet pulp containing the cocoa beans (Photo: Jan-Marcel Schubert).



■ Fig. 3: Drying the cocoa beans on large tables where they are regularly turned. A tent erected to protect the beans from the rain (Photo: Jan-Marcel Schubert).



out on the ground, tables or mats (Fig. 3). This is where the headache starts for many farming families. A middleman critically checks the quality of

"Cocoa beans from the same geographical origin have a very similar chemical composition."

the cocoa beans and fixes a purchase price before taking away the full jute sacks. This is much lower than the international market price, however, which is currently around 2,100 euros per tonne.⁴ This means that ultimately only a small proportion of the profits made in international trade actually reaches the producers.

The origin determines the price

Fortunately, more and more consumers are attaching importance to environmentally friendly and fair production, for which they sometimes even like to pay more. An innovative approach to fairer compensation is the so-called Single Origin concept. Using only cocoa beans from the same growing region for chocolate products is meant to create direct trans-

RECOMMENDED READING

S. G. Bindereif, F. Brauer, J. M. Schubert, S. Schwarzingler, G. Gebauer: Complementary use of ¹H NMR and multi-element IRMS in association with chemometrics enables effective origin analysis of cocoa beans (*Theobroma cacao* L.). Food Chemistry (2019), 299, 125105. DOI: 10.1016/j.foodchem.2019.125105.

■ Fig. 1: Cocoa fruits on a tree on a plantation in Cusco, Peru (Photo: Jan-Marcel Schubert).

"CSI-Food": On the trail of food fraud

High-quality food is more expensive – especially if it comes from a specific region or has added value in terms of health (health claims). This applies not merely to consumer prices, but along the entire value chain, i.e. also to production, processing and refining, bottling, and trade. Often, however, the information on origin and quality is incorrect. In some cases they are even deliberately falsified in order to achieve higher profit. This is known as economically motivated food fraud. The "CSI Food" research group at the North Bavarian NMR Centre (NBNC) under the direction of Prof. Dr.

Stephan Schwarzinger is therefore working on the development of analytical methods to prevent food fraud and to ensure safety and fairness along the whole value chain. Their cooperation with the Laboratory of Isotope Biogeochemistry of BayCEER, a research centre of the University of Bayreuth, is set to continue and intensify.

The expertise available at NBNC with regard to NMR methods for food testing is in demand nationally and internationally, for example on DIN, US Pharmacopoeia, and ISO expert panels.



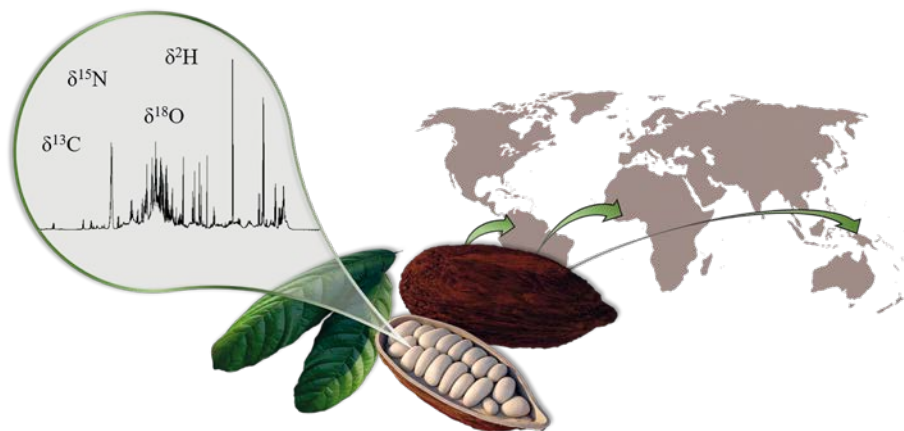
■ Fig. 4: NMR spectrometer for food analysis (Photo: Stephan Schwarzinger).

port routes, thus achieving greater transparency in the trade. When buying Single-Origin chocolate, the consumer therefore believes they know exactly where the raw materials have come from and how they were produced. This is meant to be demonstrated by numerous quality labels, which consumers can only trust. And this is exactly where the problem lies. Despite regular and careful controls, the origin of the cocoa beans can rarely be guaranteed.

Two research institutes at the University of Bayreuth have now tackled this problem:

- the Laboratory of Isotope Biogeochemistry at the Bayreuth Centre of Ecology & Environmental Research (BayCEER) and
- the research group for Quality and Authenticity for Food and Materials in the North Bavarian NMR Centre (NBNC), which brings together the research competencies of the University of Bayreuth in the field of nuclear magnetic resonance spectroscopy.

■ Fig. 5: Schematic representation of the new procedure. Based on the combination of chemical fingerprints and relative isotope abundance, the geographical origin of cocoa beans can be determined (Illustration: Stefan Bindereif).



Using a combination of methods never employed for cocoa to date, a process was developed in Bayreuth that allows the geographical origin of the cocoa beans to be determined in the laboratory (Fig. 4).⁵ As part of a project funded by the Simon Nüssel Foundation, the research team examined cocoa beans from twenty different countries.⁶ In order to be able to compare them with each other, each sample was first analysed by NMR spectroscopy to determine which ingredients were contained in which proportions. This produced a characteristic quantitative fingerprint for each sample. This technique is now routinely used to determine the quality of foodstuffs, including honey, wine, and olive oil. In order to use quantitative fingerprints to determine the origin of cocoa beans, scientists took advantage of the fact that cocoa beans from the same geographical origin have a very similar chemical composition.

At the beginning of these NMR investigations, however, there was one particular hurdle to clear that made it difficult to reliably determine the origin of cocoa beans. In part, the beans were fermented to different degrees, which significantly altered their chemical fingerprints. Therefore, all the ingredients affected by fermentation had to be excluded from the analyses. Thanks to the high signal resolution of NMR spectroscopy and in combination with fermentation experiments, this was achieved in a short time. The fingerprints obtained on this basis enabled reliable determinations of origin. Even different cocoa varieties could be distinguished with these chemical fingerprints.

“Going belts and braces:” Synergy effects through data fusion

Nevertheless, NMR spectroscopy could not be used to assign all samples to individual countries of origin with sufficient certainty. To be absolutely certain, the scientists used an additional analytical technology. In the BayCEER's Laboratory of Isotope Biogeochemistry, they determined the extent to which the stable (i.e. non-radioactive) isotopes of the elements carbon, nitrogen, oxygen, and hydrogen are present in the cocoa beans. Especially the investigations of the latter two isotopes proved to be very informative, because the proportions of oxygen and hydrogen isotopes together form the characteristic isotope pattern of water. Like all plants, the cocoa tree needs water to thrive. In the growing regions of Africa, South America, and Asia,



■ Fig. 6: Classic cocoa plantation with agroforestry. Here, elements of arable farming and forestry are combined (Photo: Jan-Marcel Schubert).

it is supplied exclusively by local rainfall. Hence, the decisive factor for reliable determination of origin is that precipitation (i.e. water) all over the world bears site-specific isotope patterns that can be measured. If a plant absorbs water from regional precipitation, it too carries this site-specific signal. For example, rain on a plantation in Brazil has a completely different isotope pattern to that of rain in Peru (Fig. 5).

The Bayreuth scientists have now succeeded in combining the ingredient fingerprints of NMR technology with the results of isotope analysis with the help of complex statistical methods. The tests show that, in principle, both methods are suitable for determining origin, but only when they are combined – this is also referred to as data fusion – do they work really well. The significance and reliability of the determination of origin are thus significantly increased. In the not too distant future, consumers

will be able to rely a little more on the geographical origin indicated when they reach for their food of the gods.

Nevertheless, the potential of the two interlinked high-tech processes is far from exhausted. Recently, the Bayreuth researchers have applied the two processes to cereals. By adding other technologies established at the University of Bayreuth, such as infrared and Raman spectroscopy, they have succeeded in establishing an analytical ecosystem. In the AgrOr project⁷, which was funded by the Federal Ministry of Food and Agriculture, it was possible to examine more than 1,700 grain samples for origin with great accuracy. Once again, it was data fusion that led to the decisive added value in the identification of species, varieties, harvest years, and geographical origins. Currently, the biggest hurdle is the distinction between conventional and organic cereals, but this research goal is also within reach.

- 1 Cf. Pro-Kopf-Konsum von Schokolade in Europa nach Ländern 2017, published on 17. 09. 2019, <https://de.statista.com/statistik/daten/studie/20040/umfrage/jaehrlicher-schokoladenkonsum-pro-kopf-in-ausgewaehlten-laendern/>
- 2 S. T. Beckett et al.: Beckett's industrial chocolate manufacture and use (5th ed.). New York 2017.
- 3 N. Camu et al.: Fermentation of cocoa beans: influence of microbial activities and polyphenol concentrations on the flavour of chocolate. *Journal of the Science of Food and Agriculture*, (2008), 88(13), 2288-2297. DOI: 10.1002/jsfa.3349.
- 4 International Cocoa Organization (ICCO): Daily prices of cocoa beans. <https://www.icco.org/statistics/cocoa-prices/daily-prices.html>
- 5 See recommended reading.
- 6 https://www.bayceer.uni-bayreuth.de/ibg/de/forschung/proj/detail.php?id_obj=151327
- 7 Cf. Regional und Bio oder Fake? Verbraucherschutz durch Lebensmittelanalyse. Press release of the University of Bayreuth dated 13. 02. 2017. <http://uni-bayreuth.de/de/universitaet/presse/pressemitteilungen/2017/013-bio-oder-fake/>

AUTHORS



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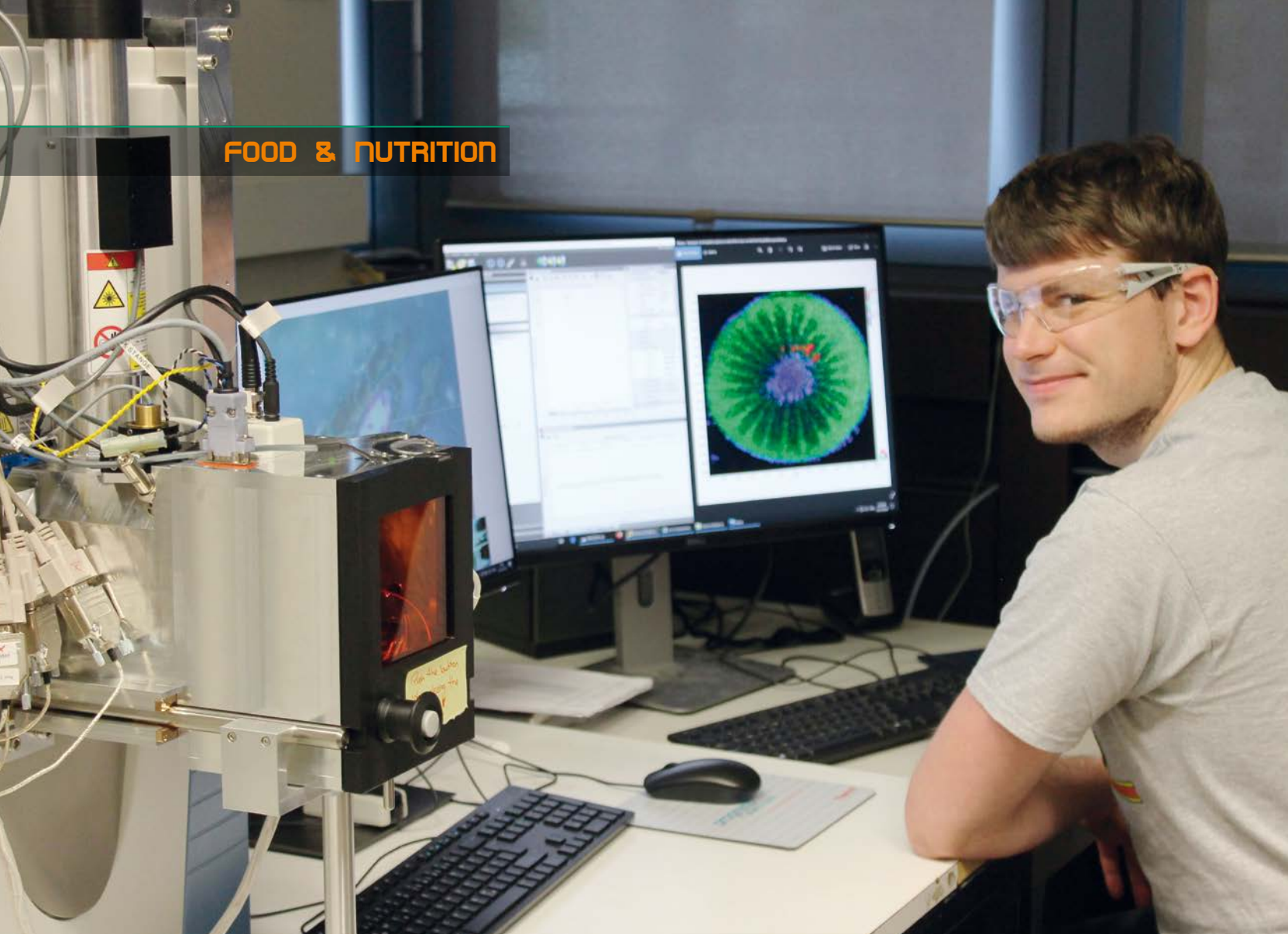
■ Prof. Dr. Gerhard Gebauer is Head of the Laboratory of Isotope Biogeochemistry at the Bayreuth Centre of Ecology & Environmental Research (BayCEER).



■ Prof. Dr. Stephan Schwarzwinger is Managing Director of the North Bavarian NMR Centre (NBNC) and heads the research group for Quality and Authenticity for Food and Materials ("CSI Food").



■ Jan-Marcel Schubert B.Sc. completed his Bachelor thesis at the North Bavarian NMR Centre. Since then he has been working for the cocoa and chocolate manufacturer Original Beans.



■ Andreas Römpf
Axel Treu
Oliver Wittek

Molecular images for the life sciences

From foods to pharmaceutical compounds

■ *Axel Treu M.Sc. at work with the MALDI imaging system at Bioanalytical Sciences & Food Analysis (Photo: Christian Wiffler).*

In many areas of the life sciences, the detection of certain substances, such as food ingredients or active pharmaceutical compounds, is of central importance. In many cases, not only the concentration of these substances but also their spatial distribution in a complex system play an important role. Consequently, the Bioanalytical Sciences & Food Analysis research group at the University of Bayreuth is developing new methods that provide spatially resolved information. Mass spectrometry (MS) is one of their areas of focus. This is a versatile physico-chemical method that can be used to identify unknown substances by their mass. Strong magnetic and/or electric fields are used for the measurements required for this purpose. These fields are used to separate gaseous ions in a high vacuum based on their mass-to-charge ratio.

Mass spectrometry – a million times more accurate than kitchen scales

MS differs from other common analytical methods such as UV, fluorescence, infrared, or nuclear magnetic resonance spectroscopy in that it does not depend on specific properties of molecules and atoms – i.e. neither on light absorption or fluorescence nor on nuclear spin, the angular momentum of an atomic nucleus around its centre of gravity. MS can therefore detect a wide range of substances simultaneously without the need for specific labelling or modification of these substances. If two molecules or atoms differ in their mass, this difference can be made visible by mass spectrometry. Put simply, a mass spectrometer is a set of scales for atoms and molecules that is several million times more accurate and sensitive than any kitchen scales.

Prior to any mass spectrometric analysis, it is necessary to ionise the molecules of the substances to be identified – these are the target molecules – to produce charged particles. Ionisation is necessary because only charged particles can be deflected and accelerated by the magnetic and electric fields used in the mass spectrometer. Nowadays there are a number of different methods to ionise molecules. They usually work with high electrical voltages or laser light to convert the target molecules into a charged state. One common ionisation method, which is also used at the Bioanalytical Sciences & Food Analysis research group, is matrix-assisted laser desorption/ionisation (MALDI). Here, a matrix substance applied on the sample and then irradiated with a laser, which eventually leads to the

ionisation of the target molecules. Mass spectrometry imaging (MS imaging) goes one step further: It combines the molecular information of MS with spatial information. As the laser scans a sample surface and irradiates a different spot on the sample, pixel by pixel, a mass spectrum can be recorded for each point struck by the laser.

Making ingredients visible: The kiwi fruit example

To analyse the ingredients of a foodstuff, for example, the sample to be analysed has to be deep-frozen. In a cryomicrotome, a temperature-controlled cold chamber with a cutting device, sections of the sample are cut with a thickness of just a few micrometres. Particularly challenging samples, such as brittle cereal grains, can be fixed in an embedding medium beforehand, so that a higher quality of sections can be achieved. In the following, the examination of a kiwi fruit is used as an example to illustrate the process of the MS imaging workflow.

The frozen section of a kiwi fruit is first placed on a microscope slide. This sample is then sprayed with the MALDI matrix in a chamber equipped with a programmable spray head. During this process, the nebulisation of the matrix solution in a stream of nitrogen ensures that the matrix molecules form crystals on the surface of the sample that are as small and dense as possible. This results in co-crystallisation with molecules on the sample surface. In

■ Fig. 1: Oliver Wittek adjusting the automatic matrix sprayer (Photo: Christian Wiffler).



■ Fig. 2: The spray head in the chamber approaches the sample to spray the MALDI matrix (Photo: Christian Wißler).

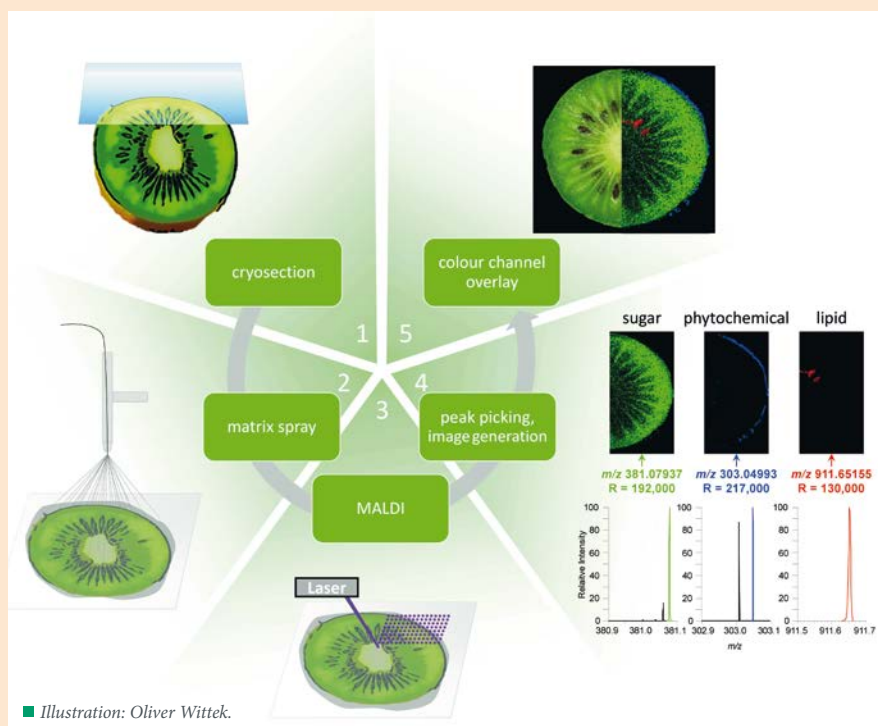


turn, this results in crystals containing both molecules of the matrix and molecules of the kiwi fruit. The sample covered with matrix crystals is now introduced into the ionisation chamber of the mass spectrometer and attached to a moving stage that can be moved in all directions. During measurement, depending on the focus setting of the laser, a

defined area of the sample is briefly irradiated. The crystals evaporate and the sample molecules are released – they desorb. Immediately afterwards, a complex sequence of chemical reactions begins, which finally leads to the ionisation of the molecules. The ions produced in this way are now directed into the mass spectrometer, where their respective masses are analysed. Meanwhile, the moving stage with the sample moves on by a defined path length so that the next laser pulse hits the next point of the sample. Thus, pixel by pixel, mass spectra of the entire surface of the slice of kiwi fruit are generated.

After measurement, signals of interesting compounds can be selected. The recorded mass spectra of all pixels are then searched for these signals and displayed in a "chemical image" which shows the different intensities of the signals. In this way, it is possible to visualise the distribution of the ingredients of a sample, in this case the kiwi fruit, across the sample surface. The mass resolution of the mass spectrometer depends largely on the type of analyser. The higher the mass resolution, the narrower

The five steps of the mass spectrometry imaging workflow



1. Preparation of sample sections in a cryomicrotome at temperatures between minus 10 and minus 40 degrees Celsius. The section thickness is usually 10 to 30 micrometres.
2. Application of a matrix compound via a nitrogen gas flow; the matrix molecules form crystals and incorporate molecules of the sample surface.
3. Matrix-assisted laser desorption/ionisation (MALDI) with irradiation spots of between 5 and 100 micrometres in diameter. The laser scans the sample pixel by pixel, a mass spectrum is being generated for each exposed pixel.
4. Selection of suitable signals in obtained mass spectra and image generation. Green = sugar (disaccharide potassium adduct), blue = polyphenol (protonated quercetin), red = kiwi fruit-typical lipid (triglyceride 54:9 potassium adduct). m/z is the ratio of the mass of an ion to its charge. High mass resolution (R) enables 'clear' images without interference of background signals.
5. Superposition of individual ion channels (m/z ratios) to form a multi-coloured image and comparison with the microscopic image.

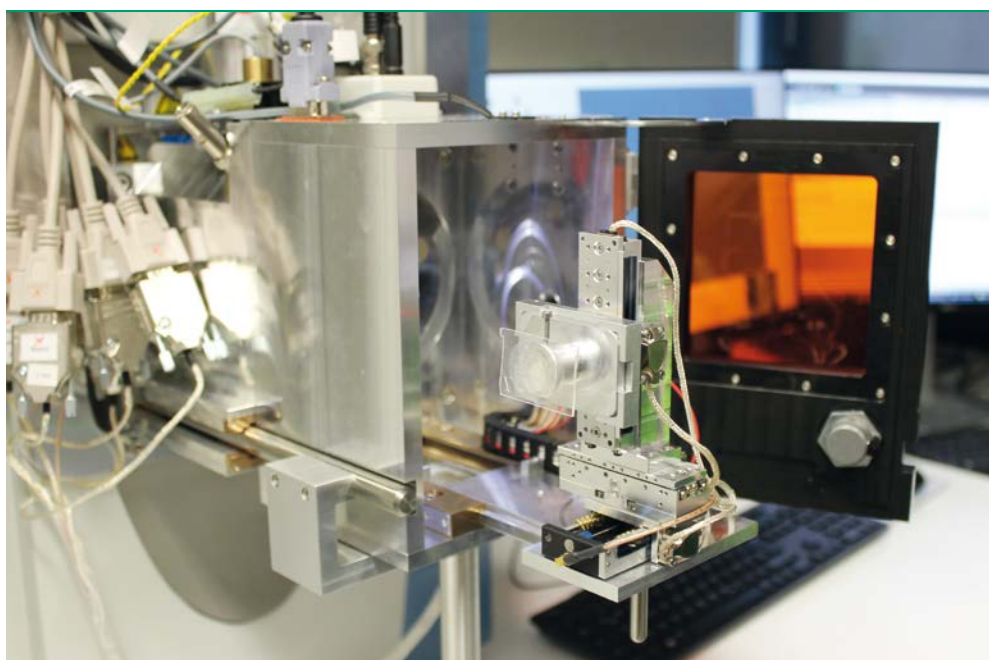
are the signals in the mass spectrum, and the more specifically certain substances in the sample can be represented. If several signals of interest are selected and displayed in different colours, an overlay – for example, of a green, blue, and red channel – can be created by superimposing the individual chemical images.

In the example of the kiwi fruit shown here, the Bayreuth researchers have selected sugar molecules (disaccharides), an antioxidant polyphenol, and a fat (lipid) characteristic of kiwi oil. All the pixels that show the corresponding signals were displayed in green, blue, and red respectively. This makes it easy to see that the sugar in the kiwi fruit is mainly found in the flesh of the fruit, to be precise, in the mesocarp. The stalk and fruit compartments, on the other hand, contain very little sugar. The polyphenol, on the other hand, is mainly found in the skin, while smaller amounts are found in the kiwi fruit's stalk. As expected, the fat is concentrated in the kiwi fruit's seed.

On the trail of food additives

Compared to other imaging methods (histology, microscopy), the advantage of mass spectrometry imaging is that ingredients can be identified without the need to label the molecules with dyes or other "labelling" methods. Instead, all molecules on the sample surface can be examined as long as they are desorbed and ionised. This means that the distribution of ingredients that are not visually detectable, such as vitamins, mycotoxins and fungicides, can be made visible.

Does a fungicide that is supposed to kill fungi or their spores on the surface of a food penetrate into the inside of the food – and if so, how far? This question was investigated in more detail at the Bio-analytical Sciences & Food Analysis research group. Natamycin is a fungicide that is effective against mould and mildew. As a food additive with the E-number E235, it is used for the surface treatment of some sausage products, such as salami, as well as cheese. It is either added to the dipping baths in which the cheese wheels are immersed before maturing, or it is brushed directly onto the wheels. In its Regulation (EC) No 1333/2008, the European Union has defined a limit value for natamycin which may not be exceeded on the surface of the cheese wheel. This regulation also stipulates that natamycin must not penetrate more than five millimetres



into the interior of the cheese. Whether the latter requirement is actually met or not is very difficult to verify using standard food analysis methods. With mass spectrometry imaging, on the other hand, the penetration behaviour of natamycin can be determined with very high accuracy. A cross-section of the cheese surface serves as the sample. The MS

■ Fig. 3 (above): Food chemist Oliver Wittek examining a kiwi fruit sample with a digital microscope (Photo: Christian Wißler).

■ Fig. 4 (bottom): A sample prepared for the MALDI imaging measurement is attached to the 3D stage of the ionisation chamber (Photo: Christian Wißler).

signal of the fungicide can be visualised here and followed from the rind until it disappears completely with micrometre precision. This research work is being carried out in cooperation with the Bavarian Health and Food Safety Authority (LGL). It is contributing to the evaluation and improvement of existing methods of routine analysis and monitoring in the field of cheese products. In addition, the findings can be used to optimise mould control on surfaces, so that less fungicide has to be used for this purpose.

"Mass spectrometry imaging is a measurement technique whose potential in the life sciences is far from exhausted."

The example of the cheese wheels makes it clear: mass spectrometry imaging could become considerably more important for food analysis in the future. After all, the rationale behind food analysis is often legal requirements for the protection of consumer health and protection from fraud. Especially when desired or undesired substances in food are to be precisely localised, "MS imaging" is becoming increasingly important as a versatile measurement technology.

New pharmaceutical substances against tuberculosis

In the area of medicine, mass spectrometry imaging has been used much more extensively than for food sciences. Tuberculosis is an infectious disease caused by the bacterium *Mycobacterium tuberculo-*

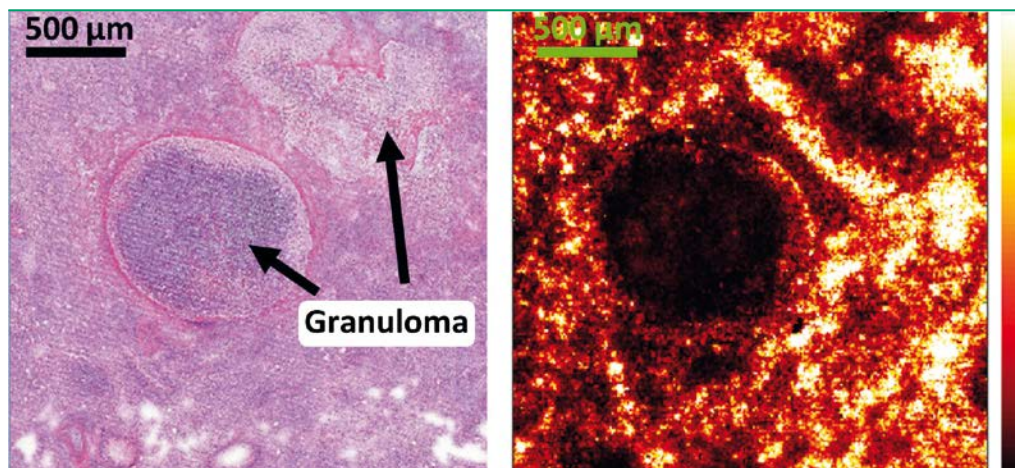
A new data format

As in many areas of modern analytical sciences, data analysis is playing an increasingly important role in mass spectrometry imaging. Automated processes and high-resolution instrumentation have led to a rapid increase in the amount of data generated. For this reason, Prof. Dr. Andreas Römpp has been coordinating the development of the data format imzML for over ten years, which has now become the international standard for mass spectrometry imaging. As a result, measurement results can be evaluated much more efficiently and exchanged between different working groups.

www.imzml.org

sis (Mtb). According to the World Health Organisation (WHO), an estimated 10 million people worldwide were newly infected with this disease in 2018, while 1.3 million people died of it. According to the WHO, tuberculosis is the infectious disease with the highest mortality rate worldwide, ahead of HIV/AIDS and malaria. In most cases, an infection is restricted to the lungs, where it leads to the formation of so-called granulomas. These structures are local centres of inflammation with high levels of mycobacteria. The immune system ensures that these foci are encapsulated by the surrounding tissue. In order to be able to treat tuberculosis successfully, the antibiotics – for example pyrazinamide or rifampicin – must penetrate into the interior of the granulomas in sufficient concentration so that they

■ Fig. 5: Mass spectrometric analysis of the anti-tuberculosis drug clofazimine. Left: Two granulomas in the lung tissue of a mouse, made visible by a haematoxylin-eosin stain. Right: The anti-tuberculosis drug clofazimine is not able to penetrate to the centre of the granulomas (Images: Axel Treu).



kill the mycobacteria there. This is why the treatment is very lengthy: It takes at least six months, which favours the formation of antibiotic-resistant Mtb strains. In order to continue the development of pharmaceutical compounds against tuberculosis, precise information is needed on whether and how these substances penetrate granulomas.

This is the crucial point from which current research work at the Bioanalytical Sciences & Food Analysis research group begins. Mass spectrometry imaging is the only method that can simultaneously visualise the distribution of several pharmaceutical compounds or their degradation products in tissue. As an associated partner of the German Centre for Infection Research (DZIF), the research group uses this technique to investigate exactly how these compounds behave when they penetrate granulomas. This involves both pharmaceuticals that are already in use, and newly developed substances whose exact mode of action needs to be evaluated. The aim is to accelerate the development of new active substances against tuberculosis and thus contribute to the fight against this global pandemic.

Prospects

Mass spectrometry imaging is a measurement technique whose potential in the life sciences is far from exhausted. The Bioanalytical Sciences & Food Analysis research group is therefore also involved in the "Microplastics" Collaborative Research Centre (SFB 1357) at the University of Bayreuth. One of the aims here is to investigate the impact of microplastic particles in tissue and thus to better understand potentially harmful effects on the organism. Methodologically, this project is based on work on the characterisation of colon cancer tissue. By combining different ionisation methods, it has been possible to visualise changes in tissue at the molecular level. With this approach – the combination of complementary analytical methods, close interdisciplinary cooperation, and new bioinformatics approaches – the Bioanalytical Sciences & Food Analysis research group will continue to advance the development of imaging analytical methods in the future. The aim is to produce meaningful images, based on specific and reliable analytical information.

AUTHORS



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RECOMMENDED READING

Andreas Römpp, Bernhard Spengler: Mass spectrometry imaging with high resolution in mass and space. *Histochemistry and Cell Biology* Bd. 139 (2013), Heft 6, 759-783. DOI: 10.1007/s00418-013-1097-6.

Axel Treu et al.: Integrating High-Resolution MALDI Imaging into the Development Pipeline of Anti-Tuberculosis Drugs. *Journal of the American Society for Mass Spectrometry* (2020). DOI: 10.1021/jasms.0c00235.

The following publication of a research group coordinated by Andreas Römpp was awarded the Beyon Award of the journal *Rapid Communications in Mass Spectrometry*:

Nicolas Desbenoit et al.: Correlative mass spectrometry imaging, applying time-of-flight secondary ion mass spectrometry and atmospheric pressure matrix-assisted laser desorption/ionization to a single tissue section. *Rapid Communications in Mass Spectrometry* (2018), 32(2), 159-166. DOI: 10.1002/rcm.8022.



■ Laura M. König

On the trail of healthy eating behaviour

Studying the psychology of eating at the University of Bayreuth

■ It has now been scientifically proven: The way a meal is arranged on the plate influences the taste expectation and the amount consumed (sst).

On average, we eat four meals a day – breakfast, lunch, dinner, and a snack.¹ We can choose from an almost infinite variety of food available at almost any time of the day or night. Which food we choose depends on a variety of factors: Is the price right? Does the dish look good? Do we expect it to taste good? Do we think it is healthy? It is precisely the possible health effects of nutrition that have become increasingly important. For half the population of Germany, they are even the most important criterion for choosing food.²

Interdisciplinary networking in research and teaching

The relatively new field of *Public Health Nutrition* has established itself internationally to investigate how consumers can be encouraged to eat healthy. One focus is on research into the framework conditions that need to be created to give people from all sectors of the population easy access to healthy nutrition. To achieve this, specialist expertise from various disciplines such as nutritional science, medicine, and sociology is required. These are specifically networked in the research field of *Public Health Nutrition*. At the same time, students in this field are taught in specialised master's programmes. Here, they are familiarised with the technical basics of each the subjects involved, and thus develop an interdisciplinary approach to the topic of "Nutrition".

At the University of Bayreuth, this field of research is being addressed for the first time by the junior professorship for *Public Health Nutrition*, established in 2020, in the new Faculty of Life Sciences: Food, Nutrition & Health. This working group places particular emphasis on the inclusion of theories and methods

**"As the saying goes:
'The first bite is with the eye.'"**

from the field of psychology. As a science of human experience and behaviour, psychology is particularly well suited to promote the understanding of how people make decisions about their diet, and how to support them in making health-promoting choices.

It is particularly important to incorporate this knowledge because previous health policy measures to promote healthy eating have not achieved

sufficient success. Although everyone is talking about healthy eating, and most Germans are interested in the subject, many people do not succeed in actually eating healthy. For example, more than 80 percent of the German population does not follow the recommendations of the German Society for Nutrition regarding the consumption of vegetables. Instead of the recommended 400 grams³, we eat an average of only 266 grams of vegetables per day.⁴ At the same time, we consume on average almost twice as much meat as the recommended 300 to a maximum of 600 grams per week.⁵ It is therefore important to understand why the recommendations are currently not being met. Then it will also be possible to say with greater certainty what needs to be done, for example, to increase the consumption of vegetables or reduce the consumption of meat.

Nutrition labelling – a means of changing eating behaviour?

In order to provide consumers with comprehensive information about products, nutrition labelling has been mandatory for all packaged and bulk-sold foods in the EU Member States since December 2016. Nutrition labelling provides information on the energy, fat, carbohydrate, protein, and salt content of the food. However, there are several reasons why this measure does not have enough impact on the eating habits of consumers:

RECOMMENDED LINK

Statista. Interest of the population in Germany in healthy eating and healthy lifestyles from 2016 to 2020.

<https://de.statista.com/statistik/daten/studie/170913/>

■ Fig. 1: Visual cues often determine purchasing decisions (sst).



Nutrition Facts	
Serving Size 1 cup (228g)	
Servings Per Container 2	
Amount Per Serving	
Calories 250	Calories from Fat 110
	% Daily Value*
Total Fat 12g	18%
Saturated Fat 3g	15%
Trans Fat 3g	
Cholesterol 30mg	10%
Sodium 470mg	20%
Total Carbohydrate 31g	10%
Dietary Fiber 0g	0%
Sugars 5g	
Protein 5g	
Vitamin A	4%
Vitamin C	2%
Calcium	20%
Iron	4%

* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Fig. 2: Nutritional information on a package (sst).

Current research suggests that nutritional information is difficult for consumers to understand. Most people cannot conceive of values like 445 kcal in concrete terms. As a result, it is often not possible for them to correctly estimate the amount of calories or nutrients they have already consumed.⁶ However, such an assessment would be necessary in order to relate food already consumed to the recommended calorie or nutrient intake. Furthermore, the values are usually given for 100 grams of the product, or for some arbitrarily defined serving size. Therefore, an additional calculation is often required to obtain the nutritional values for the whole package, or for the quantity taken, in order to then compare them with the recommendations. Both of these factors make it difficult to incorporate nutritional information into everyday decisions such as dinner planning.

Nutritional information is often only one of many decision criteria. Price, placement, and presentation of the product can also play an important role, for example when shopping in the supermarket.⁷ We usually lack the time and concentration to look at and analyse each product in a targeted manner. Decisions are therefore often made as spontaneous reactions to reference cues or simply out of habit.⁸ Accordingly, it is not surprising that many consumers may little or no attention to nutrition labelling.

Nutritional information is only available on packaged foods. If we buy unpackaged food, such as at the bakery, or eat in the canteen or restaurant, information on the calorie or nutrient content of the food is often completely absent. We cannot therefore rely solely on nutritional information to choose healthy food.

Gut decision: "Eat colourfully!"

In order to promote healthy eating in everyday life, other strategies apart from nutrition labelling are probably necessary. These should be able to reach the respective target group through measures that are easy to understand and readily perceptible. Scientific studies show that the visual impressions play an important role in the selection of food. For example, the appearance of a food and the way it is presented on the plate can have a major influence on taste expectations and the amount of food eaten.⁹ As the saying goes: "The first bite is with the eye."



Fig. 4: Variously coloured sweet potatoes from Kenya (Photo: Serah Kiragu-Wissler).

If you take a closer look at healthy foods such as fruit and vegetables, you will notice that they come in almost all the colours of the rainbow. Fried and sweet foods, on the other hand, often have differ-



Fig. 3: "The first bite is with the eye." Fruits in all the colours of the rainbow (sst).

RECOMMENDED READING

L. M. König, B. Renner: Colourful = healthy? Exploring meal colour variety and its relation to food consumption. *Food Quality and Preference* (2018), 64, 66-71. DOI: 10.1016/j.foodqual.2017.10.011.

L. M. König, B. Renner: Boosting healthy food choices by meal colour variety: Results from two experiments and a just-in-time Ecological Momentary Intervention. *BMC Public Health* (2019), 19, 975. DOI: 10.1186/s12889-019-7306-z.

ent shades of brown. One might easily suspect that colour variety in food could be a relatively easy-to-perceive indication of healthy food. A number of recent studies confirm this assumption.¹⁰ Both experimental laboratory studies and the evaluation of meals photographed in everyday life showed that more colourful dishes contained more vegetables. However, no link could be found with the consumption of sweets. Moreover, a single short text message a day sent to the participants' mobile phones as part of a study already ensured that more vegetables were consumed. So the rule of thumb "colourful is healthy" could indeed be used to promote healthy eating in a simple and understandable way.

This knowledge can now be used in a number of ways - for example, in health policy, marketing, and advertising. Similar to the study, consumers can be encouraged to eat "colourful" food and made aware of the benefits of a "colourful" diet. Restaurant or canteen operators could add visually appealing and healthy meals to the menu, and thereby encourage their patrons to eat more healthily.

New impetus for healthy nutrition

The combination of psychology and nutritional science provides exciting new impulses for the promotion of healthy eating. In order to study further prevention measures, a behavioural science laboratory is to be set up on the new campus of the University of Bayreuth in Kulmbach over the coming years. There, students will have the opportunity to try out new research methods in their courses,

Research in nutritional psychology in Kulmbach

Within the framework of the new *Public Health Nutrition* field of research, various novel research methods are to be established on the campus of the University of Bayreuth in Kulmbach, which will make it possible to investigate the various influences on nutrition under realistic conditions. For this purpose, a new behavioural science laboratory will be set up, including a buffet filled with realistic food replicas. The laboratory will offer the possibility to experimentally investigate the effects of individual influencing factors – such as the amount of selection alternatives available or specific instructions for selecting food ("Choose a dish that is as colourful as possible") – in a controlled environment. In addition, smartphones and corresponding software for *Ecological Momentary Assessments* will be purchased, which will enable study participants to document their everyday diet. The first studies are to start in spring 2021. If you would like to take part in trials, you can find more information on the homepage of the *Public Health Nutrition* working group.

www.phn.uni-bayreuth.de



■ Fig. 5: Food replicas for studies of eating behaviour (Photo: Laura M. König).

and to get a taste of current research projects in the context of internships or theses. In addition, interdisciplinary work is to be expressly furthered in courses in order to lay the foundation for innovations in nutrition.

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- 2 B. Renner et al.: Why we eat what we eat: The Eating Motivation Survey (TEMS). *Appetite* (2012), 59, 117-128. DOI: 10.1016/j.appet.2012.04.004. – Techniker Krankenkasse: Iss was, Deutschland. TK-Ernährungsstudie 2017. Hamburg 2017.
- 3 A. Jungvogel: Lebensmittelbezogene Ernährungsempfehlungen in Deutschland. Bonn: Deutsche Gesellschaft für Ernährung e.V. (DGE), 2014.
- 4 Bundesministerium für Ernährung und Landwirtschaft: Statistik und Berichte des BMEL. Pro-Kopf-Verbrauch von Gemüse nach Arten. Berlin 2019.
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- 6 L. M. König et al.: Quantifying actual and perceived inaccuracy when estimating the sugar, energy content and portion size of foods. *Nutrients* (2019), 11, 2425. DOI: 10.3390/nu11102425.
- 7 Cf. M. Schulte-Mecklenbeck et al.: A lack of appetite for information and computation. Simple heuristics in food choice. *Appetite* (2013), 71, 242-251. DOI: 10.1016/j.appet.2013.08.008.
- 8 B. Renner: Ernährungsverhalten 2.0. Veränderungen durch explizite und implizite Interventionen. *Ernährungsumschau* 2015; 1, M 36-M 63.
- 9 Cf. Anm. 7 und D. Wadhwa, E. D. Capaldi-Phillips: A review of visual cues associated with food on food acceptance and consumption. *Eating behaviors* (2014), 15, 132-143. DOI: 10.1016/j.eatbeh.2013.11.003.
- 10 See Recommended Reading.

AUTHOR



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David Mann
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Active studying means better studying

Movement-enhancing
library workplaces increase
productivity and well-being

■ A height-adjustable work desk with floor mat in the University
Library on the Bayreuth campus (Photo: Christian Wißler).



Physical activity and exercise can have a comprehensive health impact in all age and population groups if it is conducted systematically, regularly, and in sufficient amounts. They strongly promote the prevention of risk factors and non-communicable diseases, including diabetes mellitus type 2, high blood pressure, obesity, and depression. They also strengthen the development of health resources, such as physical fitness and self-concept.

In Germany, it has been possible in recent decades to motivate people to be systematically and regularly more physically active in sufficient amounts. Irrespective of the level of physical activity, however, epidemiological research has been establishing for some years now that long hours spent sitting are an independent risk factor for diseases of civilisation.¹ "Sitting is the new smoking!" is now THE slogan of prevention and health promotion. Compared to other European countries, Germany records above-average sitting times, especially among people with a high educational and social status who primarily perform cognitive work. Although young adults are considered the healthiest and most active population group, it is precisely they who are affected by this problem: People between 18 and 29 spend up to nine hours a day sitting – more than any other age group.² Although the universities have constantly expanded their sports and physical activity facilities and made them more versatile, the image of "learning while sitting" remains firmly entrenched. Lecture halls are permanently seated – it is not possible to change your sitting posture during a lecture. The situation is the same in many libraries: Reading, learning, and writing – core activities of students – must take place primarily while sitting at tables. Students usually do not have the freedom to change their posture or study while alternating between sitting, standing, and walking.³

Learning in motion, a current Bayreuth study

As part of the "Smart Moving" project, movement-enhancing library work places (PWDs) were set up in the Central Library of the University of Bayreuth, which enable students to continuously change between sitting and standing while studying. These PWDs each consist of a continuously height-adjustable table, two height-adjustable seats without backrests (Swopper and Muvman by aeris®) and a floor mat for working in a standing position (Muvmat by aeris®). A study embedded in the project

investigated the question of how popular these offerings were, and what effects they have on the sitting behaviour, work productivity, and the health-related well-being of students.

The study was conducted in July 2019, towards the end of the lecture period and before the start of the examination phase, with ten students from seven bachelor's and master's programmes.⁴ The students were to spend at least four days a week in the library during the two-week study period – at least four hours a day. During this time they wore activPAL4® motion sensors, which could record all movements and body positions while sitting, standing, walking, and lying down. In this way, individual movement and sitting profiles were created for all ten students.

„Long sitting means rusting.“

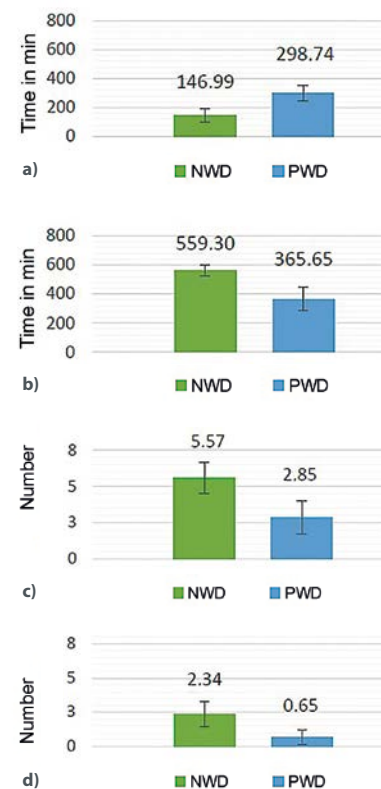
– Line from Victor von Scheffel's "Lied der Franken" (1859) –

In the first week, the students worked in a seated position at normal work places (NWD). Only conventional, non-height-adjustable library desks were available to them for this purpose. In the following week, on the other hand, they studied at movement-enhancing work desks (PWD). Quantitative comparisons between the movement profiles in the first and second week show significant differences:

- In the NWD week, the average daily sitting time of the students was 9 hours and 19 minutes. It thus corresponded fairly exactly to the average sitting time of 18 to 29-year-olds in Germany as determined in other studies.⁵ In the PWD week, however, the average daily sitting time of students fell to around 6 hours, while their average daily standing time increased by more than 2 hours. This means that students stood for more than twice as long on average in the PWD week as in the NWD week. Conversely, they spent considerably more time sitting than in the PWD week during the NWD week.

- The number of daily phases in which students worked continuously for 30 minutes or longer in a sitting position was significantly lower in the PWD week than in the NWD week. Correspondingly, the number of daily phases of sitting that lasted 60 minutes or longer without interruption was also reduced by around a third in the PWD week.

The scientific literature does not yet contain any concrete recommendations on maximum daily sitting times that should not be exceeded from a



■ Fig. 1: Quantitative analysis of the sitting and standing behaviour of students: (a) average daily standing time in minutes, (b) average daily sitting time in minutes, (c) average daily number of sitting phases of at least 30 minutes, (d) average daily number of sitting phases of at least 60 minutes. NWD = measurement days at normal work desks, PWD = measurement days at work desks promoting physical activity (Source: D. Mann et al. (2020), see recommended reading).

“Smart Moving”

Reducing the sitting times of students and encouraging them to be more active in their everyday lives is the goal of the "Smart Moving" project, in which three departments of the University of Bayreuth are co-operating: "Social & Health Sciences in Sports" (Prof. Dr. Susanne Tittlbach and Jessica Helten), "Theory & Practice of Sports and Movement Fields" (Dr. Sascha Hoffmann), and "Marketing & Consumer Behaviour" (Prof. Dr. Claas Christian Germelmann). External partners are the University of Regensburg and the Competence

Centre for Nutrition (KErn). Techniker Krankenkasse (TK) is funding the project over a period of three years (2018 - 2020). During this period, study conditions at the University have been improved in some areas, meaning that students can quickly and easily switch between sitting, standing, and moving during their working hours. In general, there are now more opportunities for everyday physical activity on campus.

Following the nudging method, an attempt is being made to achieve the use of these opportunities by influencing the contexts of decision-mak-

ing, without resorting to prohibitions, commands, or economic incentives. To this end, the Universities of Bayreuth and Regensburg have developed measures to promote physical activity and avoid sitting, for example with active breaks during classes and the visualisation of paths and distances on campus. In addition, activating study furniture has been installed, for example in libraries. The changeover to online courses due to coronavirus conditions led to some measures being redesigned in digital form in the 2020 summer semester.

www.smart-moving.bayern



■ Prof. Dr. Claas Christian Germelmann is the Chair of Marketing & Consumer Behaviour at the University of Bayreuth.

RECOMMENDED READING

D. Mann et al.: Bewegungsfördernde Bibliotheksarbeitsplätze an Hochschulen: Eine Studie zu Wirkung und Akzeptanz bei Studierenden, in: Prävention und Gesundheitsförderung, (2020). DOI:10.1007/s11553-020-00806-9.

J. Helten et al.: Smart Moving: Bewegungs- und Sitzverhalten von Studierenden, in: B. Wollesen et al. (eds.): Interdisziplinäre Forschung & Gesundheitsförderung in Lebenswelten. Hamburg 2020, 80-85.

health perspective. However, as a guideline, it is recommended to interrupt sitting every 30 minutes and to change posture in order to positively influence metabolism.⁶ The change of posture has proven to be superior to even moderate physical activity in terms of its preventive effect. The results obtained in the "Smart Moving" study allow the following conclusion to be drawn. By using movement-enhancing workplaces in libraries, the daily sitting time of students can be reduced by a good three hours and progress toward the guideline value can be achieved.

Increased well-being and productivity

In order to be able to motivate people to make sustainable changes in behaviour, it is necessary that

the framework conditions are well-accepted and experienced as pleasant. For this reason, additional interviews on qualitative aspects of the PWDs were conducted with four students as part of the "Smart Moving" study. All four respondents showed a high level of acceptance and rated the new library workplaces extremely positively. As reasons, they cited the possibility of individual adaptation to their own body size, but also the possibility of switching between sitting and standing. The floor mat was described as an important aid for standing while studying. Simple standing tables without corresponding floor mats and seating options, on the other hand, were judged by the interviewees to be less suitable in their previous experience.

The investigated students emphasised that their work productivity and the length of their working



■ Fig. 3 and 4: The "Smart Moving" project also includes instructions for active breaks (Photo: Claudia Meier).

hours had increased as a result of the PWD. They justified this with the experience that changing postures increase alertness at work. They also described positive effects on health, for example less back pain and increased physical and mental well-being. All respondents expressed their willingness to continue to use the new work desks in the future.

Conclusion for practice

The results of the Bayreuth study show that by reducing sitting times and increasing standing times, movement-enhancing work desks can contribute to a health-preserving and health-promoting work behaviour. They can strengthen the well-being of students and are assessed positively by them throughout. Universities should therefore make more movement-promoting work opportunities available in their libraries. It would also be welcome if they were to inform their students to a greater extent than in the past about ways of reducing sitting times while studying, being more physically active, and thus making their own lifestyle healthier.

Physical activity recommendations for adults				
A	or	B	or	C
Moderate-intensity physical activity		Vigorous-intensity physical activity		Moderate-to-vigorous-intensity physical activity
Examples: fast walking, cycling, swimming		Examples: running, fast cycling, fast swimming		Combination of physical activities from A and B
At least 150 minutes per week (e.g. 5 x 30 minutes daily)		At least 75 minutes per week (e.g. 5 x 15 minutes daily)		
In any case, additional muscle strengthening exercise on at least 2 days per week. Example: functional gymnastics exercises, lifting weights.				
... and besides that: Avoid long periods of sitting and interrupt sitting with physical activity. Examples: short walks, working in a standing position.				

■ Source: Bundeszentrale für gesundheitliche Aufklärung im Auftrag des Bundesministeriums für Gesundheit (ed.): *Menschen in Bewegung bringen*. Köln 2019, 12.

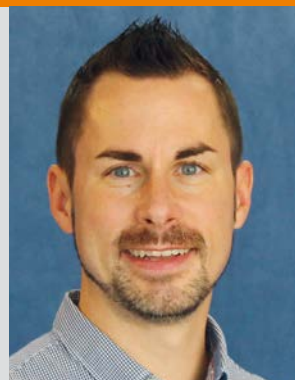
AUTHORS



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■ David Mann M.Sc. completed his master's degree in Sport, Business & Law at the University of Bayreuth, and is currently working as a venture development manager at Choco Communications.

- 1 J. Bucksch, B. Wallmann-Sperlich: Aufstehen, Hingehen, Treppensteigen – die gesundheitliche Relevanz von Alltagsaktivitäten. *Public Health Forum* (2016), 24(2), 73-75. DOI: 10.1515/pubhef-2016-0029.
- 2 J. Y. Chau et al.: Daily Sitting Time and All-Cause Mortality: A Meta-Analysis. *PLoS One* (2013), 8(11). DOI: 10.1371/journal.pone.0080000.
- 3 O. Castro et al.: How Sedentary Are University Students? A Systematic Review and Meta-Analysis. *Prevention Science* (2020), 21(3), 332-343. DOI: 10.1007/s11121-020-01093-8.
- 4 The group of ten test persons consisted of three men and seven women. Six of them were completing a bachelor's programme, and a master's programme. Due to the limitation of the study to only ten subjects and the short test period of two weeks, the results only offer initial insights. Generally valid statements cannot be made without larger-scale studies being conducted over a longer period of time.
- 5 Like footnote 3.
- 6 Like footnote 1.



■ Michael Frisch

Increased performance in running

Setting new records with technological innovations

■ Middle distance runner Dennis Gerhard on a treadmill in the Department of Sport Science's Training and Movement Science Lab at the University of Bayreuth (Photos: Michael Frisch).

"Faster, higher, further" – this has always been the maxim of the Olympic Games in modern times. The history of sport shows that the most varied attempts to increase performance have long concentrated on improving physical characteristics and functions according to the requirements of the specific sporting discipline. Today, scientific training investigations, biomechanical analyses with sensors and special software and, last but not least, nutritional support for athletes help to ensure that sporting records are constantly being broken. However, this trend towards optimizing the body often has a dark side: prohibited medications that are not only ethically irresponsible, but in the long run are harmful to health.

In order to enable athletes to run faster, jump higher, and run further, various scientific and technical approaches have been available for some time that aim to optimize the sports equipment and clothing they use. This development is now the subject of controversial debate, and the term "technological doping" is often used. One example is swimsuits (banned in 2010) which were developed according to the bionic principle of scaly shark skin. The buoyancy in the water, water resistance, and the compression effect on the muscles could be significantly improved in this way. It is therefore no coincidence that around 130 national and international swimming records were set between 2008 and 2010. However, the World Swimming Federation put an end to this record series with its ban. In support of this, it referenced the possible lack of equal opportunity. This is because some sports federations had already negotiated exclusive equipment contracts with selected manufacturers, while other companies were unable to keep up with rapid technological change.

Focus on running shoes: ideas and experiments

The heated discussions in swimming at that time are now reaching the sport of running with a similar dimension. If the long-awaited dream of running a men's marathon in less than two hours could be fulfilled, sponsors' hearts would beat faster and there would be new financial incentives for athletes and sports organizers. Kenyan marathon runner Eliud Kipchoge, who set the current world record in Berlin in 2018 with a running time of just over two hours, compared this vision with the dream of a moon landing: An apparently unreachable goal is within reach, yet is (still) far away.

"Partner University of Professional Sports"

In 2018, the University of Bayreuth and the German University Sports Association (adh), the umbrella organization of university sports facilities in Germany, signed a cooperation agreement to support students who are top athletes. Outstanding athletes can organize their studies at the University of Bayreuth with a flexibility that is truly compatible with the requirements of top-class sport. These very successful athletes include triathlete Andreas Dreitz, who studied Sport, Business & Law (M.Sc.) at the University of Bayreuth and in the LL.M. programme Sports Law, in addition to middle-distance runner and triathlete Dennis Gerhard, a graduate of Sport, Business & Law (B.Sc.) and Business Administration (M.Sc.). Today, both support the research work on running economy as test persons for the University of Bayreuth's Department of Sport Science with the aim of further developing running shoes from using materials science.



■ Fig. 1: View of the University of Bayreuth's campus – the Department of Sport Science is front right (Photo: UBT).

With the aim of enabling new top performance in marathons and beyond, companies and partners from the field of sport science have been working with increasing intensity on the optimization of running shoes over the past ten years. Running shoes usually consist of an upper material, a lacing system, a midsole, and an outsole. Especially in the area of the midsole, many experiments with new ideas and developments have been carried out recently. Opinions among sport scientists were originally divided: Some argued that runners need good cushioning and therefore a midsole; others disagreed, arguing that the natural rolling mechanism must be maintained and the foot muscles strengthened – which is why almost no cushioning is required. However, companies such as Adidas and Puma recognized that a sole with increased energy return (*rebound effect*) could improve performance. In 2013, in cooperation with BASF, they developed the material *Infinergy*, which is now an indispensable part of Adidas shoes in the "Boost" collection. Chemically speaking, it is expanded thermoplastic polyurethane (e-TPU). The point of this material is that a large portion of the kinetic impact energy is returned to the runner, so that less force is required when running. This innovation helped Kenyan

Dennis Kimetto to beat the world record in Berlin in 2014 in the men's marathon by 26 seconds.

"Running economy in competitive sports can be significantly improved through technological innovations."

Increasing bending stiffness: a key to running shoe optimization

The faster runners on a certain course length are the higher is usually the physical performance. Improved performance depends heavily on the efficient conversion of chemical energy into mechanical energy at the cellular level in the body. The "running economy" is the rate of energy consumption during running at a load just below the performance limit. In order to improve the energy consumption rate with running shoes, it is necessary,

- to increase the stiffness of the running shoe and the energy return,
- while reducing the weight of the running shoe and energy consumption.¹

■ Fig. 2: Muscle activity is recorded wirelessly during the test of new running shoes (Photo: Michael Frisch).



The stiffness of a running shoe is mainly determined by its longitudinal bending stiffness (LBS). This means that the shoe is not very flexible, especially on its longitudinal axis. Studies in sports medicine have shown that an increase in LBS has significant consequences: At the metatarsophalangeal joints, which connect the metatarsal bone with the five toe bones, significantly less energy is absorbed.² In addition, it is now clear that increasing LBS can reduce oxygen uptake and thus metabolic turnover – which has a beneficial effect on performance.³ The

■ Fig. 3 (right): Andreas Dreitz, born in Upper Franconia, is on the list of Germany's top triathletes for the Ironman distance (Photo: Michael Frisch).

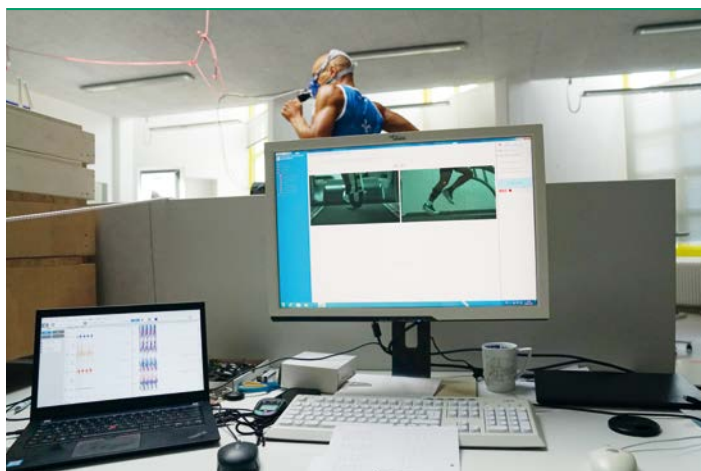
oxygen uptake (VO₂) is the amount of oxygen that the body takes from the inhaled breath per unit of time. It is measured in the laboratory using spirometry. In this diagnostic procedure the test person wears a breathing mask. While exposed to increasing physical stress, for example on a treadmill or bicycle, the gases contained in the exhaled air are measured and compared with the inhaled gases. The findings show how the heart and circulation system, respiration, metabolism, and cardio-pulmonary performance react to physical stress. In addition to VO₂, the respiratory compensation point (RCP) is often used to evaluate performance. This point is reached with increasing physical exertion when a drop in the CO₂ concentration in the air breathed is measured.

Innovative materials: Carbon plates and foam

Initial investigations with the aim of increasing LBS by means of carbon fibre reinforced plastic (CFRP) midsoles were carried out in 2006 in cooperation with Adidas.⁴ Tests with such a carbon plate in the shoes have shown that this way the metabolic rate of runners can be thereby reduced by almost one percent. However, no significant differences were found with regard to energy absorption at the metatarsophalangeal joints. Although these studies have shown that increased LBS can improve performance, the technology of the carbon plate in running shoes has not been pursued further.

It was not until 2018, in cooperation with Nike, that a new study with a stiffened outsole followed.⁵ It





■ Fig. 4 and 5: Left: In the Department of Sport Science's Training Science & Kinesiology Lab, spiroergometric measuring devices, high-speed cameras, and electromyographic techniques are used. Right: Professional athlete Andreas Dreitz testing a prototype of new running shoes (Photos: Michael Frisch).

turned out that the energy consumption of all 18 runners tested was reduced – by four percent on average. But the special thing about this new shoe called "Nike Vaporfly 4%" was not only the carbon plate. The real innovation was rather the foam in which the plate was embedded. The plate itself only extends the lever arm for power transmission. The new foam, however, is able to temporarily store the energy generated by the carbon plate while running and then release it again. As a result, the energy return is increased and energy loss is reduced. With this combination of innovative foam and carbon plate, Nike created the next revolution in running. The current ten fastest running times in the men's marathon were achieved with shoes employing this technology. At the World Athletics Half Marathon Championships in Gdynia in 2020, 108 of 117 participants ran with shoes that integrated carbon elements and an innovative foam. Almost every manufacturer of running shoes is now working on further developing this combination. Instead of a carbon plate, Adidas has recently incorporated so-called "EnergyRods" into their shoes. These are rod-shaped elements made of carbon fibre reinforced plastic, which imitate the midfoot.

Outlook

The University of Bayreuth's Department of Sport Science is also contributing to the development of innovative running shoes in cooperation with renowned manufacturers. Among other things, the interdisciplinary Sports Technology research group is based here and is coordinating a new master's


programme in this field. A team from the research group Exercise Physiology & Metabolism and the research group Training and Movement Science has investigated the differences in running economy between amateur and competitive athletes on the basis of this sport technological expertise. Various prototypes of new running shoes were tested by means of spiroergometry, high-speed cameras, and muscle activity (electromyography), whereby the subjective perception of the test persons was also included. These tests involved the application of new types of fibre-reinforced plastic elements not previously used in sports shoes. The trend was confirmed that running economy in competitive sports can be significantly improved through technological innovations. The extent to which carbon shoes prove their worth in popular sports still needs to be investigated in more detail. It must be taken into account that the risk of fatigue fractures, arthrosis, and muscle injuries increases when less well-trained amateur athletes try to reach the level of competitive athletes as quickly as possible with the help of new technological developments.

AUTHOR



■ Dr.-Ing. Michael Frisch is a research associate in the research group Sport Science I - Training and Movement Science at the University of Bayreuth, where he is responsible for the research area "Sports Technology".

- 1 N. Flores et al.: Does an increase in energy return and/or longitudinal bending stiffness shoe features reduce the energetic cost of running? *European Journal of Applied Physiology* (2019), 119, 429-439. DOI: 10.1007/s00421-018-4038-1.
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A woman in black athletic wear is running on a rocky trail in a forest. The trail is covered with pine needles and moss. The background shows tall pine trees and a large rock formation.

SPORT & EXERCISE

■ Anne-Maria Schweizer
Veronika Mitterwallner
Volker Audorff
Manuel Steinbauer

Sport Ecology

The ecological dimension
of outdoor sport

■ Running is becoming increasingly popular during the Covid-19 lockdown, as here on Buchstein, on the southern outskirts of Bayreuth (Photo: Veronika Mitterwallner).

Hiking through a picturesque landscape, climbing a mountain under your own steam, or paddling white water – for many people, outdoor sports offer valuable experience of nature and enrich their everyday lives much beyond their mere sporting aspects. Unlike in a fitness studio, sportspeople do not only achieve a training effect in nature, but the surrounding landscape offers space for comprehensive recreation. It promotes stress reduction and has a relaxing effect on the psyche. At the same time, physical exercise in nature strengthens one's own self-esteem and contributes to the experience of symbolic unity with nature, and to a general improvement in the quality of life. For many people today, outdoor sports are the most important way to experience nature.

The challenge: Sport in harmony with the environment

Outdoor activities have been booming for years and are attracting more and more people into the natural world. Yet what happens if evermore sports enthusiasts want to spend time there? In this case, outdoor sport can be designed in an eco-friendly manner by means of an adapted visitor guidance system. Here, well-planned, attractive sports opportunities, tour suggestions, and visitor information are often more successful than bans. What is more, interaction with nature in sport leads to a direct bond between sportspeople, to greater appreciation of the landscape, and a greater willingness to protect it. Even if, for example, rock vegetation is damaged by climbing, the activity, which takes place over hours in a very small area, can at the same time strengthen the sportpersons' bond with nature. Outdoor sport therefore has the potential to increase environmental awareness, which in turn benefits nature. Athletes and nature are in a mutually beneficial relationship. Especially now, in times of the climate crisis, it is particularly important to strengthen this relationship. In the long term, people benefit from the sustainable use of natural areas.

However, along with this enthusiasm for outdoor activities, incidents of conflict are also increasing – on the one hand between the different types of human land use categories, and on the other hand between sportspeople and nature. In some places, the expansion of sports and tourism infrastructure is leading to a gradual destruction of the structure of the landscape. Habitats become fragmented or



are lost altogether. The result is a loss of species diversity in flora and fauna, creating a serious imbalance in native ecosystems.

■ Fig. 1: On Gepatschferner in the Ötztal Alps (Austria). Hikers climb the Fluchtkogel, almost 3,500 metres above sea level (Photo: Veronika Mitterwallner).

In order to understand these developments, the Professorship of Sport Ecology at the University of Bayreuth is applying quantitative research methods and linking the constantly growing data sets in the fields of ecology and sport. These data sets also include image data. Among other things, infrared-based visitor counting systems and wildlife cameras are used to record the activity patterns of wild animals. The automated identification of wildlife in this extensive image data is achieved by machine learning. In this way, outdoor sports, such as hiking and mountain biking in summer and cross-country skiing in winter, can be comprehensively recorded and analysed with regard to their interaction with their social and natural environment. In addition to image data, the scientific field of Sport Ecology also uses audio data, motion data, and remote sensing data. The aim is an integrated recording of human-influenced ecosystems.

Sport is subject to dynamic developments, either through the emergence of new sports or through technical progress. One development that is registering increasing popularity is the e-mountain-bike. It gives older, physically limited people, or less well trained sportspeople the opportunity to be physically active in nature. However, this technical progress also opens up a new riding experience for experienced mountain bikers, as a result of being able to overcome challenging distances so simply. However, these new possibilities often lead to problems. Despite or perhaps because of the technical innovations that these bikes offer, natural and physical demands are often underestimated. As a



■ Fig. 2 and 3: Activity patterns of wild animals, here at Ochsenkopf in the Fichtelgebirge, are documented with the help of wildlife cameras. The data obtained in this way allows to deduce the influence of outdoor sports activities. Meanwhile, the lynx on the right has accidentally been shot by a hunter (Photos: Ecology of Sport, UBT).



■ Fig. 4: Rapid descent: Mountain bikers on Ochsenkopf in the Fichtelgebirge (Photo: © Cube Bikes).

result, accidents occur, but conflicts with the social and natural environment are also increasing due to lack of experience with the sport. This is because the better accessibility of the sport and the easier overcoming of previous spatial boundaries have resulted in an increase in e-mountain-bikers enter-

"In the long term, people benefit from the sustainable use of natural areas."

ing sensitive ecosystems. Previously remote regions can now be accessed more easily and quickly, which in turn can lead to the disturbance of previously untouched biotopes and to conflict with nature conservation.

Sustainability as the guiding principle of Ecology of Sport

The issues being investigated at Sport Ecology at the University of Bayreuth cover a wide range of natural, cultural, and economic science topics in research and teaching. These include, for example, sports tourism and its effects on ecosystems, the environmentally compatible design of sports facilities, and the interactions between sports behaviour, the experience of nature, and health. But also in practice, the outdoor sports courses at the University of Bayreuth – climbing, mountain biking, cross-country skiing, and ski mountaineering – place great emphasis on teaching environmentally conscious sports practice. In all of these subjects, the principle of sustainability is very much in the foreground.

Outdoor sport in times of Covid-19

A current example of Sport Ecology research is an ongoing Bayreuth study on the behaviour of outdoor sportspeople during the Covid-19 pandemic. Data from fitness apps, which are used during training to record one's own performance or for orientation, is being evaluated in this study in order to be able to make statements on any change in sports behaviour caused by lockdown. This app data comprises a multitude of anonymous, spatio-temporal activity data, which is voluntarily provided by the users. They therefore form a broad basis for scientific studies. However, the fact that fitness apps are being used by more and more people is problematic, meaning that it is not possible to draw immedi-



■ Fig. 5: Students in the cross-country skiing course at Bayreuth University enjoy good snow on Bleaml-Alm in Neubau am Ochsenkopf in the Fichtelgebirge (Photo: © Tourismus & Marketing GmbH Ochsenkopf).

ate conclusions from this growing database about the rising popularity of outdoor sports activities. As a result, trends – such as the increasing popularity of apps or weather-related behaviour – can only be deduced from models created before the lockdown-related increase in outdoor sports activity became evident.

Public appeals and recommendations for action by federal and state governments to prevent the uncontrolled spread of Covid-19 have led to a steep increase in outdoor sports activities, especially in urban areas. This finding is consistent with studies

from other European countries, which also show a sharp increase in outdoor activities during the period of government-imposed restrictions on movement. Being physically active is seen as an important strategy in staying mentally and physically healthy during a crisis like the current pandemic. After all, being healthy and fit equips people to better cope with potential infection. Outdoor sports have a particularly important role to play here. The natural environment and physical activity both reduce stress. It thus increases resilience in the face of greater stress levels associated with the COVID-19-related restrictions in daily life.



■ Fig. 6: A group of outdoor sports enthusiasts on a ski tour at Ochsenkopf, Fichtelgebirge (Photo: © Tourismus & Marketing GmbH Ochsenkopf Andreas Munder).

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■ Stephanie Thomas
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Mosquitoes spread infection

Climate change and biodiversity influence virus transmission

■ Asian tiger mosquito (*Aedes albopictus*) (sst).

Before the outbreak of the Covid-19 pandemic, hardly anyone in Germany knew the term "zoonoses". However, it covers a great many diseases – for example plague, Ebola, BSE, dengue and even Zika fever, and West Nile fever. Some of these zoonoses are not transmitted directly, but via so-called vectors, for example mosquitoes. So far, we have been little affected by such diseases in Germany. But even in this country, vector-borne zoonoses have been around for some time, such as tick-borne early summer meningoencephalitis. Native mosquitoes can also transmit new zoonotic pathogens, such as West Nile virus.

Transmitted by mosquitoes: new zoonoses in Germany

The West Nile virus (*Flaviviridae*) causes West Nile fever. It was named after the place of its discovery in Uganda. The virus circulates mainly between mosquitoes and birds, and is therefore a vector-borne zoonosis. To date, 949 bird species are known to be hosts for the West Nile virus – that is about 8.8 percent of all bird species worldwide. In addition, the virus has so far been detected in more than 43 different species of mosquitoes. The role of biodiversity in the chain of infection therefore still poses major research questions. Two species of mosquitoes are of particular importance with regard to their distribution, their habitats, and their role in the transmission of West Nile fever: the northern house mosqui-

to (*Culex pipiens*), which is widespread in Germany, and the Asian bush mosquito (*Aedes japonicus*), an invasive alien species. The widespread occurrence of this species in Germany has been known since 2008. Some mosquitoes can infect not only birds but also mammals. In most cases, an infection does not cause any symptoms in humans. Occasionally, however, an inflammation of the brain occurs, in few cases resulting in death.

As with other zoonoses, it is not possible to determine exactly where and in which organisms the West Nile virus originally occurred. The driver for a pathogen to jump from its natural habitat into a new community is often the loss of natural habitats and the resulting new contact with humans and animals. In recent years, the virus has spread worldwide via migratory birds. Transmission in commercial goose raising operations have also been documented. In the EU there were more than 2,000 infections of horses and humans only in 2018 - more than in the years 2011 to 2017 combined. In 2019, West Nile virus was detected in an individual in Germany for the first time, who was infected via the bite of a mosquito. Already one year before, several birds and horses had fall ill and died in the same region as a result of a West Nile infection. The reason for the occurrence of these viral infections in Central Europe is the increasingly warm summer months, which promote the replication of the virus in the mosquito. It can be assumed that in the future an increasing number of cases will appear due to climate change.

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Zoonoses

A zoonosis is any disease or infection naturally transmissible from vertebrates to humans (WHO). In the last two decades, about 60 percent of newly emerging infectious diseases in humans have originated in animals. However, transmission can also occur from person to person, or even from person to animal. Zoonotic diseases can be caused by bacteria, viruses, parasites, or prions. The SARS-CoV-2 pathogen most probably originated in bats, and tanuki, among other species, have become known as intermediate hosts. Covid-19 therefore is a zoonosis.

Vectors and hosts

Vectors are organisms that transmit pathogens to humans or animals. However, they themselves do not become ill. Many of these organisms are blood-sucking insects such as mosquitoes or fleas, or even arachnids such as mites or ticks. During a blood meal, a vector takes pathogens from an infected host (human or animal). The pathogens multiply (replicate) in the vector and can then be transferred to a new host. Vector-borne zoonoses, including malaria, early summer meningitis, West Nile fever, Zika fever, dengue fever, and Chikungunya, account for 17 percent of all infectious diseases worldwide, and cause more than 700,000 deaths annually.

One Health

The One Health concept is an integrative, interdisciplinary approach that focuses on the interrelationships between humans, animals, the environment, and health. Experts on human and animal health, the environment, food and food security, and agriculture work together closely - whether in research or in the design and implementation of policies and legislation. This will lay the foundations for efficient health policy and effective intervention strategies. One Health is strongly supported by the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE).



Non-native mosquitoes as disease vectors

Pathogens that have not yet occurred in Germany are increasingly being transmitted by non-native invasive mosquitoes. The Asian bush mosquito (*Aedes japonicus*) was originally widespread in Korea, Taiwan, Japan, South China, and Russia, but today it is also frequently found in the south and west of Germany. It is active during the day and twilight and prefers mammals for blood meals. Its overwintering eggs are very resistant to frost and dehydration. The Asian bush mosquito is a possible vector of West Nile virus, Chikungunya and dengue virus, as well as Rift Valley fever virus, and can also transmit other viruses that cause encephalitis.

The Asian tiger mosquito (*Aedes albopictus*), originally from the forests of Southeast Asia, has spread worldwide over the last few decades, including to Germany. Established populations have recently been found in Baden-Württemberg and Thuringia, and in 2019 a population was recorded in the city of Fürth in Central Franconia. This species is considered to be an aggressive day-biting mosquito. Hosts are humans, domestic and wild animals, reptiles, birds, and amphibians. The Asian tiger mosquito occurs mostly in urban and suburban regions. There it finds sufficient natural and artificial water containers such as rainwater barrels, rainwater gutters, or used tires to breed. Even the smallest accumulations of water are sufficient for the development of the larvae. This mosquito species can also transmit a variety of viruses, including the Chikungunya, dengue, and Zika virus, but also yellow fever, Rift Valley fever and West Nile virus.

What role do man play?

Climate change, changes in land use, loss of natural habitats, urbanization, travel, and transport – these

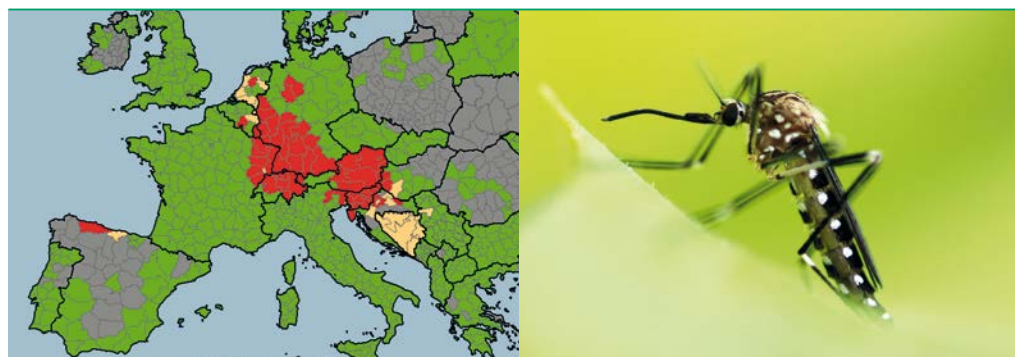
keywords stand for very different anthropogenic processes that mutually reinforce each other and cause environmental changes on a global scale. Such developments often influence unnoticed the occurrence of hosts, vectors, and pathogens, and their contact with humans:

- The number of mosquitoes, the number of generations, the resulting vector-host ratio, and the frequency of blood meals are important temperature-dependent factors in the transmission process. The time between uptake of a virus by a vector and the ability of the vector to transmit the virus to other susceptible hosts is also temperature dependent. Therefore, long-term changes in temperature and precipitation distribution can promote or impede the spread of a virus. For example, climatically suitable habitats of mosquitoes and hosts may shift to higher latitudes and altitudes. Conversely, survival may be restricted where temperature thresholds are exceeded. While the influence of long-term global warming on these processes can be projected into the future in terms of space and time, the impact of heat or cold spells, drought or floods on the risk of transmission is difficult to assess.

- The biological diversity of a region constitutes the background music to the infection storyline, so to speak. Microbiota, vectors, and hosts are involved in diverse biotic interactions with other species. Various hypotheses try to explain how the loss of habitats and species is related to newly emerging infectious diseases. Frequently there is talk of a "dilution effect". This means that viruses are transmitted less frequently within communities of high species diversity than in communities with low species diversity. This effect occurs because the probability of transmission events decreases as a result of high diversity: The proportion of animals that can replicate the virus is lower. However, ecological systems are very complex, and the dilution effect has so far

■ Fig. 1-4 (above): The birds most frequently infected with West Nile virus in urban Europe are blackbirds (*Turdus merula*), magpies (*Pica pica*), house sparrows (*Passer domesticus*), and crows (*Corvus corone*) (sst).

■ Fig. 5: The Asian bush mosquito is already established (red) or has been introduced (yellow) in some European regions, while in other regions it is not yet present (green). For some regions (grey) no data is available yet (Graphic: European Centre for Disease Prevention and Control and European Food Safety Authority, Status 2020. Original graphic: www.ecdc.europa.eu; Photo right: sst).



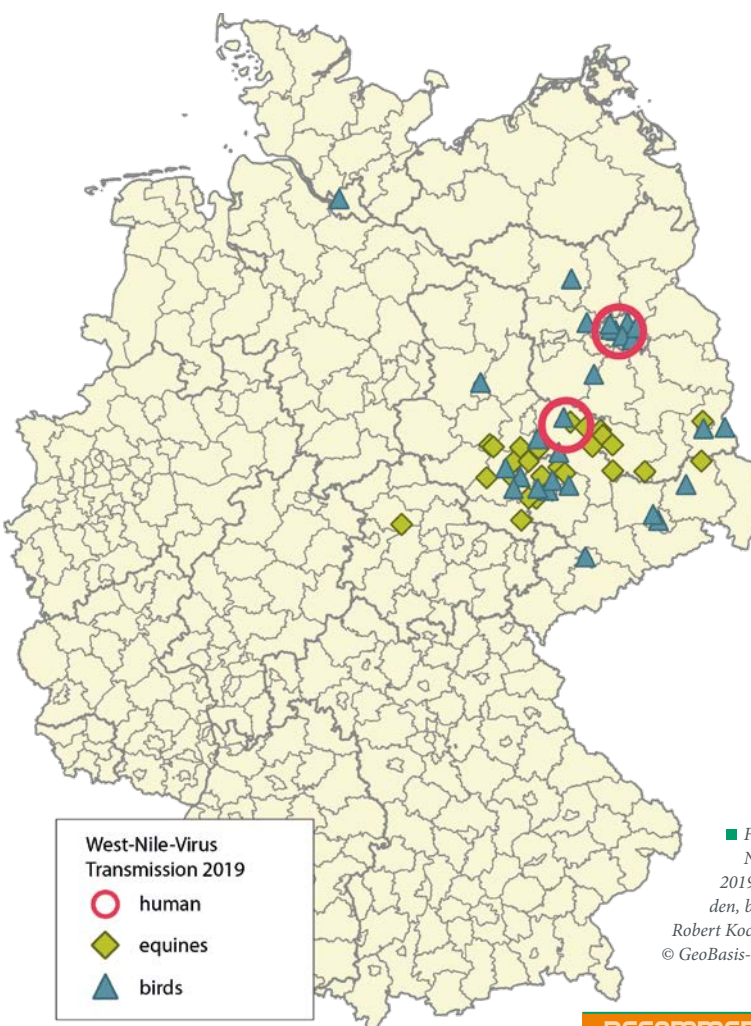
only been demonstrated by empirical studies for certain chains of infections.

Bayreuth research projects strengthen the competent handling of zoonoses

Currently, too little is known about the impact of climate change and biodiversity loss on pathogens, vectors, and hosts, and on their biotic interactions. But this much is clear: The destruction of habitats and ecosystems, especially in species-rich biodiversity hotspots around the world, is increasingly leading to contact between humans and various zoonotic pathogens. These can be transmitted to humans by mosquitoes, for example. Due to their travel habits, humans can spread these pathogens worldwide in a very short time. Climate change is also accompanied by a change in environmental conditions. Even in temperate regions such as Central Europe, certain climate and weather conditions are occurring more and more frequently, albeit temporarily, which allow the transmission of diseases previously known as tropical diseases. Finally, the spread of introduced vectors further facilitates the spread of such diseases.

At the Biogeography research group at the University of Bayreuth, scientists are working on the "Mosquito-borne arboviral diseases in Bavaria – BayVirMos" research project, funded by the Bavarian State Government as part of the joint project "Climate Change and Health". The research group models the influence of climate change on four mosquito-borne zoonoses in Bavaria. This lays the foundation for an information platform that uses daily weather data to project the risk of disease transmission in Bavaria, and makes this information available online to the medical profession and the public health system on a daily basis.

In addition, the Chair of Biogeography coordinates the Europe-wide joint project "DiMoC – Diversity components in mosquito-borne diseases in the face of climate change", in which the University of Bayreuth, the Bernhard Nocht Institute for Tropical Medicine, the Institute of Tropical Medicine Antwerp, Institut de Recherche pour le Développement in Montpellier, and the National Autonomous University of Mexico are all cooperating. The partner institutions are jointly investigating the links between biological diversity and mosquito-borne zoonoses. The most modern research approaches are being used in this context:



■ Fig. 6: Cases of West Nile in Germany in 2019 (Graphic: Nils Tjaden, based on statistics of Robert Koch-Institut. Geodata: © GeoBasis-DE / BKG 2018).

- Saliva tests of mosquitoes provide information on which viruses they are carrying.
- Molecular methods can be used to detect blood meals of vertebrates in mosquitoes.
- Laboratory studies reveal interspecific interactions between invasive and native mosquitoes.
- New species distribution models consider the biotic interactions of different species.

Many questions still remain open. If they can be answered – sooner rather than later – our society will hopefully be well prepared for dealing with vector-borne zoonoses.

"The role of biodiversity in the chain of infection therefore still poses major questions for research."

RECOMMENDED READING

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C. Beierkuhnlein, S. M. Thomas: Stechmückenübertragene Krankheiten in Zeiten des globalen Wandels. Flugmedizin – Tropenmedizin – Reisemedizin – FTR (2020), 27(01), 14-19. DOI: 10.1055/a-1079-2469.



■ Klaus Nagels

Medicine in the context of society and the economy

Findings from Bayreuth's health services research

■ *Studies in the field of care research often have to relate medical and social aspects in order to meet the daily life of patients (sst).*

The Covid-19 pandemic has demonstrated that health is not only a medical issue, but is embedded in complex epidemiological, economic, social, and legal contexts. This also applies to scientific and technical innovations that open up new paths in the fields of prevention, diagnostics, therapy, and care, and expose today's health care systems to a sometimes considerable pressure to transform. The resulting challenges and questions are the focus of the work carried out by the University of Bayreuth's Chair of Healthcare Management and Health Services Research. One focus is on the effects of innovative developments on patients, relatives, and doctors, as well as access to new diagnostic and therapeutic options. In what follows, some research findings will be presented against their respective clinical background.

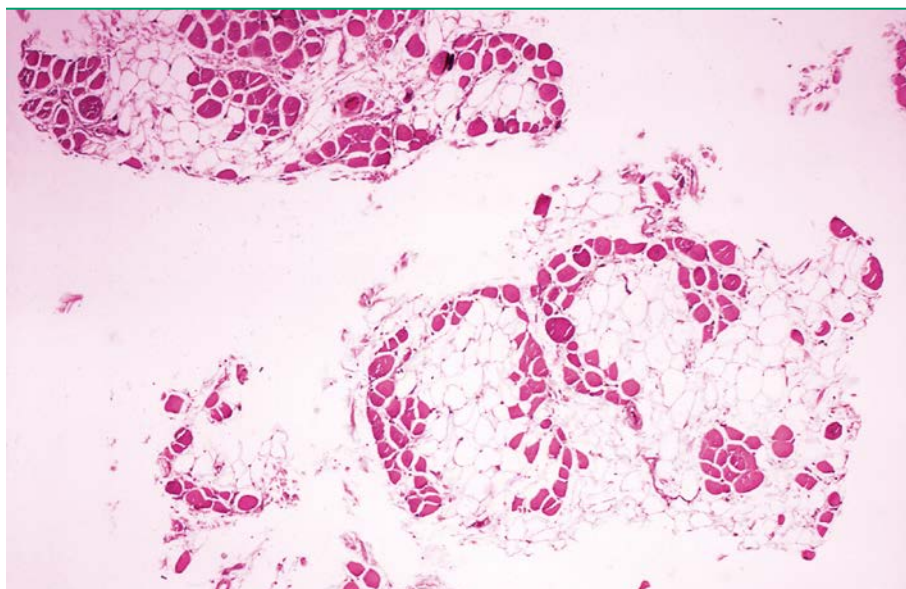
Neuromuscular diseases

Neuromuscular diseases have many different manifestations and are often associated with severe, sometimes life-threatening symptoms. Often, those affected already suffer from considerable limitations starting after birth. Many of these diseases are hereditary and are classified as rare. In early stages, diagnosis can be difficult. For this reason, the attending physicians depend on genetic diagnostics in order to initiate the appropriate treatment at an early stage in the case of a proven hereditary predisposition. It is only in the past five years that some neuromuscular diseases have become more treatable with effective drugs, although these are often very expensive. However, for some of these rare diseases, medical interventions have so far been limited to supportive therapies that neither stop nor delay the progression of the disease, but can alleviate the symptoms.

The University of Bayreuth's Chair of Healthcare Management and Health Services Research, together with the Friedrich-Baur-Institut of the LMU Munich, is investigating the quality of life and the preferences of patients during the course of their illness. At the same time, it is a matter of completely recording the costs of illness and the health economic modelling of neuromuscular diseases. The results so far show that the costs for long-term care, ventilation, and operations, which serve for example to stabilize the spine, are considerable. To this must be added the currently still very high costs for treatments that address the causes of the disease. Yet there is also a ray of hope: In the future, therapy

costs could fall significantly as a result of expiring drug patents and could even fall below the costs that would arise without treatment.

A further project investigates the extent to which caregiving relatives are affected by their duties. The clinical focus of this study is on spinal muscular atrophy (SMA), Duchenne (DMD) and Becker-Kiener



■ Fig. 1: Histopathological image of a cross-section of the calf muscle (*musculus gastrocnemius*) of a patient with Duchenne muscular dystrophy. The red stained muscle fibres were replaced by fat cells (optically empty = white) during the course of the disease (Photo: wikimedia commons / Dr. Edwin P. Ewing, Jr. / US Department of Health and Human Services / PD US HHS CDC).

(BMD) muscular dystrophies, hereditary neuropathies (including Charcot-Marie-Tooth disease, CMT), and inclusion body myositis (IBM). Especially in the case of neuromuscular diseases that begin in childhood, the burden may last for many years. While the care of geriatric patients has already been studied in many cases, informal caregivers of seriously ill children are underrepresented in research to date. If the disease does not appear until middle age, with a steady decline in independence and unclear progression, caregiving relatives must constantly adapt to new situations. Understanding their experiences and life situations is a special challenge. The reason for is that this group of people cannot be identified directly via patient registers or health insurance data. Nevertheless, within the scope of the study by researcher in Bayreuth it was possible to interview caregiving relatives of patients who have SMA, DMD, and BMD. As a result, it became visible for the first time who is providing care and how the lives of these relatives are changed by caregiving – both professionally and privately.

The investigation clearly shows that the stress caused by caregiving has a considerable impact on

■ Fig. 2: The long-term care of relatives is associated with burdens for all family members that should not be underestimated (sst).



ly use constructive coping strategies, such as relaxation techniques, self-help groups, sports, or other leisure activities. Nevertheless, they often report psychosomatic symptoms. Overall, the families note a lack of support and information. Communication with official bodies such as health insurance companies is also becoming an additional challenge for many people in addition to care.

The data obtained documents deficits in the care of rare neuromuscular diseases and point to previously untapped potential for effective treatments. It also provides a valuable basis for the design and implementation of digital health applications (DiGA). These can only lead to the care effects desired by health policy if the preferences of patients and relatives are known. A recent study on inclusion body myositis confirms these findings. This is a chronically progressive disease that cannot be stopped by therapies. The qualitative interviews conducted with patients can make a significant contribution to integrating their views and needs into the organization of their day-to-day lives. This is a central concern of health services research, far beyond the field of neuromuscular diseases.

Precision oncology

Genetic alterations in cells play a decisive role in tumour development and evolution. Over the past 15 years, our understanding of molecular biology has grown exponentially and has been incorporated into both clinical diagnostics and new targeted therapies. These therapies enable patients to achieve

longer overall survival than conventional cytostatic drugs. Sequencing techniques, such as *Next Generation Sequencing*, enable the broad detection of genetic changes using tissue samples and liquid biopsies.

Liquid biopsy is a minimally invasive biopsy of liquids, for example blood. It is used for therapy-accompanying diagnostics (*companion diagnostics*). Compared to invasive tissue biopsy, it has the advantage that it is less stressful for patients. This is particularly important if the mutation-driven evolution of a tumour and its increased resistance make it necessary to take a biopsy more frequently. In addition, the heterogeneity of a tumour can be diagnosed with high accuracy by molecular genetics using liquid biopsy. This enables precise therapeutic decisions to be made, which in turn leads to clinically relevant improvements for NSCLC patients. In those cases in which tissue samples cannot be taken or can only be taken at high risk due to an unfavourable localization of the tumour, liquid biopsy is in fact the only way to a targeted therapy.

Non-small cell lung carcinoma (NSCLC) is particularly well-suited for the application of liquid biopsy. It enables continuous precise diagnostics and, based on this, rapid therapy adjustments, which lead to better treatment results. Liquid biopsy is particularly suitable for the early and comprehensive detection of molecular changes that promote tumour growth and are therefore referred to as driver mutations. Treatment strategies targeting these mutations are becoming increasingly important for the therapy of advanced NSCLC since EGFR tyrosine kinase in-

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hibitors have become available to control tumour growth. Non-small cell lung carcinoma affect about 80 percent of all patients diagnosed with lung cancer, while about 19 percent of these patients suffer from small cell lung cancer. Although significant progress has been made in diagnostics and therapy in recent years, the prognosis is poor. The relative 5-year survival rate of NSCLC patients is 13.9 percent in stage III and only 4.4 percent in stage IV. For the year 2016, the number of new cases in Germany was estimated at 57,460 (35,960 men and 21,500 women). The relative 5-year survival rate for lung cancer is 15 percent for men and 21 percent for women.

A research group working under the Chair of Healthcare Management and Health Services Research is developing new ways to assess the cost-benefit of liquid biopsy using the example of NSCLC. The chosen evaluation approach combines clinical and health economic procedures. The first step is to determine the clinical effects of the molecular biological findings obtained using liquid biopsy – and also the effects of the therapies derived from them. The treatment results are then compared with the direct medical costs. The data obtained so far shows that the supply situation has improved considerably as a result of liquid biopsy. Depending on the use of liquid biopsy, the course of the disease can vary significantly. In addition, the continuous monitoring of genetic changes also has a favourable effect on treatment costs. The Bayreuth study therefore justifies the demand to comprehensively include liquid biopsy in the care of NSCLC patients at the current state of demand.

Digitization in outpatient medical care

Contract physician care contains a number of possibilities for digitizing everyday processes in medical practice that have so far been carried out in analogue form, with manual support and on paper. These are in particular processes that serve to combine findings of laboratory physicians, other specialists, or hospital doctors in such a way that the physician is able to derive the appropriate therapy recommendation on the basis of differential diagnostics. In addition to these core processes, a number of other administrative activities come to the fore, which are involved in documentation (medical records), assessment (certificate of incapacity to work), or therapy management (prescriptions). Their digitization is also being worked on intensively, with new buzzwords such as “e-prescriptions” emerging.

In addition, there are now new possibilities to support attending physicians digitally in their medical decisions. This is the starting point for a new study by the Chair of Healthcare Management and Health Services Research. The central question is to what extent digital systems to support decisions are accepted by outpatient physicians. First, qualitative guideline interviews with more than 300 outpatient physicians in Germany were conducted and evaluated. The results obtained in this way then formed the basis of web-based quantitative data collection. As it turns out, registered doctors have a great deal of interest in decision support systems. On the other hand, however, they consider the effort required to integrate the digital solutions into the processes of everyday practice to be very high. Many see this as a great burden for practical operation.

Virtual reality applications using the example of dialysis patients

Around 80,000 people in Germany have chronic dialysis requirements. These patients develop a significant decrease in physical activity due to illness, so that their muscle mass decreases. Physical inactivity is associated with increased morbidity and mortality, impairment of quality of life, more frequent cardiovascular events (strokes and heart attacks), and depression. However, if patients with chronic kidney disease suffer from depression, this makes regular participation in exercise-based rehabilitation programmes more difficult. These pro-

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■ Fig. 3: Concept of the electronic medical record (sst).

■ Fig. 4: Patient during dialysis (sst).



grammes are usually not integrated into the clinical care process. This results in a pathophysiological process, as a consequence of which the risk of cardiovascular complications constantly increases due to a self-reinforcing degenerative effect. There are currently no satisfactory solutions for the resulting supply needs. In order to counteract cardiovascular risks and improve the quality of life of patients, it is very important to know how the active and passive muscle development of dialysis patients can be strengthened. Then it is also possible to reduce the number and duration of necessary medical treatments.

Against this background, a study by the Chair of Healthcare Management and Health Services Research is exploring the extent to which virtual reality (VR) applications are suitable for helping dialysis patients overcome physical limitations and reduce psychological stress. In medical practice, VR is used, for example, for distraction therapies that aim to distract patients from pain sensations and

■ Fig. 5: Technical equipment of a room for haemodialysis (sst).



thereby weaken their perception of painful stimuli. However, the potential of VR applications extends beyond such rather short-term effects. This is the result of a Bayreuth pilot study in which patients, relatives, and nursing staff were interviewed about the effects of different VR applications. The survey comes to the conclusion that VR can certainly contribute to a lasting improvement in the quality of life. Especially promising seem to be approaches that combine VR applications with digital technologies for therapeutic muscle stimulation. For this reason, another Bayreuth study currently underway is examining the question of what opportunities such a combination offers in order to facilitate the day-to-day lives of dialysis patients in particular and to strengthen their physical and mental condition. The findings are expected to be published in spring 2021.

Innovations in radiooncology

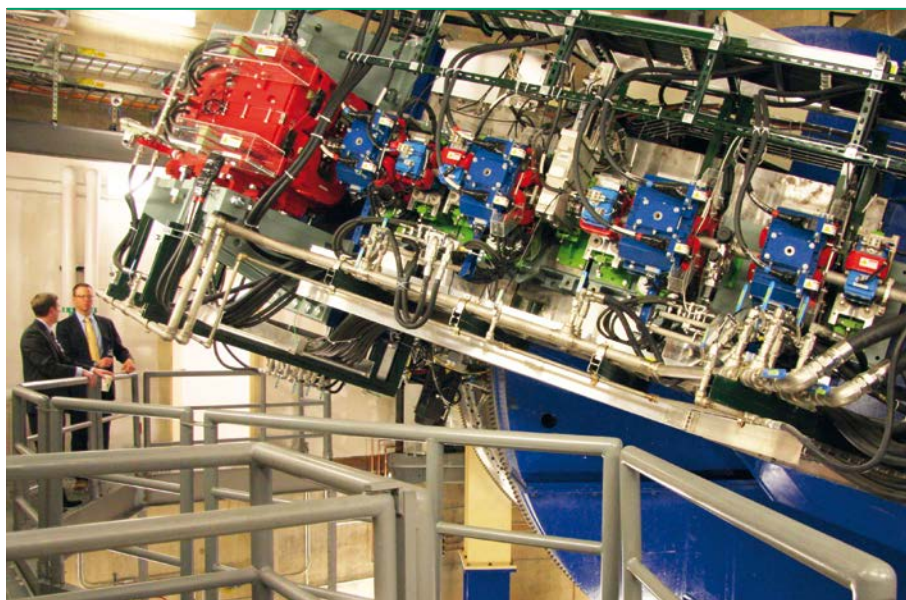
Every year almost 500,000 people in Germany are diagnosed with cancer. Treatment is based on three pillars, namely surgical treatment (tumour surgery), radiation (radiotherapy), and pharmaceutical treatment (drug therapy). These so-called modalities are combined depending on the stage of the disease. Radiotherapy is of great importance in this context – both in terms of delaying the progression of the disease and in terms of curing tumour diseases. For more than 50 percent of all cancer patients, radiation treatment is an integral part of their medical care. Thanks to a variety of technological innovations in irradiation technology, which also includes digital components for precise control, the accuracy and effectiveness of this treatment method has increased enormously over the past two decades. Nevertheless, radiation-induced collateral damage to healthy tissues is a risk that limits the application possibilities of radiotherapy. High, curatively effective radiation doses are therefore often not applicable in the case of an unfavourable localization of the tumour.

Here, proton therapy opens up new opportunities for the patients concerned. In contrast to the photon emitters widely used today, which use high-energy electromagnetic waves, proton therapy uses positively charged protons – or in some cases carbon ions. These are brought to such high speeds in particle accelerators that the particle beams charged with kinetic energy cause severe damage to the tumour tissue: The affected cells die off.

Healthy tissue through which the radiation passes until it reaches the tumour is, on the other hand, much less damaged than with conventional radiotherapy with photon irradiators. It is therefore possible to use higher radiation doses.

Research work carried out under the Chair of Healthcare Management and Health Services Research deals with proton therapy from the perspective of medical innovation and technology management. In a first study, it was shown that more and more patients worldwide have access to this technically sophisticated form of therapy. In Japan and the USA it is already being used on a large scale for the treatment of solid tumours. On the other hand, a comparison carried out under health economic aspects showed that the investment and operating costs for proton irradiation facilities on the one hand and photon facilities on the other hand diverge so widely that economic competition with regard to the treatment of tumour patients is ruled out. Both facilities enable the treatment of 1,200 to 1,500 patients per year. But while the investment costs for photon facilities amount to between 12 and 15 million euros, the investment costs for proton irradiation facilities are ten times higher at 150 to 200 million euros. The differences in operating costs are also considerable.

These Bayreuth research findings have awakened the interest of the responsible clinical staff at the European proton radiation centres, which are united throughout Europe in the European Particle Network (EPTN) under the umbrella of ESTRO in Brussels. A research group on health economics was formed, which is headed by Prof. Dr. Klaus Nagels in Bayreuth together with Prof. Dr. Yolande



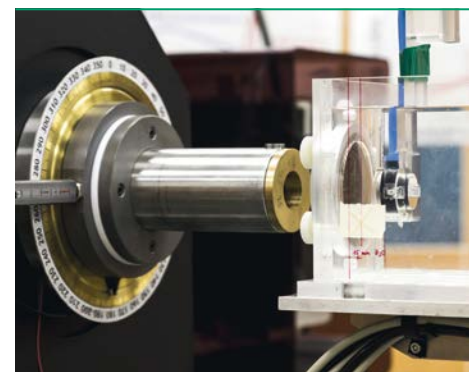
Lievens in Ghent. It builds on previous studies and takes a look at more recent developments in medical technology. More compact facilities for proton irradiation are now available. Although they have a lower treatment capacity, the investment costs are

■ Fig. 6: Synchrotron for proton therapy at the Mayo Clinic Rochester, Minnesota/USA (Photo: wikimedia commons / Jonathunder / GFDL-1.2).

"The qualitative interviews conducted with patients can make a significant contribution to integrating their views and needs into the organization of their day-to-day lives. This is a central concern of health services research."

only about 30 million euros and the operating costs are also lower. This changes the health economic profile of proton irradiation considerably, so that the costs per treatment are significantly reduced.

The research group is currently investigating a new irradiation approach. Here, the required irradiation dose is administered in one to five fractions with extremely high partial doses – instead of 20 to 35 irradiation cycles as before, whose costs are considerably higher. The study focuses on the results of preclinical research, which have been published internationally with increasing frequency for about two years and provide indications of the clinical potential of this new approach. If the initial findings are confirmed, there is much to suggest that the health economic status of proton therapy may improve significantly. This is expected to make this technology available to a growing number of patients.



■ Fig. 7: Device for proton therapy of carcinomas of the eyeball at the Institute of Nuclear Physics in Krakow (Photo: Dominika Zara / Shutterstock.com).

■ Fig. 8 (left): Observation of the patient during radiotherapy (Photo: Nicolas Randall / Shutterstock.com).



■ May Bintl
Ksenia Ibler
Eckhard Nagel

Overweight in adolescents

Participatory research as a promising approach
for the prevention of overweight in adolescents

■ *Friends and peers play an important role in successful measures to prevent overweight among young people (sst).*

Being overweight or obese is a serious health risk for adolescents, which is associated with many diseases and health conditions. In Germany, 16 percent of girls and 18 percent of boys are categorized as overweight among adolescents aged 14 to 17 years.¹ Overall, 40 percent of young people stated that they want to lose weight as a result of feeling overweight.² This evidence alone shows that it is important to tackle overweight on an individual and societal level.

Especially in adolescence, there is a great potential to prevent obesity. During this developmental phase, health-promoting behaviour can be shaped and encouraged. However, this can be achieved, if adolescents are reached by interventions to prevent overweight. Today hope is being placed especially in approaches that actively involve young people in the development, implementation, and evaluation of such projects. For that, the key word is "participation".

A current research project at the University of Bayreuth

This was the starting point of the PRÄVENT.PARTITION research project at the Institute for Healthcare Management and Health Sciences (IMG) at the University of Bayreuth. The project processed the current state of knowledge into participatory approaches and aimed at preventing obesity in young people. The published scientific literature was systematically reviewed and compiled. In addition to that, an analysis of evaluated projects' reports on overweight prevention in clinical databases was conducted. A complementary component of the project were focus group interviews with young people³ and discussions with experts in health promotion.

In this way, the first step was to identify factors, which support the successful implementation of participatory projects and measures. After gaining knowledge in this process, it was implemented in a practice-oriented manner in order to strengthen the dialogue between science and practice. A step-by-step manual was written which is understandable to all stakeholders and supports the implementation of the findings in practice.

In all projects, it always needs to be remembered that such "one" youth does not exist. Rather, young people are characterised by the interplay of different – sometimes conflicting values, such as solidarity on the one hand, and egocentrism or the desire for self-realisation on the other.⁴ Participatory approaches will only be successful if they are planned within a consideration of the values and wishes of young people.

Participation, Empowerment and Motivation

In everyday language, participation is often associated with terms such as "attend", "take part", or "join in". However, participation means much more: For the target group, active participation represents a way of influencing decision-making processes in accordance with its own ideas and wishes. In health promotion and prevention, participation means that the members of the target group can contribute in all phases of the public health action cycle – from needs assessment, planning, and implementation, to the evaluation of an action. In doing so, the degree of participation can vary greatly. A widespread model for participation in health promotion distinguishes a total of nine levels. The greater the degree of participation, the greater the influence the target group has on decisions (Fig. 1).

In the focus group interviews, young people indicated that they were critical of the level of self-organisation. Their expectations are primarily focused on their ideas being heard and implemented. At the same time, they desire to be accompanied and supported by an experienced adult. It is therefore advisable to introduce adolescents to participation slowly, and – if there is a lack of willingness to participate – to initially implement only preliminary stages of participation.

The attractiveness of a project, and also motivation to participate, often depend on the personal benefit which the members of the respective target group expect to gain from participation. These can be, for example, gain knowledge or experience, or short-term, immediate rewards. Such rewards also have the effect of increasing the attractiveness of the project for young people. Competitions follow-

RECOMMENDED READING

M. Bindl et al.: Partizipative Projekte zur Prävention von Übergewicht bei Jugendlichen – Eine Schritt-für-Schritt-Anleitung. Bayreuth 2020. Digital version available: www.img.uni-bayreuth.de/de/forschung/praevent-partition/

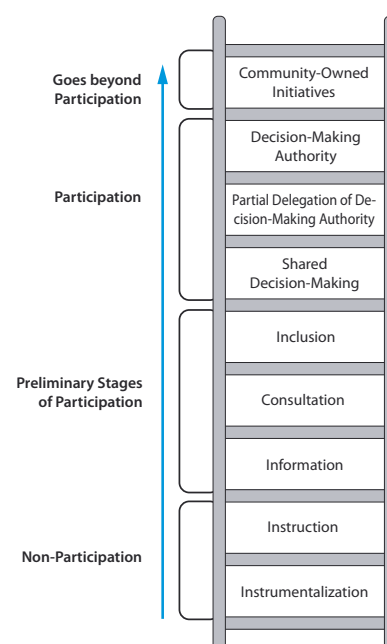


Fig. 1: Levels of participation according to Michael T. Wright.⁵ Instrumentalization, instruction, and preliminary stages of participation can be found frequently in practice. Actually participatory projects (from level 6) are rare (Source: M. Bindl et al., Bayreuth 2020, see recommended reading).

"The participation of young people requires a rethinking of the role of all participants."

ed by prize-giving, healthy catering, the use of fitness trackers, and vouchers for sports shops have proven to be appropriate incentives. Interest in the topic, the prospect of having fun, and the pleasure of planning and implementation together as a circle of friends also strengthen willingness to participate (Fig. 2).



■ Fig. 2: Motivational factors of youth participation (Illustration: Ksenia Ibler).

A central finding of the research project is that a lack of time weakens young people's motivation to participate actively. A limited time budget is even the most frequently mentioned reason the respondents not getting involved. Participation in additional projects proves to be particularly difficult during examination phases and with a high level of extracurricular engagement. Therefore, these young people prefer projects that are integrated into existing structures, such as school lessons or group lessons at leisure facilities.

An insufficient level of knowledge, inadequate soft skills, and problems in the social environment can lead to adolescents feeling overburdened with the planning and implementation of measures to prevent overweight. Therefore, they should be supported and prepared for active participation according to their abilities, characters, and life circumstances. For example, qualifying seminars and training courses are suitable for this purpose, which are immediately followed by the first steps towards acting on one's responsibility, e.g. by getting young people to form "health teams" or become involved as "student ambassadors". Learning by doing is another way of

developing their skills. Last but not least, it is generally desirable to strengthen family and social resources to counteract the general social trend of declining willingness to participate.

Influence groups and communication channels

The social environment and everyday life have a considerable influence on the nutritional and physical activity behaviour of young people and on their willingness to participate in measures to prevent obesity. In the discussions that took place within the framework of the research project, the adolescents particularly highlighted the importance of their parents for their own nutritional and physical activity behaviour. Nevertheless, friends and peers as well as group leaders, teachers, and mentors in schools, church institutions, and associations also play an important role. Therefore, projects to prevent overweight should be planned and implemented where young people feel at home, live, study or work and spend their leisure time. Peer concepts have proven to be particularly promising. These are pedagogical measures that are carried out by groups of peers themselves. However, young people who were interviewed fear some difficulties in the implementation. The reason for this was a possible lack of mutual respect within a group of peers. Consequently, peer-to-peer interventions should preferably be carried out by older teenager for younger people.

It has been shown that classical formats such as personal contacts and posters or flyers are still particularly suitable channels of communication to reach young people today. Nevertheless, their focus is increasingly shifting to social media such as Instagram, Facebook, and Instant Messenger. In this area, so-called influencers are currently gaining increased influence.

Involvement of young people already in the planning phase

When planning a participatory project, it is important not to dictate the needs of the target group, but to identify those needs in a dialog with them. Adolescents can be involved through personal or written surveys, joint inspections or the Photovoice method⁶, for example. In the course of the project, it became evident that young people would like to ac-



■ Fig. 3: Influencers in social media have a growing influence on young people who want to avoid overweight (sst).

tively participate and shape the project by bringing in their own ideas and would like to be supported accordingly – whether in the selection of topics, in forming groups independently, in the distribution of tasks or the organisation of meetings. Participation in the sense of taking part in joint project development is the key to the success of a project.

As a general rule, projects for obesity prevention should consider whether the measure should be aimed at people of normal weight (primary prevention) or specifically at people who are already overweight (secondary prevention). Each measure should be designed in such a way as to avoid possible stigmatization. This can be achieved by not focusing on body weight and by making participation in the project explicitly voluntary. A gender-specific approach should be individually agreed upon with the members of the target group because all do not necessarily desire it.

Participatory projects increase the chances that measures are tailored to the respective target group. They can increase the acceptance of interventions and prevent misinvestment because they are not planned in line with the wishes and abilities of the target group. However, the participation of young people requires a rethinking of the role of all participants. The personal willingness of the adult project participants, in particular, to open up to the

ideas, needs, and wishes of the adolescents and to take these into account in further planning is an important prerequisite for the successful implementation of participative projects.

Conclusion

Health is seen today by many young people as an important value and has become a trending topic. The desire of adolescents to engage in healthy behaviour and avoid becoming overweight is correspondingly widespread. PRÄVENT.PARTITION has succeeded in closing a research gap in the participation of young people in the field of overweight prevention. The results should and can contribute to future concepts of preventive and health-promoting interventions being based on the best available evidence. This is the only way to ensure that such concepts are suitable for practical application and that the specific target group can be motivated to make the desired behavioural changes. Some of the insights gained in the research project, which relate to the attitudes, abilities, and motivations of young people, can certainly be generalised. For this reason, they offer a helpful orientation in the design of strategies aimed at engaging young people to take part in health-promoting interventions that – such as the prevention of overweight – are in their well-understood interest.



■ Fig. 4: The nutritional and physical activity behaviour of many adolescents is essentially shaped by their parents (sst).

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- 1 Cf. A. Schienkiewitz et al.: Übergewicht und Adipositas im Kindes- und Jugendalter in Deutschland – Querschnittergebnisse aus KiGGS Welle 2 und Trends. *Journal of Health Monitoring* (2018), 3, 16-23. DOI: 10.17886/RKI-GBE-2018-005.2.
- 2 Cf. Schwenninger Krankenkasse: *Zukunft Gesundheit 2018. Jungen Bundesbürgern auf den Puls gefühlt.* Villingen-Schwenningen 2018.
- 3 Focus group interviews are a method for collecting qualitative data. Six to ten participants discuss a specific topic in a moderated group discussion based on interview guidelines prepared in advance. This method is particularly suitable for identifying attitudes, expectations, and standpoints with a variety of aspects and perspectives.
- 4 M. Calmbach et al.: *Wie ticken Jugendliche 2016? Lebenswelten von Jugendlichen im Alter von 14 bis 17 Jahren in Deutschland.* Wiesbaden 2016.
- 5 Vgl. M. T. Wright (ed.): *Partizipative Qualitätsentwicklung in der Gesundheitsförderung und Prävention.* Bern 2010.
- 6 Photovoice is a method of visual data collection. In the process, the participating individuals are equipped with a camera and instructed to take photos of their living environment. In return, they are given a concrete question, which they are to answer based on the visual documentation. The photos are then discussed from the perspective of the target group and processes of change are initiated.



■ Eckhard Nagel
Reiner Hofmann



MedizinCampus Oberfranken

Future-oriented cooperation in science and practice

■ *Big image: View over the campus of the University of Bayreuth (Photo: UBT).
Small Image: Welcoming of the first students at the entrance of Klinikum Bayreuth (Photo: BR/Kristina Kreutzer).*

MedizinCampus Oberfranken is based on a partnership between Klinikum Bayreuth, the University of Erlangen-Nuremberg, University Clinic Erlangen, as well as the University of Bayreuth. A feasibility study and its independent assessment by a high-ranking expert commission was followed in February 2019 by the decision of the Bavarian state government to enable 100 students per year to study medicine at MedizinCampus Oberfranken. Since the 2019/2020 winter semester, the basic pre-clinical study programme has been up and running in Erlangen, where it is integrated into the established Erlangen medical degree programme. Prospective doctors will come to Bayreuth for clinical studies from the 2022 summer semester at the latest. Here they will complete their professional training both in the medical centre and at the University of Bayreuth, as well as in a growing number of Upper Franconian cooperation firms and practices. In total, MedizinCampus Oberfranken will have 600 places to study human medicine and about 250 directly created university jobs.

At Klinikum Bayreuth, 30 professorships and supporting positions in science and administration will be created. At the University of Bayreuth, ten profile professorships will be established in conjunction with further positions in research and administration. They will be supplemented by a research platform which will enable, strengthen, and inspire cooperation among scientists and students, but also cooperation with partners in Erlangen, various scientific communities and, last but not least, the region.

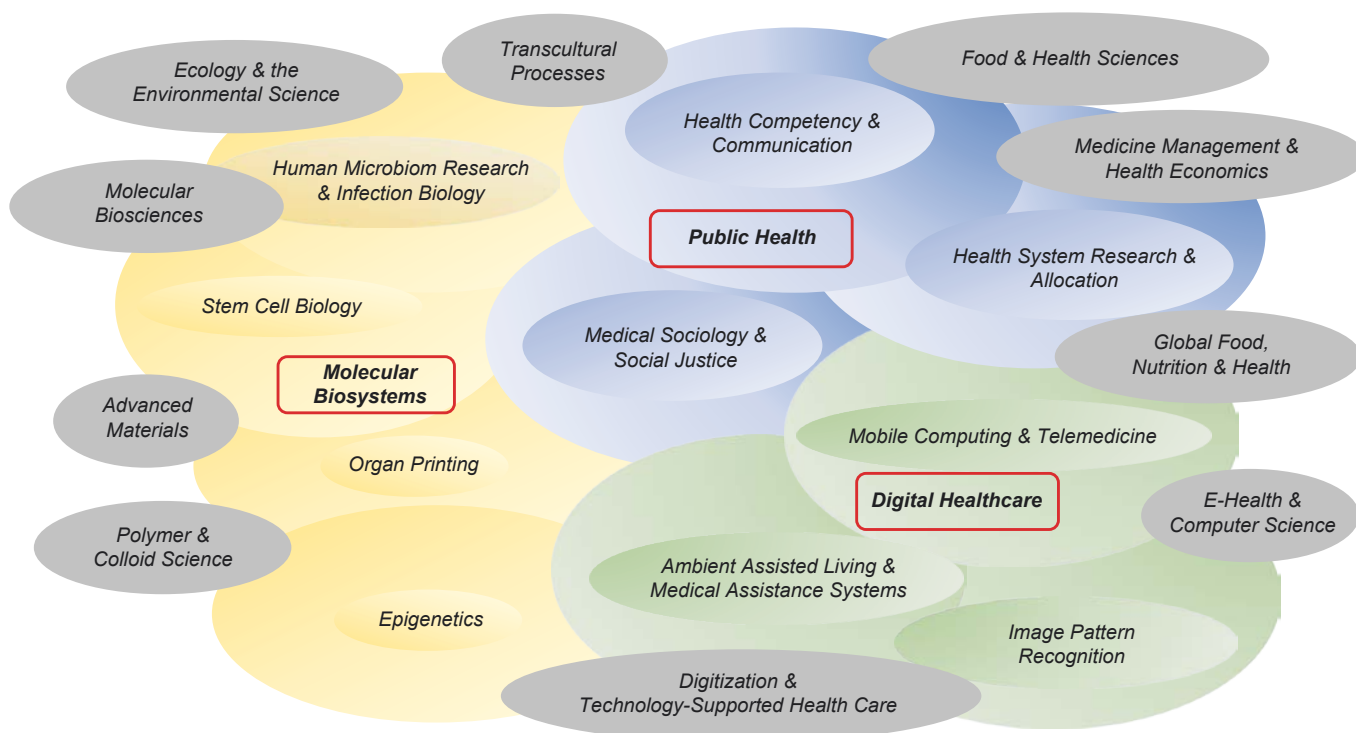
Focus on health and medicine Interdisciplinary research and teaching

For two decades now, the University of Bayreuth has been intensively investigating health care issues and their connection with structural social

"The idea of interprofessional cooperation must also be applied to medical care."



■ Fig. 1: Minister of Science Bernd Sibler welcomes the first students of the Erlangen-Nuremberg/Bayreuth medical degree programme (Photo: Jürgen Rennecke).



The new profile professorships in the priority areas of "Public Health", "Digital Healthcare", and "Molecular Biosystems" contribute significantly to the interdisciplinary networking at MedizinCampus Oberfranken. The areas and the respective scientific disciplines and topics involved are marked in blue, green, and yellow. The grey fields show examples of the manifold points of contact for new cooperations in research and practice, which strategically expand the range of services offered by MedizinCampus Oberfranken. This constellation is unique and truly outstanding for its range of expertise and the resulting teaching and research approaches. The interweaving of natural sciences, engineering, and health sciences with social, economic, and legal skills strengthens scientific excellence and promotes the implementation of innovative concepts in the world of Health 4.0 (Illustration: Reiner Hofmann).

■ Fig. 2: Digital support for networked medical treatment: The concept of the electronic medical record (sst).

developments. For example, the health economics degree programme – once the first of its kind in Germany – is dedicated to the research and practical design of medical care systems in an interdisciplinary approach combining medicine, business administration, and economics. This is particularly concerned with their further development under the conditions of a constantly changing, globalized society. Topics such as digitisation or the fairness of health opportunities are specifically included. At the same time, true scientific excellence has developed on the Bayreuth campus in the fields of polymers, new materials, and molecular biology – right at the interface of chemistry and biology. In their inquiry and findings, these basic sciences are approaching more and more concretely the burning questions of everyday medical life, so that here, too, the focus areas of the University of Bayreuth are becoming increasingly related to medical issues and perspectives. This has already led to the development of a number of research alliances and courses of study, which today represent points of contact for medical education, research, and health care.



ledge. They will be located in the priority areas of Public Health, Digital Healthcare, and Molecular Biosystems. This will significantly strengthen MedizinCampus Oberfranken's approach of fostering innovative health care from its scientific fundamentals to its application-oriented models, particularly in its practical implementation and further development. Moreover, opportunities for the constantly growing network of teaching and research partners – in the region and beyond – are expanding. This will enable MedizinCampus Oberfranken to develop a special profile: innovative, technologically-supported medical care, Health 4.0.

In doing so, the University of Bayreuth is strengthening both the conceptual guiding ideas of MedizinCampus Oberfranken in research and teaching as well as the development of its own profile. It emphasises the interdisciplinary approach required to work on health-related issues, and enables the classical study of human medicine to be linked with medical research in both application-oriented and basic research areas. The new profile professorships, each of which deals with subject-specific issues in their three priority areas, are of central importance in this context.

The priority areas of the new profile professorships

■ "Public Health" is a young, application-oriented field of study which is primarily concerned with population and system-related questions of health promotion, disease prevention, and life prolongation. Characteristic of this comparatively young field is its versatility and interdisciplinarity, which integrates methods from a wide range of disciplines. In doing so, a wide range of sub-areas are dealt with, including ethical aspects, such as social medicine or health services research, right through to health reporting and health policy. On the basis of this, vari-

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■ Dr. Reiner Hofmann heads the University of Bayreuth's project administrative office for MedizinCampus Oberfranken.

Medicine as individual help and social science

The concept of MedizinCampus Oberfranken is based on driving these promising developments forward, inspiring young people to complete their medical studies, in future-oriented areas, in this environment, and working towards better care for patients in Bavaria, especially in Upper Franconia. The ten new profile professorships at the University of Bayreuth are embedded in this concept. They are based on well-founded knowledge and will contribute to the development of an excellent new course programme. This programme is intended to gain a specific identity that motivates students to understand medicine both as individual aid and as social science. It is evident that this will require addressing general issues of public health, topics such as digitisation, scientific knowledge, and ensuring rural health care. The new course offerings of MedizinCampus Oberfranken will strengthen the attractiveness of study and research in Bayreuth, as well as the future development of both the City and region. They will also contribute to the creation of new attractive jobs.

The ten profile professorships will be thoroughly in line with Bayreuth's tradition of seeking close interdisciplinary collaboration in the transfer of know-

ous particular interests resulting in conflicting goals can be identified and weighed against one other. A classic consideration is, for example, to provide every citizen of a health system financed on a solidarity basis with what is medically necessary, but not with everything that can be wished for. In this sense, the three public health profile professorships deal with topics that are particularly affected by increasingly rapid social and technological change. The way in which competence and communication can influence treatment, and how health systems should be designed with a view to the socially equitable distribution of health opportunities will be central issues.

■ "Digital Healthcare" is the name of a field of teaching and research that deals with new technological developments in health care and the resulting, rapidly, and significantly expanding possibilities. A wide range of health-related areas fall within this field. They range from the identification of relevant problems and questions, their processing and evaluation, to the finding of solutions and user-oriented integration into medical practice. A key role is played by the network infrastructure, data-processing servers, and application-related terminal equipment (hardware), but above all by specialised programmes and applications (software). Thus, a network of stationary and mobile applications and databases can support health care in both the general medical and specialist areas. This includes support for independence in everyday life, or reliable, inconspicuous, and location-independent medical assistance. Of growing importance is the support of medical decisions through the digital analysis and interpretation of pathology results. Pattern recognition is able to detect and interpret the smallest regularities, repetitions, similarities, or uniformity in speech, text or images. It therefore represents a building block for future AI applications.

■ "Molecular Biosystems" form a sub-area of biology at the interface of medicine, health care and laboratory diagnostics. This interdisciplinarity combines contents and questions of experimental medicine with various fields and methods such as biochemistry, genetics, molecular biology, and cell biology. This involves research into the basics of life and pathological changes in order to learn about their causes, treat them, and prevent them. In view of the social and technological challenges of the 21st century in the field of regenerative medicine, the development of novel processing technologies – in conjunction with basic research in the fields of stem cells, human microbiome, infection biology,

and epigenetics – is also essential. Hierarchically structured and complex systems based on the simultaneous processing of materials and stem cells will surely shape the research landscape of regenerative medicine. However, influencing factors such as the human microbiome and epigenetics will also play a decisive role in future medical care.

MedizinCampus Upper Franconia as node and motor

The idea of inter-professional cooperation, as expressed in the orientation of the profile areas of MedizinCampus Oberfranken, must – following the principle of translation – also be applied to medical care. The regionalisation of physician training under the responsibility of university medicine is considered very forward-looking in this respect. In fact, the need for action to develop new types of care models is greatest in the outpatient sector outside of conurbations. Modern approaches and models of innovative care in rural areas are being tested here in increasing numbers. In Germany, these are being put into concrete terms in projects carried out in regions of low population density, declining employment figures or a rising average age of doctors or citizens – for example in Vorpommern-Greifswald, Südharz-Kyffhäuser, and in northern Bavaria. In all cases, such projects face the challenge of achieving sustainability after the end of public funding. To achieve this, it is necessary, via the attractiveness of such models, to attract prospective or practising doctors to the region in question, to retain them, and allow them to form roots there. This is greatly facilitated by the interdisciplinary cooperation within MedizinCampus Oberfranken, which spans both research and practice. The new profile professorships and the research platform will be a central hub and motor of numerous joint activities between research, health care, citizens, politics, and business.



■ Fig. 3: An example of research into molecular biosystems at the University of Bayreuth: Studies on gene regulation by non-coding RNA (Photo: Christian Wißler).



■ Birgitta Wöhrl
Thessa Jacob
Julian Hendrich

In the microcosm of allergens

New findings on isoallergens can improve therapy

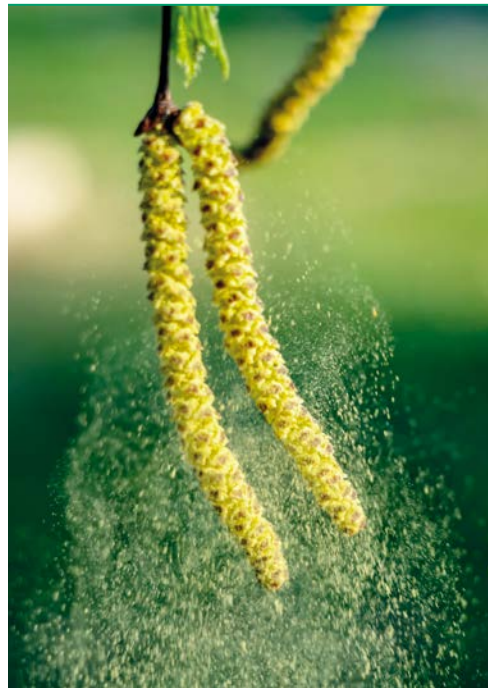
■ Carrots with a pipette for research on food allergens. In the foreground the structure of the carrot allergen Dau c 1 (Image: Ralf Weiskopf).

Allergies occur when the immune system develops an immune reaction against harmless substances, for example against tree pollen. The main risk factors for the development of an allergy are genetic predisposition, climate change, exposure to harmful substances, and the Western diet with its numerous food additives. Today's greatly improved hygiene could also be a cause. If contact with microorganisms is less frequent in childhood, the immune system is unable to "mature", thus the development of allergies can be promoted. However, none of the many different theories have been proven to date, and it is possible that the development of allergies is due to a combination of different factors.

Hay fever and other allergies

Around 15 percent of Germans suffer from hay fever. Doctors refer to hay fever as an allergy to pollen. It usually starts with itching of the eyes and nasopharynx, the mucous membranes swell up, and allergy sufferers get a constantly runny or congested nose. Facial swelling, skin reactions, and asthma is also observed, not to mention gastrointestinal problems. Allergic reactions to early flowering trees such as birch, hazel, and alder are particularly common. Unlike insect-pollinating plants, these wind pollinators emit large quantities of pollen to ensure pollination. The pollen can be spread by the wind over kilometres (Fig. 1).

In the case of a pollen allergy, the body's own immune system does not react against the pollen grains themselves, but against certain proteins that are abundant in pollen but are actually harmless to



■ Fig. 1: Start of the birch blossom: Male birch catkins scatter pollen in the wind (sst).

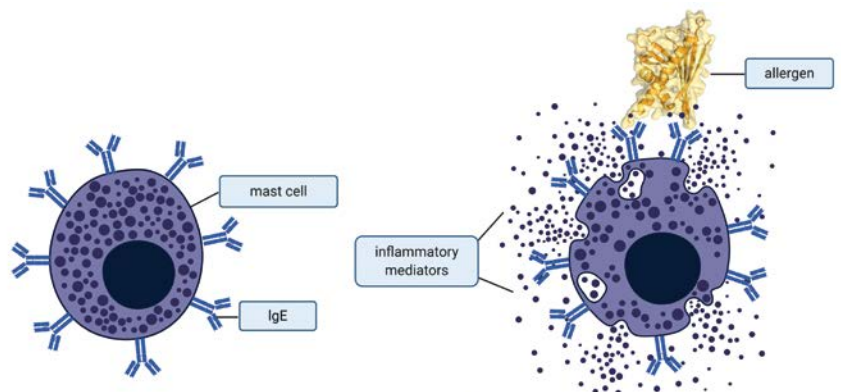
specific antibodies of the immunoglobulin type E, and are therefore also called IgE antibodies. The antibodies now bind to the surface of mast cells, which serve the body's own defence and are located in the mucous membranes in particular.

■ Only after *second* contact with the allergen does the actual allergic reaction occur. The IgE antibodies bound to mast cells recognise certain areas of the allergen, the epitopes, and bind to them. In doing so, they release histamine and other substances that cause the symptoms and inflammatory reactions typical of pollen allergies.

"The analysis of individual isoallergens may well help to improve the diagnosis of allergies."

the body. Biochemically speaking, these allergens are PR-10 proteins (pathogenesis related class 10). The development of an allergy takes place in two steps (Fig. 2):

■ At *first* contact, i.e. sensitisation, specific white blood cells recognise the PR-10 proteins and induce the production of antibodies. These are allergen-



■ Fig. 2: Course of an allergic reaction (Illustration: Thessa Jacob).

1 Specific IgE antibodies formed during sensitization to the allergen bind to mast cells.

2 Upon contact with the allergen, it is bound by IgE and the mast cells release inflammatory mediators that trigger the typical allergy symptoms.

■ Fig. 3: The figure displays the structural homology of PR-10 allergens. An overlay of the very similar three-dimensional structures of allergens from different plants is shown: Fra a 1 from strawberry (pink), Bet v 1 from birch pollen (yellow), Pru av 1 from cherry (cyan), Cor a 1 from hazelnut (black) and Dau c 1 from carrot (orange). Software: Pymol, version 1.8 (Illustration: Thessa Jacob).

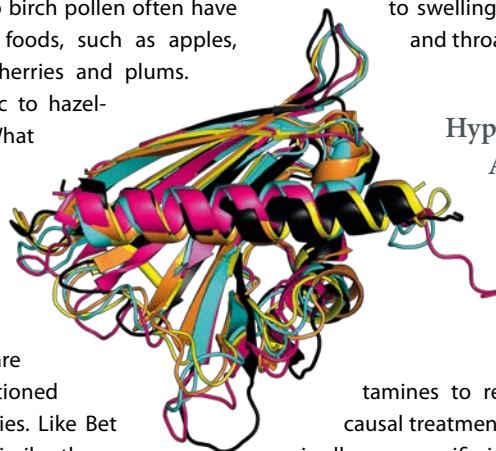
How can birch pollen cause food allergies?

People who are allergic to birch pollen often have problems eating certain foods, such as apples, pears and peaches, or cherries and plums. They may also be allergic to hazelnuts, celery, or carrots. What are the causes of this? 92 percent of pollen allergy sufferers in Germany are sensitised to the PR-10 protein Bet v 1, which comes from birch pollen. Related proteins are found in the above-mentioned fruit and vegetable varieties. Like Bet v 1, they all have a very similar three-dimensional structure which contains the following elements:

- a long C-terminal α helix,
- two shorter, v-shaped α helices,
- a seven-strand antiparallel β leaflet.

These elements surround a cavity that can bind various small hydrophobic molecules – so-called ligands (Fig. 3). Because of the structural similarity of the PR-10 proteins, IgE antibodies originally produced in response to the birch pollen protein Bet v 1 also recognise related PR-10 proteins from fruit, vegetables, or other plant foods. This results in allergic "cross-reactions". As a consequence, birch pol-

len allergy sufferers often show allergic symptoms after eating these foods. However, the symptoms are usually relatively mild and are limited to swelling and tingling in the mouth and throat (oral allergy syndrome).



Hyposensitisation: A way to treat allergies

There are different strategies for treating allergies, such as avoiding contact or taking medication like antihistamines to relieve symptoms. The only causal treatment of allergic diseases to date is allergen-specific immunotherapy. The patient is given the allergen in small but increasing doses at regular intervals so that the immune system can "get used to" the contact. The success of this therapy – which is called hyposensitisation – seems to be due to the fact that the body produces antibodies of the immunoglobulin type G during the course of treatment, i.e. IgG antibodies. These antibodies bind and neutralise the allergen, competing with the IgE antibodies that cause the allergy. IgG antibodies do not trigger the release of histamine, thus the allergic reaction can be greatly attenuated.

Personalised immunotherapy

Personalised allergy therapy, i.e. therapy tailored to the individual patient, is becoming increasingly important in research. It has been observed that hyposensitisation meets with little or no success with some patients. This is because PR-10 allergens, such as Bet v 1 in birch pollen or Cor a 1 in hazel pollen, consist of more than just one protein. Rather, each PR-10 allergen is a mixture of numerous very similar proteins. These protein variants – they are called isoallergens – have a homologous structure and are more than 67 percent identical in terms of their amino acid composition. In Bet v 1, 27 such variants have meanwhile been identified. However, the composition may vary depending on the genes and the environmental conditions of the individual tree. In most cases not all isoallergens of the mixture are known. When, for example, the serum of a birch pollen allergy sufferer is tested, the IgE antibodies usually do not recognise all Bet v 1 isoallergens. And if the sera of different allergy sufferers are compared, it turns out that it is not always

RECOMMENDED LINKS

www.allergieinformationsdienst.de

www.allergen.org

■ Fig. 4: Thessa Jacob, M.Sc, applying a protein sample onto an HPLC to separate the protein mixture chromatographically via a column (Photo: Christian Wißler).



the same Bet v 1 isoallergens that are recognised by the IgE antibodies. This may explain why in some cases a hyposensitisation therapy in which an unknown mixture of birch pollen proteins is administered to a patient shows little or no effect. In such cases, the isoallergens to which the patient is allergic are not present in the mixture, or only in very small amounts. As a result, no IgG antibodies are produced to "reprogramme" the immune system.

New isoallergen analyses improve diagnostics and therapies

It is precisely here, with the different components of PR-10 allergens, that current research work at the University of Bayreuth sets off. A research group headed by Prof. Dr. Birgitta Wöhrle has set itself the goal of elucidating the composition of PR-10 protein mixtures from different plants. The aim is to analyse the biochemical and biophysical properties of the individual isoallergens, which differ despite their often very similar amino acid composition. For this purpose, the isoallergen mixture is isolated from birch or hazel pollen or from carrots, for example. The protein composition can then be determined with the aid of mass spectrometry. In addition, individual isoallergens are produced recombinantly in the Bayreuth laboratories using genetically modified bacteria. The advantages of production in bacteria and their subsequent purification are greater yield, purity, and standardisation.

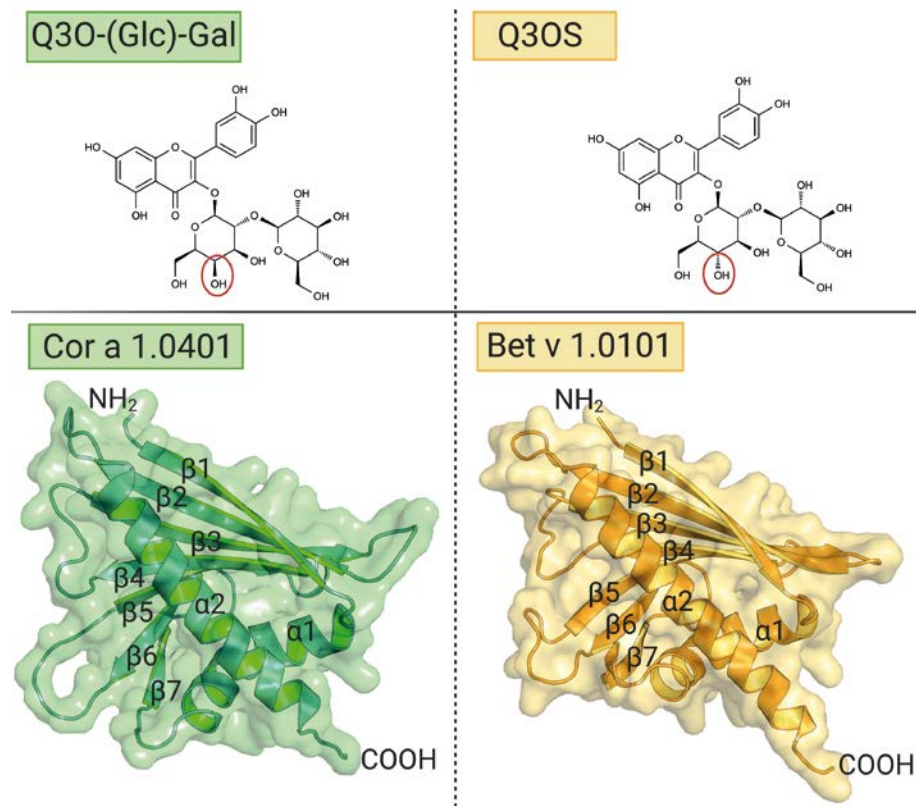
The analysis of individual isoallergens may well help to improve the diagnosis of allergies. On the basis of this, it is possible to determine exactly which isoallergens a patient is really allergic to. Treatment with the isoallergens identified in this way makes the therapy much more efficient and safe.

Physiological functions

Further studies will focus on the question of what physiological functions the PR-10 proteins have in plants. Not much has been discovered about this so far, even though they occur in numerous plant families. Some PR-10 genes are activated during defence responses against abiotic or biotic stress stimuli, whereas others are expressed constitutively or only in certain developmental stages of the plant. For the birch pollen allergen Bet v 1, various research groups were able to show in vitro that it can bind numerous different ligands – such as

cytokines, fatty acids, and flavonoids – in its cavity. Whether these ligands are physiologically relevant, i.e. whether they actually exist in the plant in complex with Bet v 1, is not known.

In the course of research work at the Chair of Biochemistry IV - Biopolymers, it has been possible for the first time to isolate the birch pollen allergen Bet v 1 in complex with a natural, previously unknown

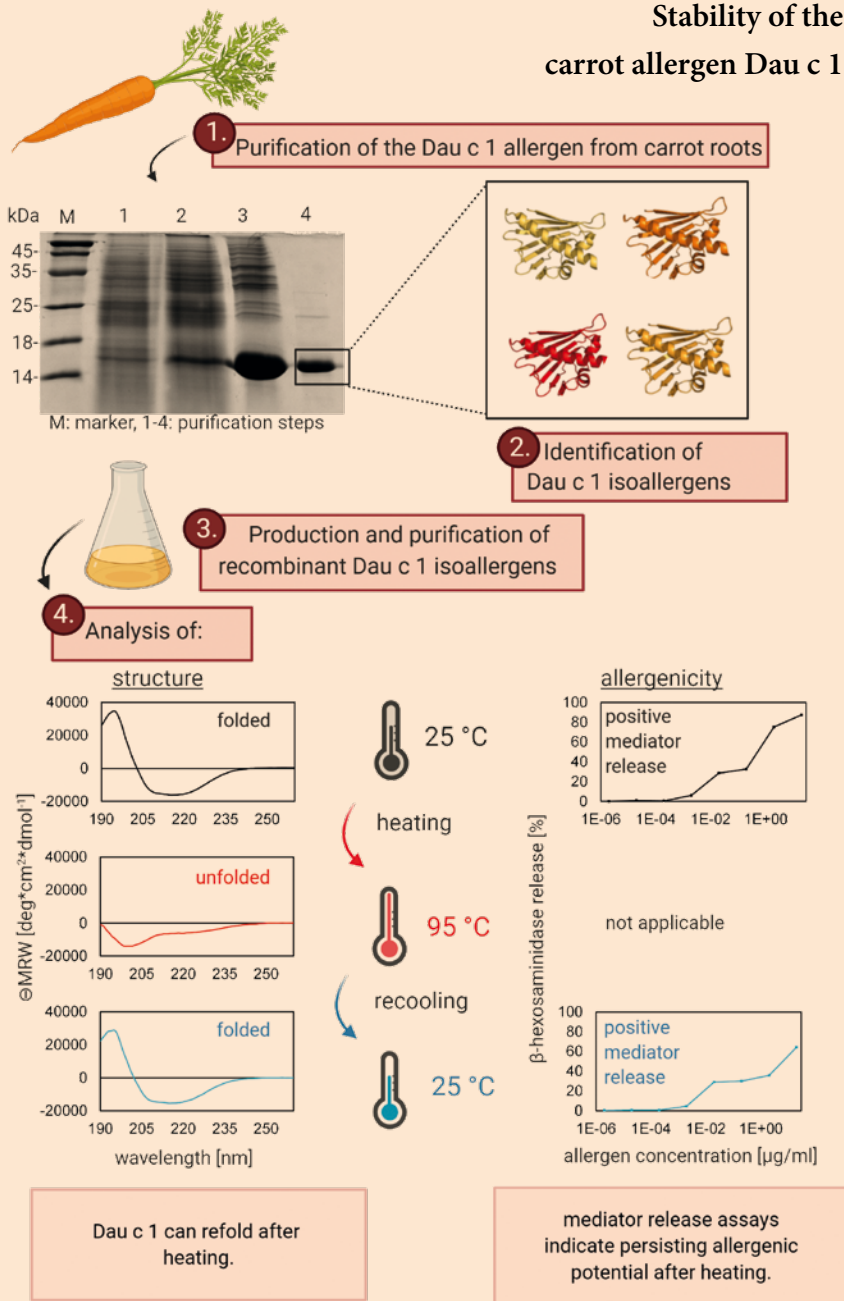


binding partner from birch pollen. The ligand was subsequently extracted from Bet v 1 and identified by mass spectrometry and NMR spectroscopy. This is the glycosylated flavonoid quercetin-3-O-sophorose (Q3OS). Similarly, a natural binding partner of the hazel pollen allergen Cor a 1 was recently identified. This ligand is also a glycosylated flavonoid, namely quercetin Q3O-(Glc)-Gal. Although the two ligands differ only in the orientation of one OH group, the binding of the respective ligand is highly specific: Bet v 1 only binds its own ligand Q3OS, but not Q3O-(Glc)-Gal, Cor a 1 only binds its own ligand Q3O-(Glc)-Gal, but not Q3OS (Fig. 5).

The identification of these ligands now allows conclusions to be drawn about the physiological func-

■ Fig. 5: The PR-10 allergens Cor a 1 from hazel and Bet v 1 from birch (bottom left and bottom right) and their natural ligands (top left and top right). The allergens show a very high specificity and only bind their own ligand (Cor a 1.0401 binds Q3O-(Glc)-Gal and Bet v 1.0101 binds Q3OS), but not the almost identical ligand of the other allergen. Secondary structure elements (α -helices and β -strands), the N-terminus (NH₂) and the C-terminus (COOH) of the proteins are labelled (Illustration: Thessa Jacob).

Stability of the carrot allergen Dau c 1



tion of these PR-10 proteins in plants. It has been established, for example, that flavonoids are essential for fertilisation as they stimulate the growth of the pollen tube. Glycosylated quercetins are initially inactive, but enzymes can cut off their sugar moieties and thus release quercetin. It is therefore reasonable to assume that the allergens Bet v 1 and Cor a 1 store the glycosylated ligands Q3OS and Q3O-(Glc)-Gal respectively, and that the release of quercetin triggers the fertilisation process.

Stability of PR-10 proteins: the example of the carrot allergen

However, finding the natural binding partner of an allergen is not only about establishing its physiological function. The bound ligand can stabilise the allergen – for example by protecting it from degradation by proteases in the gastrointestinal tract, or from the effects of heat. This influence of ligands on the stability of allergens is therefore another research topic at the Chair of Biochemistry IV Biopolymers.

To inactivate PR-10 allergens, it is often recommended to cook the respective fruit and vegetables before consumption. However, a recently published study shows that this measure does not provide sufficient protection against an allergic reaction to the carrot allergen Dau c 1. Both the protein mixture of natural Dau c 1, which was isolated directly from the carrot, and individual isoallergens produced in bacteria were exposed to temperatures of up to 95 degrees Celsius. They were examined to see how the protein structures change when heat-ed and after cooling. It was found that the natural mixture of isoallergens and almost all of the individually investigated isoallergens regained their original structure after cooling to 25 degrees Celsius. They are then able to cause allergies again.

The tests also clearly show that the structural stability of Dau c 1 also depends on the pH value, i.e. the acidity of the solution. Of particular interest is pH 3, which occurs in the stomach after food intake. Many proteins denature irreversibly at this acidic pH, i.e. their structures change irreversibly in a way that weakens or destroys their biological functions. Yet the Dau c 1 isoallergens tested retain their folded structure at pH 3. Even after heating at this pH value, they are not denatured and can therefore continue to cause an allergic reaction. The stability of allergens in the gastrointestinal tract is an essen-

The allergen Dau c 1 comprises a mixture of different isoallergens. It was purified from carrot roots and the cleaning success was verified by gel electrophoresis (step 1). Its isoallergen composition was analysed by mass spectrometry (step 2). Subsequently, individual isoallergens were recombinantly produced and purified in *E. coli* bacteria (step 3). An analysis of Dau c 1 by CD spectrometry after heating showed that most of the isoallergens can refold and regain their original structure (step 4 left). They also continue to trigger the release of allergy-inducing substances – so-called mediators – such as histamines (step 4 right). This indicates that they retain allergenic potential (Illustration: Thessa Jacob).



■ Fig. 6: To produce the carrot extract, the carrots are first shock frozen in the laboratory and then freeze-dried to gently remove the liquid (Photo: Ralf Weiskopf).

to food components. The exceptional stability of Dau c 1 could be the reason why it can act as a sensitizing allergen and also trigger systemic reactions affecting the whole organism. Carrot allergy sufferers should therefore also avoid cooked carrots.

Studies to identify new isoallergens

Further studies in Bayreuth have shown that the composition of natural Dau c 1 from carrots and natural Cor a 1 from hazel pollen is more complex than expected. Several unknown isoallergens were found. Now that it has been possible to produce some of these isoallergens in bacteria, their properties are to be analysed in future research work. Using serum from patients has already shown that one of the new Dau c 1 isoallergens is capable of triggering an allergic reaction.

Identifying new isoallergens and their biophysical and immunological behaviour is key to improving the diagnosis of allergies. It will allow the production of hypoallergens that trigger significantly weaker allergic reactions but are still effective in hyposensitisation. This could thus contribute significantly to personalised immunotherapy of food allergies. This topic will play a major role in the future, both in research and in medical applications.

tial factor in the development of clinical symptoms against plant foods, as the intestine-associated immune system plays an important role in tolerance

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■ Dirk Schüler
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Microbial magnets as medical agents?

New insights into the production and functionalization of bacterial magnetosomes

■ Dr. Frank Mickoleit, senior postdoc at the Microbiology research group, during sampling on a 100 L fermentation system (Photo: Christian Wißler).



Certain bacteria living in the sediment of aquatic habitats produce specialized intracellular magnetic organelles, so-called magnetosomes. These consist of nanometer-sized crystals of the magnetic iron oxide magnetite (Fe_3O_4), which are surrounded by a biological membrane composed of lipids and proteins. Within the cells, magnetosomes are arranged in a chain-like manner and thus form a compass needle that enables these magnetotactic bacteria to navigate along the Earth's magnetic field (Fig. 1).¹

In recent years, research has not only been interested in the biological functions that enable these bacteria to sense magnetic fields, but increasingly also focused on potential biotechnological applications of the bacteria and their biosynthesized organelles. Magnetosomes in fact represent biological nanomaterials with a number of extraordinary properties. Compared to chemically synthesized magnetic nanoparticles, they for example have a remarkably uniform shape and a size of about 40 nanometers, and a perfect crystal structure, which results in outstanding magnetic properties. These characteristics have envisioned magnetosomes as novel biomaterials for biotechnological and biomedical applications. For example, bacterial magnetosomes have already been successfully tested as contrast agents in imaging techniques such as magnetic resonance imaging (MRI) and magnetic particle imaging (MPI). Another promising application of the bacterial magnetic particles is the generation of heat by high-frequency magnetic fields in cells or tissues. This magnetic hyperthermia method has proved already promising in the thermal deactivation of tumours in animals. In all these examples, isolated magnetosomes showed a significantly higher efficacy than conventional, chemically produced magnetic nanoparticles.²

Biotechnological production of bacterial magnetosomes

At the University of Bayreuth, the Chair of Microbiology has been studying the biosynthesis and functions of these unique structures for a long time. Recently, in collaboration with partners from in- and outside the university, the biotechnical production of bacterial magnetosome particles and their potential for tailored biomedical applications has become a major objective. However, one of the main obstacles for the establishment of such applications is the difficulty to produce these particles in high amounts. Magnetic bacteria grow only relatively slowly compared to other biotechnologically relevant microorganisms. They are also extremely sensitive to deviations from their preferred environmental conditions and require consistently low oxygen concentrations for both optimal growth and magnetosome biosynthesis. Moreover, the precise control of these parameters at larger scales requires technically complex cultivation methods.

At the Chair of Microbiology special bioreactors of different sizes are used which allow to continuously monitor and control all relevant parameters with high precision. Within the "MagBioFab" project funded by the Federal Ministry of Education and Research (BMBF), these so-called fermentors are being employed to develop novel processes for the high-yield cultivation of magnetic bacteria at large scales. In close collaboration with the University's Process Biotechnology research group headed by Prof. Ruth Freitag, these efforts recently allowed the establishment of a process-controlled cultivation. In combination with an optimized strategy for the continuous nutrient feeding of the bacteria, cell yields can be expected to increase 50-fold relative to conventional flask cultivation (Fig. 2).

"A flexible modular system allows for the genetic functionalization of magnetosomes."

RECOMMENDED READING

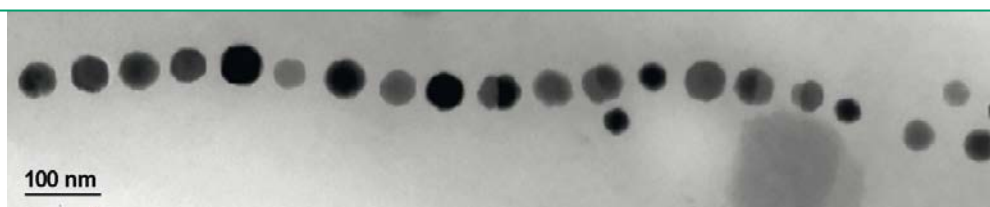
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S. Rosenfeldt et al.: Towards standardized purification of bacterial magnetic nanoparticles for future in vivo applications. *Acta Biomaterialia* (2020). DOI: 10.1016/j.actbio.2020.07.042.

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■ Fig. 1: Cell of the magnetotactic model organism *M. gryphiswaldense* with intracellular magnetosomes (left). The latter are organized in a chain-like manner (right) and form an intracellular magnetic compass needle (Electron microscopy image: René Uebe).





■ Fig. 2: Sophia Tessaro M.Sc., PhD student at the Microbiology research group at the University of Bayreuth, setting up a fermentation system for automatic mass cultivation of magnetic bacteria (Photo: René Uebe).

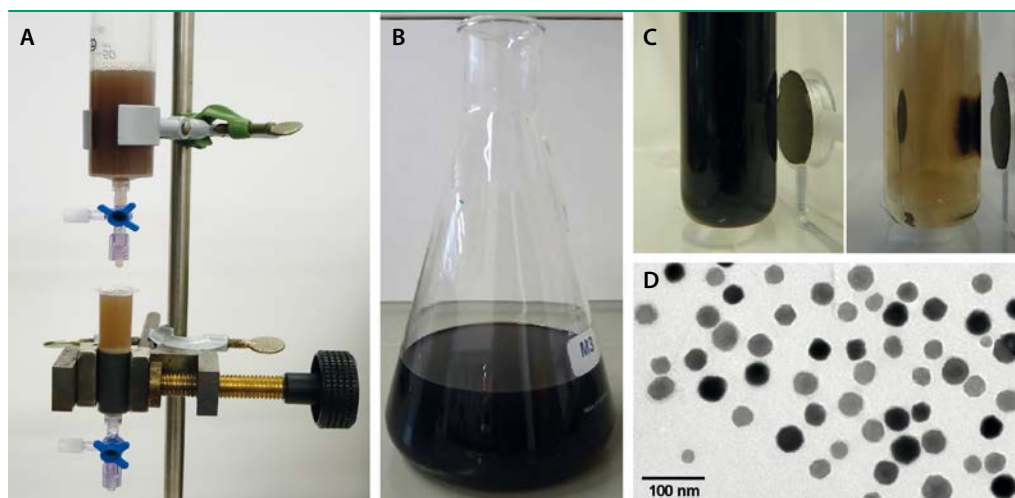
After cultivation, the magnetosome particles can be extracted from bacterial cells and separated from remaining cellular components by exploiting their magnetic properties (Fig. 3). The isolation procedure was recently optimized to allow the gentle isolation of the membrane-enveloped magnetite particles largely free of impurities. Important quality criteria such as the size and colloidal stability of the particles, their magnetization, as well as the integrity of the surrounding biological membrane can be monitored by biochemical methods, electron microscopy, magnetic measurements, and

small angle X-ray scattering (SAXS), provided by Bayreuth research groups from different departments.⁴

A genetic modular system for the generation of tailored nanoparticles

From a biotechnological perspective, it appears particularly attractive that the biosynthesis of magnetosomes, which is controlled by more than 30 genes, is fully accessible to synthetic biology approaches. This can now be used to produce magnetic nanostructures with tailored properties and completely new functionalities. While genetically unmodified "wild type" bacteria typically produce only about 15 to 25 particles per cell, the introduction of additional copies of magnetosome genes resulted in bacterial strains that biomineralize up to 120 particles per cell. Using these overproducers, the magnetosome yield can be significantly increased. Interestingly, genetic engineering can also be used to control the size of the biosynthesized nanoparticles and thus, to tune their magnetic properties – depending on the envisioned application. For example, either superparamagnetic or ferromagnetic properties can be specifically adjusted.⁵

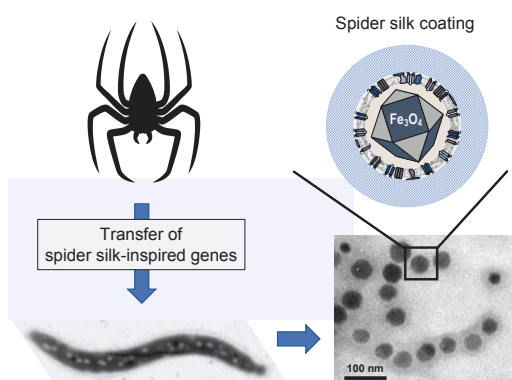
Genetic engineering also enables the coupling of foreign, bioactive molecules to the magnetite crystals via the magnetosome membrane. This can be achieved, for example, by genetic fusion with bacterial proteins that naturally occur in the magnetosome membrane and serve as anchors. By taking advantage of this method, a modular toolkit has been developed in Bayreuth, which allows the



■ Fig. 3: Isolation of magnetosomes by magnetic separation. By applying strong magnetic fields, magnetosomes are first bound to a magnetizable column. Remaining, non-magnetic components of the cell extracts, however, directly pass through the column (A). After removal of the magnetic field, the magnetosomes detach from the column and can be recovered in high concentrations (B). The magnetic properties can be demonstrated by attracting the particles by means of a magnetic field. After a relatively short time, the particles accumulate at the edge of the flask in the direct vicinity of a bar magnet (C). Transmission electron microscopy image of purified magnetosomes (D) (Image: René Uebe).

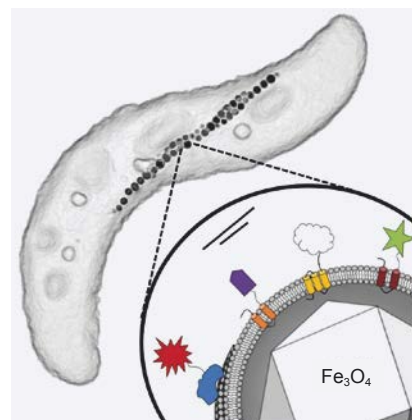
versatile genetic functionalization of the magnetosome surface.

In collaboration with the research group of Prof. Dr. Thomas Scheibel at the Dept. of Biomaterials, for example, recombinant magnetosomes enveloped by a silk-like shell were generated by genetic fusion of a magnetosome protein with a spider silk-derived peptide. This surface coating increases the colloidal stability of the particles and might also improve their biocompatibility in biomedical applications, owing to the non-immunogenic properties of spider silk (Fig. 4).⁶

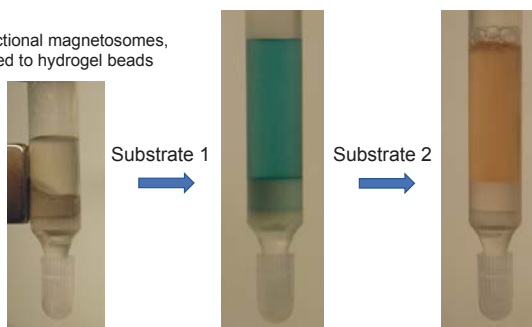


■ Fig. 4: Coating of the magnetosome surface with spider silk inspired peptides. Cells of *M. gryphiswaldense* were genetically reprogrammed to produce this novel hybrid material. The isolated particles are surrounded by a shell of up to 15 nanometers in thickness, which significantly increases the colloidal stability of the particles (Image: Frank Mickleit).

Furthermore, versatile molecular connectors can be immobilized on the magnetosome surface that allow the coupling of further functional units. Examples include the streptavidin-biotin system or short antibody fragments, so-called "nanobodies". These modifications allow the coupling of magne-

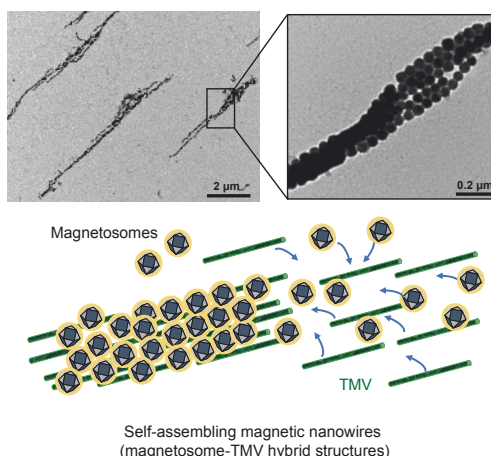


Multifunctional magnetosomes, coupled to hydrogel beads



Generation of a magnetic composite material with different catalytic activities

■ Fig. 5: Coupling of isolated magnetosomes to particles of the Tobacco Mosaic Virus (TMV). The resulting strand-like structures in the micrometer range can be magnetically aligned and provide a "platform" for further functional units, e.g. enzymes or fluorophores. The TMV particles reconstitute a scaffold that continuously recruits further magnetosomes to the growing composite. Thereby, hybrid strands of a length of up to ten micrometers can be formed (Illustration: Frank Mickleit).



tosomes to various other biological nanostructures, for example particles of the Tobacco Mosaic Viruses (TMV), thereby generating complex magnetic hybrid materials such as "nanostands" and "nanowires" (Fig. 5).⁷

Genetic coupling not only enables the display of a variety of biomolecules of interest to the magnetosome surface, but also allow to precisely adjust their copy numbers per particle. For example, by introducing genes from different organisms, magnetic bacteria have recently been genetically reprogrammed to incorporate four different foreign proteins in varying quantities into their magnetosome membrane. The genetic approach provides a high molecular precision and selectivity that is so far unachieved by any chemical coupling method. Another particularly attractive feature is that all relevant properties of this hybrid material – including its magnetic characteristics – are fully encoded within the genome of the bacteria. They thus can be easily modified, exchanged, or extended by genetic engineering (Fig. 6).⁸

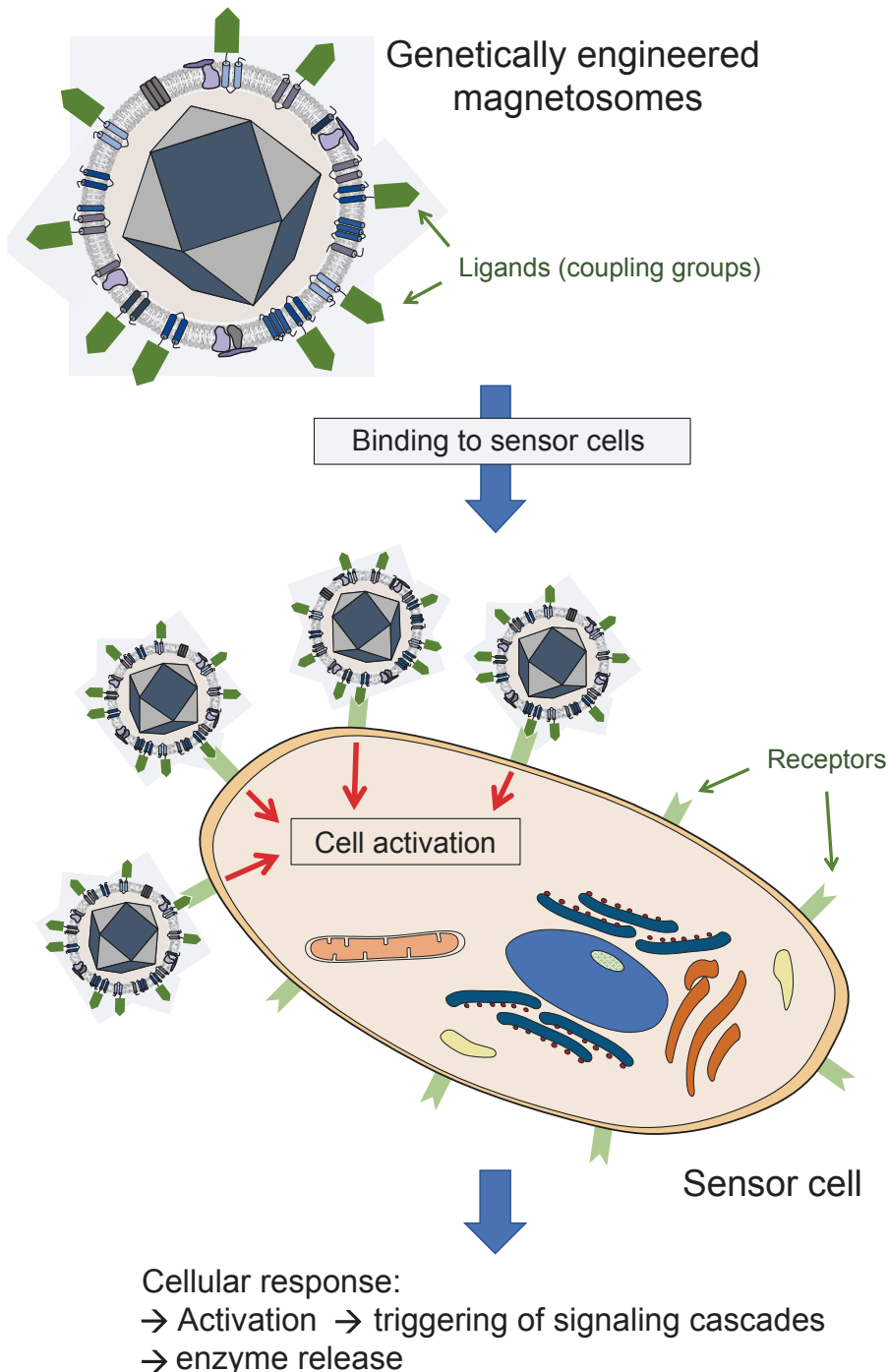
■ Fig. 6: Top left: Representation of a cell of the magnetic bacterium *M. gryphiswaldense* with interconnected magnetosomes. Lower left: Single, genetically functionalized magnetosome displaying different functional groups from foreign organisms fused to specific membrane proteins. Specifically, these are a camelid antibody fragment, a green fluorescent protein from a jellyfish, the enzyme glucose oxidase from a mould fungus, which is already used biotechnologically as a "sugar sensor" in diabetes disease, and a bacterial, dye-forming enzyme. Right: The isolated magnetosomes were bound to hydrogel beads, thereby generating a composite material with various catalytic activities. The latter can be demonstrated by the formation of differently colored reaction products (Illustration: Frank Mickleit / Clarissa Lanzloth).

Another result of the latest research at the University of Bayreuth, again achieved in collaboration with the team of Prof. Dr. Ruth Freitag and Dr. Valérie Jérôme at the Chair of Process Biotechnology has recently opened up interesting perspectives for biomedical applications. A human protein ligand, CD40L, was not only immobilized on the magnetosome surface, but also assembled into its multimer-

ic structure required for biological activity. In fact, in cell culture studies it could be demonstrated that these functionalized magnetosomes activate sensor cells which served as a model for immune cells.⁹ Thus, genetically modified magnetosomes might also be suitable for the stimulation of human antibody producing cells (Fig. 7).

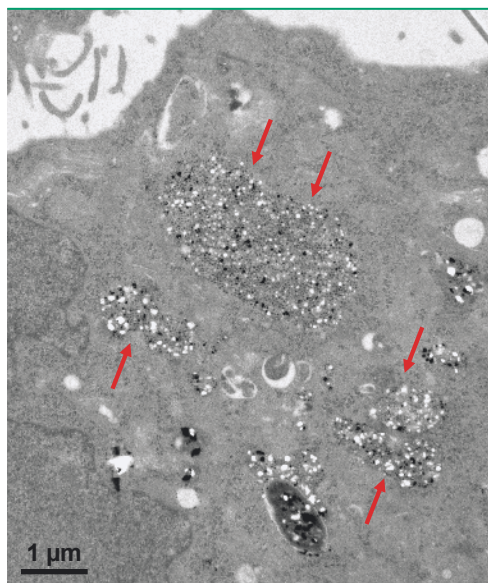
Future application in biomedicine and biotechnology?

Despite of these promising examples, a number of scientific issues still have to be addressed for future practical applications of bacterial magnetosomes. One of them is the already mentioned insufficient availability of the particles, which arises from the technically demanding production of magnetosomes. However, the recent progress in the development of new bioproduction and purification protocols give rise for optimism that sufficient quantities will soon be available for various applications, at least at a pilot scale. Due to their comparatively complex production, bacterial magnetosomes may initially be competitive with conventionally produced nanoparticles where special applications require highly functionalized particles in only relatively small quantities. In particular, bacterial magnetosome particles with a broad and adjustable functional spectrum may become attractive in cellular biotechnology as well as for various specialized biomedical applications. In addition to magnetic imaging and hyperthermia applications, "theranostatic" magnetosomes – which combine diagnostic and therapeutic functions at the same time – could become useful in the treatment of tumours. For example, they might be used to specifically detect and destroy cancer cells and at the same time might act as carrier that magnetically direct active drugs to their destination site (Fig. 8).



■ Fig. 7: Stimulation and activation of sensor cells by functionalized magnetosomes. The particles were genetically modified to display ligands (specialized coupling groups) on the surface. Specific binding to the corresponding receptors of sensor cells results in cell activation and triggers signaling cascades. These in turn lead to the release of enzymes whose activity can be easily determined (Illustration: Frank Mickoleit).

For future applications in cell culture or even in the human body, however, the toxicity and immunogenicity of the bacterial particles have to be investigated in more detail and potentially also requires modification. Promising research is being carried out in collaboration with researchers from the Jena University Hospital. In these initial studies, magnetosomes indicated good biocompatibility and only low toxicity when incubated with mammalian cells. Thus, the interdisciplinary collaborations of the University of Bayreuth form an excellent basis for paving the way for the future use of magnetosomes in biotechnology and biomedicine.



■ Fig. 8: Transmission electron micrograph of a cancer cell incubated with magnetosomes. A high number of particles has been taken up and accumulated in vesicle-like structures within the cell. Magnetosome uptake might be important for the delivery of drugs into the cells, but also for therapeutic approaches like magnetic hyperthermia (Electron microscope image: Stefan Geimer, Electron Microscopy Laboratory, University of Bayreuth).

AUTHORS



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■ Claus-D. Kuhn

Tracking down the biological function of non-coding RNAs

A new starting point for future
biomedical development

■ Felix Klatt M.Sc. analyzes variants of the Mediator
kinase module (Photo: Fabienne Lindner).



The human genome, the sum of all our hereditary genetic information, is constantly being read and copied into ribonucleic acids (RNAs). However, only 2% of these RNAs, termed messenger RNAs, serve as blueprints for the construction of proteins. They are therefore called "coding" RNAs. Proteins in turn are the essential building blocks and signal molecules of all life, from the smallest bacteria all the way to humans. The fact, that only a small proportion of all RNAs code for proteins, means that the majority of our genetic information is not directly used to build proteins. These RNAs therefore represent *non-coding* RNAs.

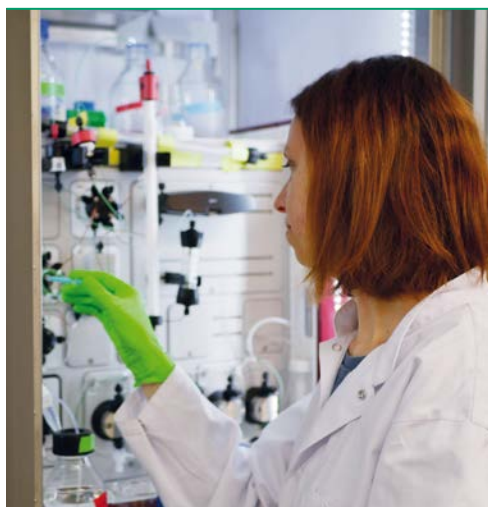
Regulatory RNAs

The vast majority of non-coding RNAs have regulatory functions. While the molecular mode of action of a few classes of these RNAs is already well understood, the function of most non-coding RNAs in humans is still unknown. With this in mind, the research team of Dr. Claus-D. Kuhn at the University of Bayreuth combines biochemistry, structural biology, and systems biology to track down the function of these mysterious RNAs.

Understanding the functions of regulatory, non-coding RNAs already has profound implications for the treatment of human diseases. In the future, this significance for biomedical applications will only increase:

- One example is the first drug based on RNA interference, which was approved in 2018 (*ONPATRO*® by *Alnylam*). Since then, other RNAi-based drugs have been developed, with others expected to follow. Common to all of these drugs is that they activate a natural mechanism in our cells that causes individual messenger RNAs to be specifically silenced rather than translated into proteins.

- Another example is the recently introduced vaccine against the SARS-CoV-2 virus, which is reported to offer up to 95% protection against viral infection. This vaccine, co-developed by *BioNTech* and *Pfizer*, is based on the idea that our body utilizes artificial viral messenger RNAs to trigger the production of antibodies against the virus. Other pharmaceutical companies are also working hard on such vaccines, e.g. *CureVac* from Tübingen in Germany. These successes, in turn, are increasing the interest in the function of non-coding RNAs, in particular their regulatory influence on their



■ Fig. 1: Vladyslava Gorbovytska M.Sc. works on the purification of recombinant protein complexes (Photo: Fabienne Lindner).

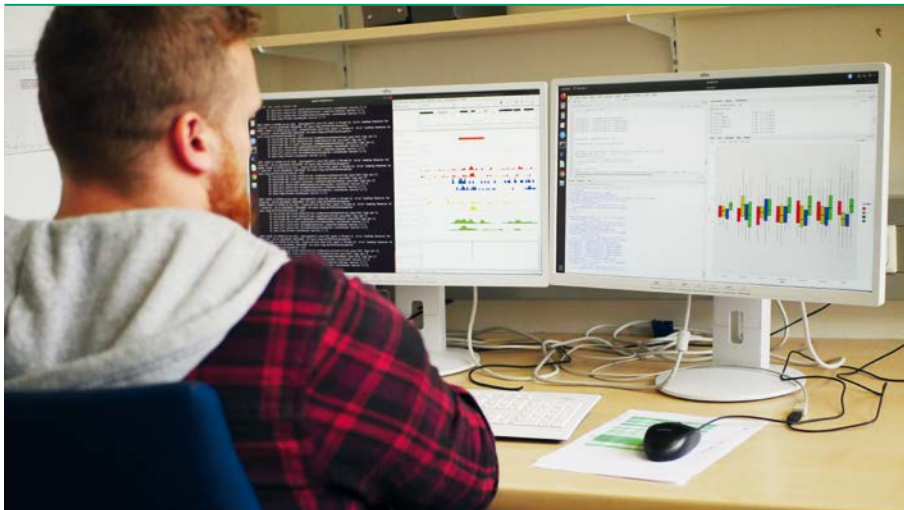
"coding siblings". Basic research in the field of non-coding RNAs will therefore have a decisive impact on drug development in a not too distant future.

What role do non-coding RNAs play during regeneration?

Planaria of the species *S. mediterranea* are flatworms that live in freshwater. They have an astonishing ability to regenerate. Even fragments that only make up one hundredth of an adult worm can regenerate into complete animals. The regeneration process is based on a large number of pluripotent stem cells that are distributed throughout the body of the worms. As required, these stem cells can differentiate into all cells with specialized functions. The research team in Bayreuth is striving to

■ Fig. 2: Fabienne Lindner B.Sc. during RNA interference experiments with planaria of the species *S. mediterranea* (Foto: Vladyslava Gorbovytska).





■ Fig. 3: Andreas Pittroff M.Sc. evaluates systems biology data (Photo: Fabienne Lindner).



■ Fig. 4: A planarian of the species *Schmidtea mediterranea* (Photo: Alejandro Sánchez Alvarado, Wikimedia Commons, CC-BY-SA-2.5).

get to the bottom of how regeneration depends on non-coding RNAs. Their focus thereby lies on a highly complex class of small non-coding RNAs known as PIWI-interacting RNAs – piRNAs for short. Molecular and systems biology research approaches help the team to clarify how piRNAs contribute to the regenerative capacity of planaria. Some fundamental findings have already emerged from these investigations:¹

■ piRNAs in planaria have a central function in the control of messenger RNA. It could be shown that piRNAs in the stem cells of planarians degrade a large number of messenger RNAs. This process, in combination with other piRNA-dependent mechanisms, supports the hypothesis that stem cells in planaria are crucially controlled by piRNAs.

■ piRNAs are also important for the epigenetic control of "jumping genes", so-called transposons. These are genes that leave their original position in the genome and insert themselves back into the genome at a different location. piRNAs ensure that these processes do not get out of hand in planarian stem cells, but enable the targeted differentiation of stem cells into all other cell types.

Recently, the research group of Dr. Claus-D. Kuhn has discovered that piRNAs are also found in the outermost cell layer – the epidermis – of planarians. This discovery is of great interest, as it points to a connection between piRNAs and innate immunity. Further investigations by the Bayreuth team are set to continue in this direction.

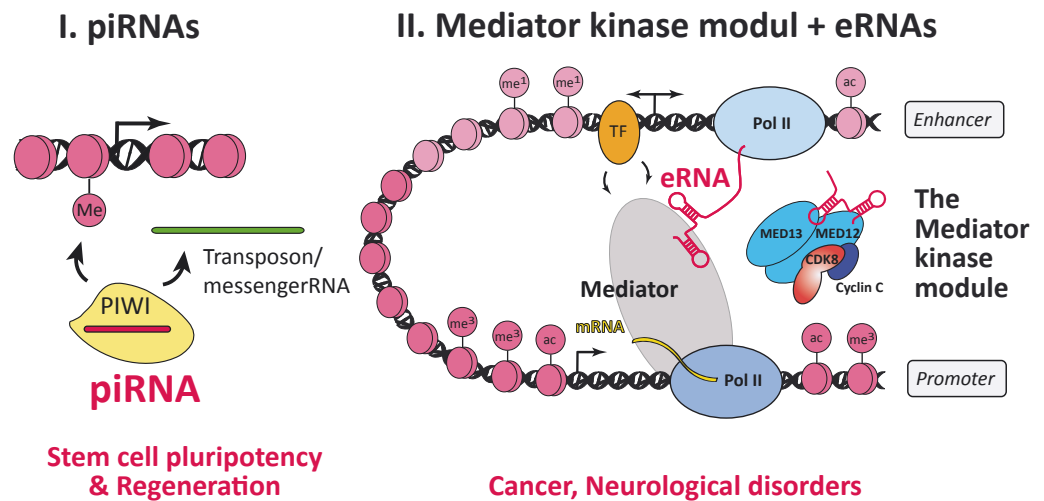
Cells are only capable of regeneration if they have two basic properties: the ability to divide and grow (proliferation) and the potential to develop into cells with special functions (plasticity). Both properties also lie at the basis of the development of cancer. Planarians must therefore have mechanisms to protect their genome from instability. This is apparently achieved, by, amongst other things, non-coding RNAs that regulate reading and copying of genetic information. The long-term goal of the Bayreuth team is therefore to elucidate the connection between these mechanisms and the regeneration competence of planarians. This knowledge will help to bring research closer to the vision of being able to control the regeneration of entire organs in humans.

RECOMMENDED READING

V. I. Kim et al.: Planarians recruit piRNAs for mRNA turnover in adult stem cells. *Genes & Development* (2019), 33, 1575-1590. DOI: 10.1101/gad.322776.118.

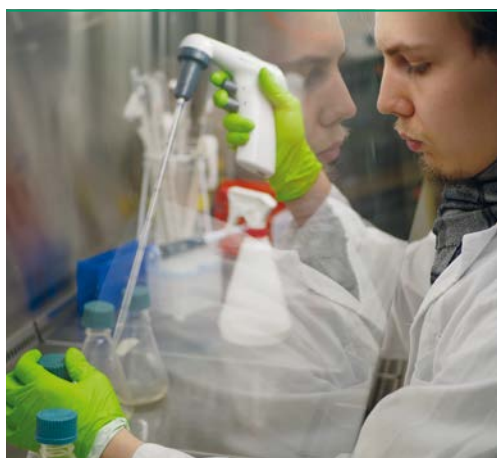
F. Klatt et al.: A precisely positioned MED12 activation helix stimulates CDK8 kinase activity. *Proceedings of the National Academy of Sciences of the United States of America – PNAS* (2020). DOI: 10.1073/pnas.1917635117.

■ Fig. 5: Two important research topics of Dr. Claus-D. Kuhn's group and their biomedical relevance: The first project (I.) deals with the regulation of messenger RNAs and transposons by small, non-coding RNAs called piRNAs (PIWI interacting RNAs). In the second project (II.), the structure and function of the Mediator kinase module and the influence of enhancer RNAs (eRNAs) on its activity are investigated. The biomedical relevance of both topics is listed underneath the respective topics (Illustration: Claus-D. Kuhn).





■ Fig. 6: Filiz Kuybu B.Sc. prepares biochemical experiments (Photo: Fabienne Lindner).



■ Fig. 7: Nathanael Wittmann B.Sc. works with insect cells (Photo: Fabienne Lindner).

C and MED12. For drug development it is important to know how CDK8 activity can be inhibited to prevent its carcinogenic malfunction. In fact, the research team found that it is mainly the MED12 protein that activates CDK8. To that end MED12 applies an unusual mechanism that is not found in most other cyclin-dependent kinases. In addition, the research team was able to show exactly how MED12 acts on CDK8. It regulates the activity of CDK8 by binding to CDK8 and thereby structurally altering the active site of CDK8. This change is cri-

"Understanding the functions of non-coding RNAs is already having a profound impact on the treatment of human disease."

New findings on the human oncogene CDK8

For all RNA synthesis in humans, a large molecular complex, known as the "Mediator" complex, is indispensable. One of its components is the kinase module, which was often found linked to human carcinogenesis. The kinase module consists of four protein units, three of which regulate the activity of the fourth partner, CDK8 (cyclin-dependent kinase 8). CDK8 is an important human oncogene. Its dysfunction contributes to the development of colon, breast, and skin cancer, among other things.

One focus of research in the "Kuhnlab" is therefore to elucidate the structure and function of the Mediator kinase module. Recently, the team could decipher the low-resolution structure of the core of the Mediator kinase module. It consists of CDK8 and two of the three regulatory protein units, Cyclin

and MED12. For drug development it is important to know how CDK8 activity can be inhibited to prevent its carcinogenic malfunction. In fact, the research team found that it is mainly the MED12 protein that activates CDK8. To that end MED12 applies an unusual mechanism that is not found in most other cyclin-dependent kinases. In addition, the research team was able to show exactly how MED12 acts on CDK8. It regulates the activity of CDK8 by binding to CDK8 and thereby structurally altering the active site of CDK8. This change is critical for the effect of small molecule inhibitors on CDK8. It results in compounds that were specifically developed against CDK8 to no longer bind to CDK8. Such drugs are therefore ineffective in human cells, in which CDK8 is (almost) always bound to MED12. In this way, the Bayreuth study has revealed biochemical details on the function of CDK8 and its activation that are of fundamental importance for the development of small molecule drugs targeted at the oncogenic role of CDK8. In practice, all future drug development campaigns aimed at CDK8 should always work with at least a triple complex of CDK8, Cyclin C, and MED12. This is the only way to ensure that CDK8-specific compounds will indeed show efficacy in cancer treatment.

Based on the results obtained so far, the team around Dr. Claus-D. Kuhn intends to use single-particle cryo electron microscopy in the future to elucidate the regulatory mechanism of CDK8 in atomic detail. With this technology, protein complex structures can be determined to near-atomic resolution. Further research will build on the finding that numerous essential paralogous variants of the Mediator kinase module exist in human cells, the function of which is still completely unknown. The detailed knowledge of the Mediator kinase module gained so far will help to investigate the influence of these variants and to understand how a currently still puzzling class of non-coding RNAs, so-called enhancer RNAs (eRNAs), influence the activity of the kinase module.

AUTHOR



■ Dr. Claus-D. Kuhn is Head of the research group "Gene Regulation by Non-Coding RNA", which is part of the Elite Network of Bavaria.

1 I. V. Kim et al.: Planarians recruit piRNAs for mRNA turnover in adult stem cells. *Genes & Development* (2019) 33, 1575-1590. DOI: 10.1101/gad.322776.118. - I. V. Kim et al.: Efficient depletion of ribosomal RNA for RNA sequencing in planarians. *BMC Genomics* (2019), 20, 909- 912. DOI: 1 0.1186/s12864-019-6292-y.



New perspectives for biomedicine and biotechnology

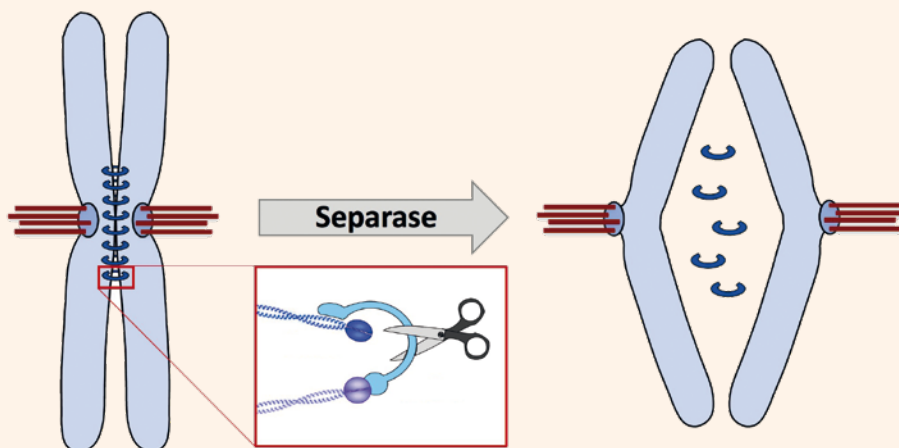
Further examples from Bayreuth's basic research

■ *Model of the DNA helix in which all genetic information of an organism is stored (sst).*

Regulated cell division: Healthy cells prevent genetic defects

■ Olaf Stemmann
Susanne Hellmuth

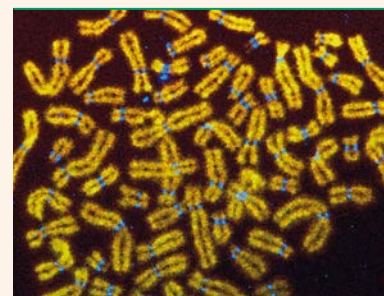
Cell division is essential for human growth and reproduction. Before a cell begins to divide, the genetic information stored on the chromosomes is replicated. Each chromosome then consists of two identical DNA threads, the sister chromatids. These are firmly enclosed by cohesin, a ring-shaped multi-protein complex – and this way the pair of chromatids remains inseparable. Even if the cohesin is removed from the arms of the chromosomes in preparation for cell division, the sister chromatids still remain together. Only after the cohesin remaining in the middle of the chromosomes is cut by the enzyme separase does the separation occur. The chromatids then move to the two opposite poles of the spindle apparatus, where their genetic information enables the formation of the two daughter cells.



■ Fig. 1: The separase cuts the cohesin rings that hold the sister chromatids together. These then migrate to the opposite poles of the spindle apparatus (Illustration: Olaf Stemmann).

To ensure that the daughter cells do not contain any genetic defects, it is crucial that the separase becomes active at the right time. If the sister chromatids are separated too early, there is no guarantee that they will be evenly distributed between the daughter cells. In this case, there is a high risk that the daughter cells will contain the wrong number of chromosomes. If this is the case, they die or they can develop into tumour cells. To prevent such genetic malfunctions, strict regulation of the separation process is needed.

ter chromatids from starting too early. Shugoshin alone is even able to regulate the activity of the separase in human cells without the parallel involvement of Securin. Such redundancy occurs quite often in the cell cycle. To ensure that a vital process runs in a well-ordered manner, nature ensures that it is controlled in more than one way at the same time. This makes such processes particularly robust, but also less transparent for research, because disruptions are not immediately apparent.



■ Fig. 2: Immunofluorescence microscopy of chromosomes with two sister chromatids each. The blue dots mark the kinetochores, the chromosomal attachment sites for the spindle fibres. Between each pair of kinetochores are the cohesin rings, which must be cut by separase to separate the sister chromatids. The DNA is marked yellow (Image: Susanne Hellmuth).

A "guardian spirit" discovered

The protein securin has long been known to prevent the separase from cutting the cohesin ring too early. Hence, biochemical textbooks still state that the separase is regulated exclusively by securin. But this assumption has always been at odds with the observation that the separase remains properly regulated even when securin is not present. The reasons for this remained obscure. Recently, however, the Genetics research group at the University of Bayreuth, in cooperation with partners at the University of Salamanca in Spain, has found the solution to the puzzle. It turns out that the protein shugoshin – a Japanese name meaning "protective spirit" – also regulates the separase. Shugoshin and Securin both prevent the separation of the sis-

Twofold control

The Bayreuth geneticists have made another discovery. The regulating influence of Shugoshin and the regulating influence of Securin are controlled by the same "central instance": the *Spindle Assembly Checkpoint (SAC)*. The assumption, well established in research, that the SAC has the sovereignty over all processes involved in chromosome inheritance was thus once again confirmed. It was already known that the SAC exerts a stabilising effect on securin, and only releases this protein for degradation when the separase is meant to become active. In Bayreuth, it was now possible to show how the SAC acts on Shugoshin in such a way that this protein also suppresses premature separase activity: namely by means of an association of Shugoshin with the SAC component Mad2.

RECOMMENDED READING

S. Hellmuth, L. Gómez-H, A. M. Pendás, O. Stemmann: Securin-independent regulation of separase by checkpoint-induced shugoshin-Mad2. *Nature* (2020), 580, 536-541. DOI: 10.1038/s41586-020-2182-3.

S. Hellmuth, O. Stemmann: Separase-triggered apoptosis enforces minimal length of mitosis. *Nature* (2020), 580, 542-547. DOI: 10.1038/s41586-020-2187-y.

■ Fig. 3 and 4: Dr. Susanne Hellmuth loading samples for the separation of proteins (Photos: Olaf Stemmann).

AUTHORS

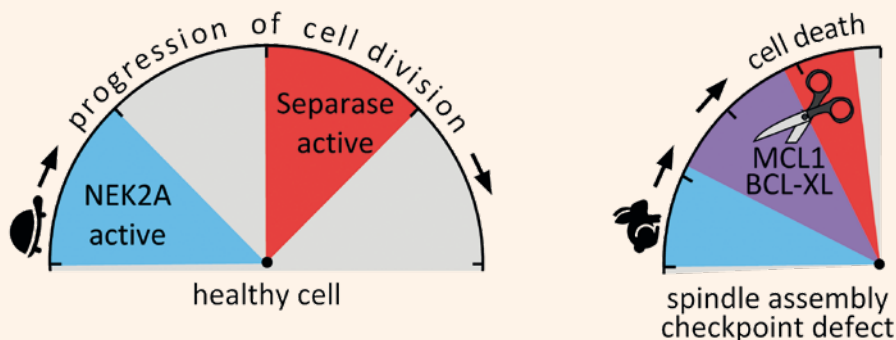


■ Prof. Dr. Olaf Stemmann is the Chair of Genetics at the University of Bayreuth



■ Dr. Susanne Hellmuth is a postdoc at the Genetics research group of the University of Bayreuth.

■ Fig. 5: Left: In a healthy cell, separase only becomes active when NEK2A has already been broken down – MCL1 and BCL-XL are not split. Right: In cells with a defective spindle assembly checkpoint, cell division is faster. The activities of NEK2A and separase overlap in time (purple area) – programmed cell death occurs (Illustration: Olaf Stemmann).

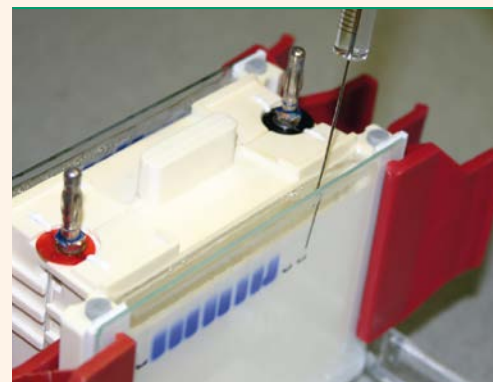


Pre-programmed cell death as protection against pathological developments

A follow-up study based on these new findings has recently uncovered a previously unknown protective mechanism of the cell. Let us assume that, despite all redundancy, a hasty attack of the separase on the cohesin rings of the chromosomes does occur. Then it is the separase itself that can make up for its mistake. It sets in motion the rapid death of the dividing cell. It does this by converting the proteins MCL1 and BCL-XL, which actually have the task of counteracting cell death. However, the separase, which becomes active too early, simply cuts these proteins open, causing them to lose their cell-protective function. Moreover, the resulting MCL1 and BCL-XL fragments even proactively promote cell death.

An emergency mechanism ensures the elimination of diseased cells

But how is it guaranteed that the separase spares healthy cells and actually only attacks the proteins MCL1 and BCL-XL in the event of an impending pathological cell development? This question could also be answered in the new study. The separase is only capable of this attack if the two proteins have been previously identified with the help of phosphate groups. The enzyme NEK2A is responsible for this labelling. However, this enzyme starts to be broken down during the preparation for cell division. Even before the cell begins to divide, the enzyme has disappeared – provided that the spindle control point ensures that cell division proceeds in a well-ordered manner. Consequently, if the separase becomes active at the right time, it cannot identify and cut the proteins MCL1 and BCL-XL. However, if the spindle control point is defective, the cell division process is accelerated. While NEK2A is still present in the cell, the separase becomes active. Now it recognises the two proteins and the programmed cell death is initiated.



This interaction of the enzymes separase and NEK2A can be aptly described in the terminology of genetics as the "Minimal Duration of Early Mitosis Checkpoint", or "DMC" for short. It is a self-protection mechanism for emergencies where a defective spindle checkpoint has created the danger of pathological cell development.

A new approach for cancer treatment

The new research results offer highly interesting starting points for new cancer therapies. It has been observed for some time that MCL1 and BCL-XL are often produced in particularly large numbers in cancer cells. In these cases, however, the two proteins protect the wrong cells from dying. Therefore, a promising approach in fighting cancer could now be to specifically promote separase-dependent fragmentation in diseased cells, and thus the repurposing of MCL1 and BCL-XL. The Genetics research group will continue to pursue this approach in cooperation with other research groups, for example, in clinical oncology and drug discovery. It is possible that this approach will enable the destruction of cancer cells with the help of proteins that healthy cells successfully use for their own self-protection.

Bacterial Gene Expression: A new Approach towards Novel Antibiotics

■ Stefan H. Knauer

Gene expression is a two-step process in all living organisms: first, the genetic information stored in the DNA is used as template for the synthesis of ribonucleic acids (RNAs), i.e. the genetic information is converted into a form that can be directly used by the cell. This process is called transcription and carried out by the enzyme RNA polymerase. Certain RNAs, the messenger RNAs (mRNAs), contain molecular blueprints. These are recognized by the ribosome and used in the translation process, the second step of gene expression, to synthesize corresponding proteins. In humans and animals, the two steps of gene expression are clearly separated spatially and biochemically. In bacterial cells, in contrast, they are coupled to each other, as has been known for more than 50 years.

Ten years ago, a research group at the University of Bayreuth led by Prof. Dr. Paul Rösch found first indications that transcription-translation coupling could be mediated by the protein NusG. However, it was only now, that the group of Dr. Stefan H. Knauer in collaboration with partners at Columbia University in New York was able to provide the first, direct structural evidence. The protein NusG consists of two flexibly connected domains: an amino-terminal domain (NTD) and a carboxy-terminal domain (CTD). The CTD binds to the ribosome, whereas the NTD interacts with RNA polymerase. By this, NusG forms a flexible bridge between the central machines of gene expression, similar to a flexible coupling connecting railroad carriages. This connection ensures synchronization of transcription and translation. These connections were visualized by experiments using high-resolution nuclear magnetic resonance (NMR) spectroscopy and were performed at the North Bavarian NMR Center of the University of Bayreuth.

These findings give rise to novel perspectives for the development of new antibiotics. If it was possible to break molecular bridge-building by NusG, the bacterial protein synthesis – and thus also the reproduction of bacteria – could be sensitively disturbed – without affecting the human organism. Initial work towards this aim carried out by the group of Dr. Stefan H. Knauer in collaboration with a research group at the University of Edinburgh has already proved to be promising.

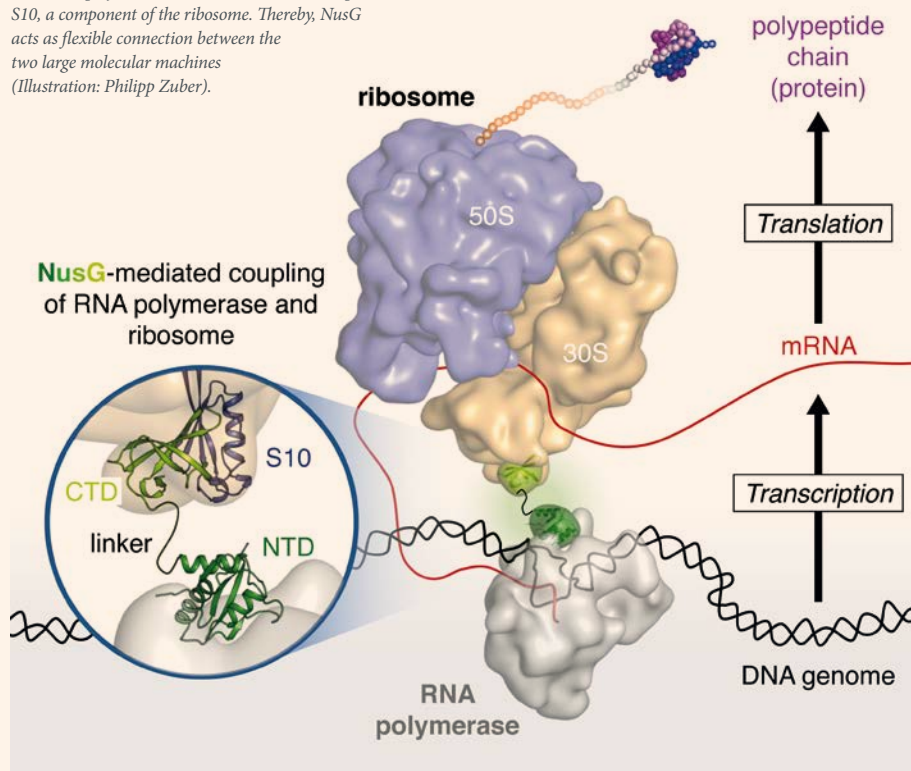
Evidence for the central role of NusG in bacterial protein biosynthesis was obtained using a combination of structural biology, biochemical and molecular biology methods. This interdisciplinary approach, as it is characteristic for the University of Bayreuth, will also be the basis for the future search for efficient active agents.

AUTHOR



■ Dr. Stefan H. Knauer, habilitating at the Chair of Biochemistry IV - Biopolymers.

■ Fig. 1: NusG-mediated transcription-translation coupling. The small protein NusG consists of two parts, the NTD and the CTD, which are flexibly connected. NusG's NTD interacts with RNA polymerase whereas its CTD binds to protein S10, a component of the ribosome. Thereby, NusG acts as flexible connection between the two large molecular machines (Illustration: Philipp Zuber).



RECOMMENDED READING

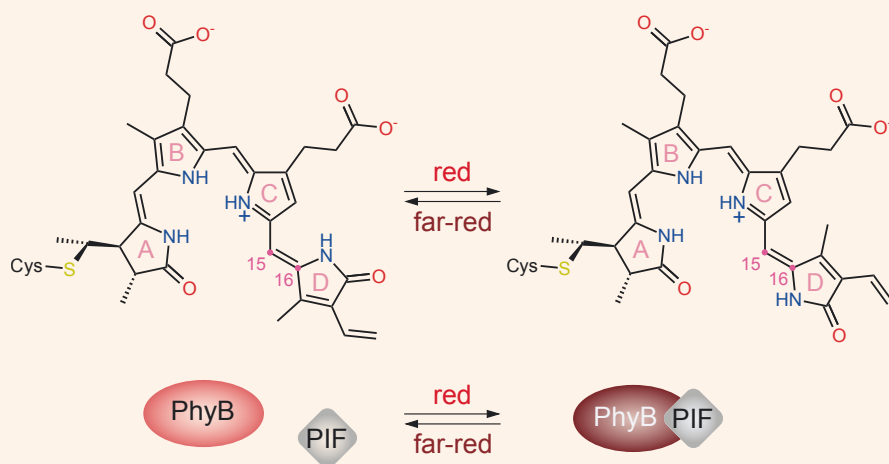
R. S. Washburn et al.: Escherichia coli NusG links the lead ribosome with the transcription elongation complex. *iScience* (2020), 23 (8). DOI: 10.1016/j.isci.2020.101352.

■ Andreas Möglich

Light-dependent molecular switches for controlling cellular processes

■ Fig. 1: Flowering thale cress (*Arabidopsis thaliana*) on a natural meadow (sst).

Like many other organisms, plants have the ability to adapt vital functions to the prevailing light conditions. Sensory photoreceptors, which absorb sunlight and convert it into chemical signals, play a central role here. These include phytochromes, which act as receptors for red and near-infrared light. They modulate biochemical processes in plants, which are, for example, significantly involved in gene expression, metabolism, growth, and the onset of flowering. In order to understand the relationships between light irradiation and biochemical processes in the plant, it is important to know exactly how the phytochromes interact with their molecular interaction partners. For it is precisely these interactions that change in response to light and form the basis of downstream physiological responses.



■ Fig. 2: Phytochromes react to the change between red light and near-infrared light with a change of molecular structures. In the *Pr* state (right) they can absorb near-infrared light, in the *Pr* state (left) red light (Illustration: D. Golonka et al. in: *Communications Biology* (2019), see recommended reading).

This is exactly where the interdisciplinary research work of Prof. Dr. Andreas Möglich's group at the Chair of Biochemistry II - Photobiochemistry comes into play. It has been known for decades that plant phytochromes react to the change between red light and near-infrared light by the pigments they contain changing their molecular structures. In the dark they show the state *Pr* and are therefore able to absorb red light. Under red light, *Pr* changes to the state *Pfr*, which can detect near-infrared light. The phytochromes therefore act like light-controlled switches that switch back and forth between two structures. The Bayreuth team, in cooperation with experimental physicists from Bayreuth under the

direction of Prof. Dr. Jürgen Köhler, recently described in detail, using the model plant *Arabidopsis thaliana* as an example, how this "structural circuit" changes the interactions of the phytochromes with their interaction partners. These include in particular the Phytochrome-Interacting Factors (PIF), which are found in different variants. While it was previously known that there is a much closer interaction between phytochromes and PIFs under red light than under near-infrared light or in the dark, quantitative information on the strength of this interaction and the speed of its formation has now been obtained for the first time.¹ The completely new findings not only contribute to the scientific understanding of essential light-dependent control in plants, but also promote innovative applications of plant phytochromes in biotechnology.

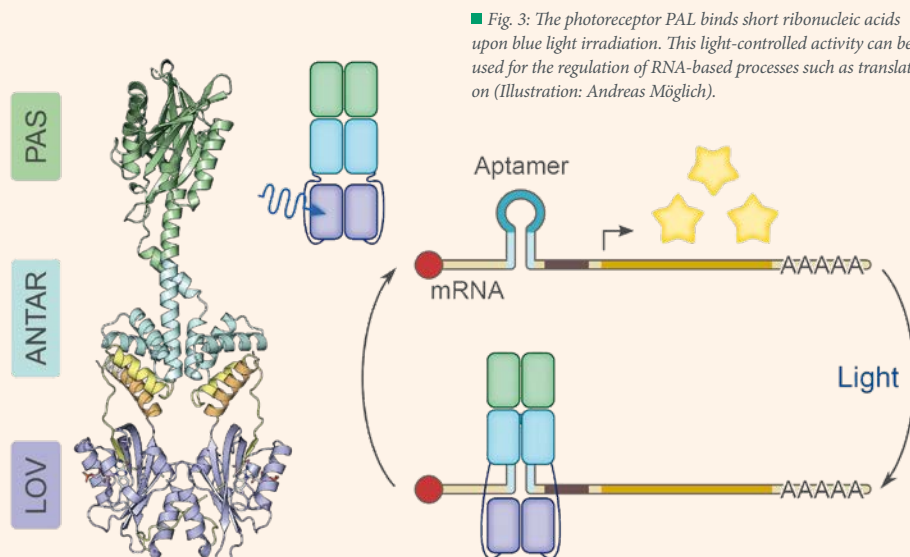
Discovery and application of a new type of blue-light receptor

Another focus of Prof. Dr. Andreas Möglich's research group is the investigation of blue-light responsive photoreceptors of the Light-Oxygen-Voltage (LOV)

family, which are found in plants, bacteria, and fungi. Not least by using such LOV receptors, it was already possible several years ago to change the transcription of genetic information – and consequently also the protein synthesis induced by RNA molecules – via light signals at the DNA level. This procedure belongs to the field of optogenetics and is now firmly established in molecular and cell biology.² The Bayreuth research team, in cooperation with partners at the University of Bonn, has discovered and mechanistically characterised the novel LOV receptor PAL. With the help of PAL, interactions and function of various RNA molecules can be specifically controlled by light for the first time. This discovery opens up completely new areas of application and thereby establishes the field of optoribogenetics, which studies the genetically mediated, light-regulated control of RNA-dependent processes.

However, the starting point of the research work was far removed from such optoribogenetic applications. In the beginning, the aim was rather to investigate naturally occurring LOV receptors in their mechanistic diversity. For this purpose, a bioinformatic search of large international sequence databases led to a promising discovery. Bacteria of the species *Nakamurella multipartita* contain a protein with a conspicuous tripartite architecture. Three different sections – so-called domains denoted "PAS", "ANTAR", and "LOV" – are arranged in an unusual sequence. The LOV photosensor domain reacts to blue light and relays the signals to the ANTAR domain. And this is where the decisive structural change occurs. RNA molecules are bound by the ANTAR domain and are therefore inaccessible. Only when the blue light irradiation ends and the ANTAR domain returns to its normal structure are the RNA molecules "freed" and able to perform their biological function. Further investigations have provided molecular insights into this previously unknown regulatory mechanism.

The change between activation and deactivation of RNA was first demonstrated on RNA aptamers – these are short, structured RNA molecules. The RNA aptamers take on a hairpin-like form and penetrate into the structure of the ANTAR domain, which is opened under blue light, so that they are bound there. This mechanism can be used to control gene expression by light directly at the RNA level in both bacteria and mammalian cells. A light switch had thus been found which makes it possible to switch on and off functions of diverse RNA molecules in a targeted manner.³



■ Fig. 3: The photoreceptor PAL binds short ribonucleic acids upon blue light irradiation. This light-controlled activity can be used for the regulation of RNA-based processes such as translation (Illustration: Andreas Möglich).

A light switch for controlled RNA degradation

In eukaryotic cells, regulatory RNAs ensure that messenger RNA molecules are specifically degraded when they are no longer needed for protein synthesis. This degradation starts precisely when the messenger RNA is recognised and bound by the regulatory RNA. Again in cooperation with partners from Bonn, the Photobiochemistry research group recently succeeded in specifically controlling this mechanism with light. The function of the light switch is again performed by the LOV receptor PAL, which binds adapted regulatory RNAs under blue light and thus inhibits their function.

This now offers the possibility of either preventing or initiating the degradation of messenger RNAs by a molecular light switch. This is because the PAL receptor opens its pocket under blue light and thus captures the regulatory RNA. In turn, this RNA can no longer fulfil its function, the messenger RNAs are not recognised and thus remain intact. However, if the blue light is switched off, PAL falls back into its original structure and releases the captured regulatory RNA. Now the destruction of the messenger RNAs can begin. This mechanism will help researchers gain new insights into where and when a protein is needed in a cell. The light switch has already been successfully tested on proteins that play an important role in the regulation of the cell cycle and cell division. This opens up new opportunities for research into dynamic processes in living cells and organisms. A particular strength of this opto-

RECOMMENDED READING

D. Golonka et al.: Deconstructing and repurposing the light-regulated interplay between *Arabidopsis* phytochromes and interacting factors. *Communications Biology* (2019), 2. DOI: 10.1038/s42003-019-0687-9.

A. Weber et al.: A blue light receptor that mediates RNA binding and translational regulation. *Nature Chemical Biology* (2019), 15, 1085–1092. DOI: 10.1038/s41589-019-0346-y.

S. Pilsl et al.: Optoribogenetic control of regulatory RNA molecules, *Nature Communications* (2020), 11, DOI: 10.1038/s41467-020-18673-5.

E. Multamäki et al.: Illuminating a Phytochrome Paradigm – a Light-Activated Phosphatase in Two-Component Signaling Uncovered, *bioRxiv* (2020), DOI:10.1101/2020.06.26.173310.

AUTHOR



■ Prof. Dr. Andreas Möglich is the Chair of Biochemistry II - Photobiochemistry at the University of Bayreuth.

ribogenetic approach is its versatility, which allows easy adaptation to almost any regulatory RNA.

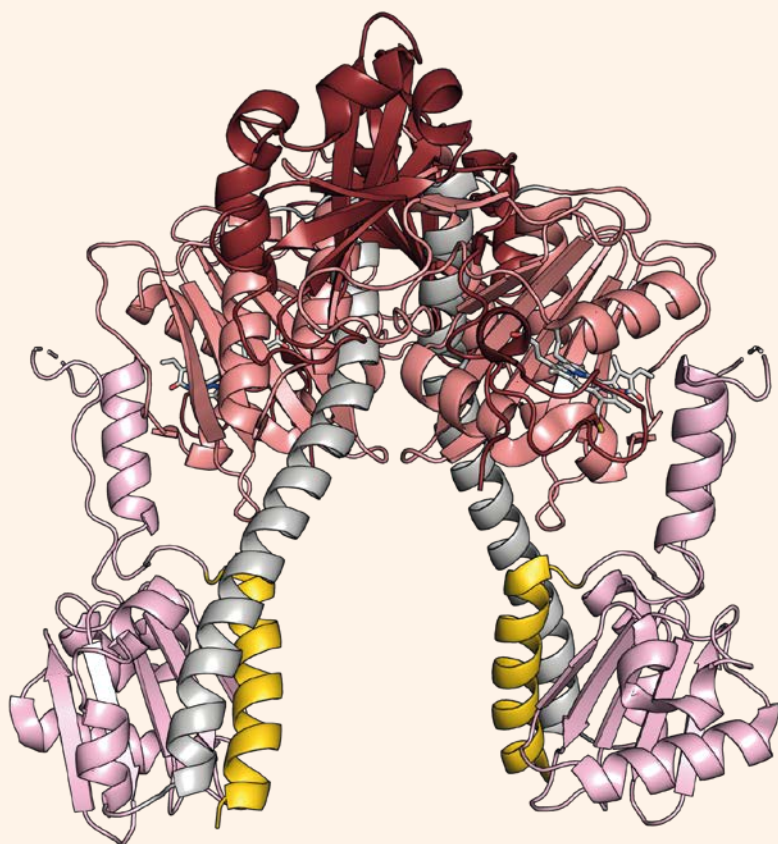
From basic research to possible therapies for neurodegenerative diseases

A central leitmotif of research in Prof. Dr. Andreas Möglich's working group is the combination of basic research and biotechnological application. It is particularly evident in the context of cooperation with working groups from Helsinki and Jyväskylä, which is concerned with the investigation of a bacterial phytochrome. In work about to be published, funded by the Humboldt Centre of the University of Bayreuth, among other institutions, the precise characterisation of the phytochrome, still unknown for more than 20 years ago, was finally achieved and a long-standing conundrum thereby resolved. These

findings are indirectly suitable for the construction of novel light-regulated tools for biotechnology.

Another example is the European joint project NEUROPA, which has kicked off at the beginning of 2020. The Bayreuth research team is playing a major role in this project, as part of which bacterial phytochromes are to be specifically activated by laser radiation to be able to gain insights into neurodegenerative diseases. To this end, the research groups involved in NEUROPA aim to develop novel phytochrome photoreceptors and to introduce them into the cells in the cerebral cortex that underlie the disease. Compact lasers with wavelengths in the micrometer range can then be used to activate the phytochromes through the skullcap and trigger downstream processes.

The multidisciplinary NEUROPA team brings together working groups from Bayreuth, Birmingham, Barcelona, Oulu, Paris, and Szeged. The European Union is funding the research work as an FET Open Project (Future and Emerging Technologies). With their expertise in optogenetics, photonics, and neurology, the research partners aim to develop gentle approaches to controlling nerve networks in the brain. Looking forward, these technologies could be used in the context of neurodegenerative diseases such as Alzheimer's or Huntington's disease, in order to better understand their molecular causes and to maybe treat them in the future.



■ Fig. 4: Example of a phytochrome photoreceptor (Illustration: Andreas Möglich).



■ Fig. 5: Stimulation of phytochromes by red light (Photo: Christian Wißler).

- 1 D. Golonka et al.: The Association Kinetics Encode the Light Dependence of Arabidopsis Phytochrome B Interactions. *Journal of Molecular Biology* (2020) DOI: 10.1016/j.jmb.2020.06.001. – D. Golonka et al. in *Communications Biology* (2019), see recommended reading.
- 2 A. Losi et al.: Blue-Light Receptors for Optogenetics, *Chemical Reviews* (2018), DOI:10.1021/acs.chemrev.8b00163.
- 3 This has already been demonstrated in previously published and ongoing work. Cf. inter alia A. Weber et al. in *Nature Chemical Biology* (2019), see recommended reading.

From vision to innovation: New EU project on artificial motor proteins

■ Birte Höcker

Motor proteins have vital functions in the cells of plants, animals, and humans. They are able to convert chemical energy into kinetic energy more efficiently than man-made combustion engines. They use this energy for their own movement within living cells, or for transporting molecular substances to their destination. Numerous biochemical and biophysical studies have already dealt with these processes, and yet their details are still largely unknown today. A new project, which aims to investigate the functioning of motor proteins, has recently been awarded an ERC Synergy Grant by the European Research Council. Over the next six years, Prof. Dr. Birte Höcker at the University of Bayreuth, Prof. Dr. Heiner Linke at the University of Lund, and Prof. Dr. Paul Curmi at the University of New South Wales will use the latest research technologies to make a fundamentally new attempt to achieve a precise scientific understanding of how motor proteins function. The combined expertise in the fields of structural and molecular biology, biochemical protein design, and single-molecule physics is of central importance in this endeavour.

The credo of US Nobel Prize winner Richard Feynman in physics will be decisive for the research work: "What I cannot create, I do not understand." The focus will therefore be on the construction of new molecular machines – using protein parts not found among other motor proteins. The design and testing of various modular blueprints is aimed at providing direct insights into how natural motor proteins function. The first step is the construction of a "clocked walker", a motor protein that – controlled from the outside – can move precisely in a defined direction. At the same time, however, the research team wants to go one step further. The common vision is the design and construction of an autonomous motor protein that is capable of independently controlling locomotion. This is a so-called "autonomous walker", which does not require constant control by external signals. If the construction of such a molecular robot were to succeed, it would be an outstanding success for synthetic biology and the still young discipline of nanoengineering. The project's short name "ArtMotor" ties in with this (currently still distant) goal. It stands for "Artificial Motor Proteins".

The results of this basic research are expected to provide starting points for far-reaching biotechnological innovations. In order to build an autonomous motor protein, it is necessary to understand and handle complex molecular processes, which in protein research are summarised under the term "allostery". If it is possible to systematically influence or even construct allosteric processes, some visions that still seem utopian today will be within reach – for example, high-performance computers based on biochemical processes or nano-machines that transport drugs specifically to their site of action.

RECOMMENDED READING

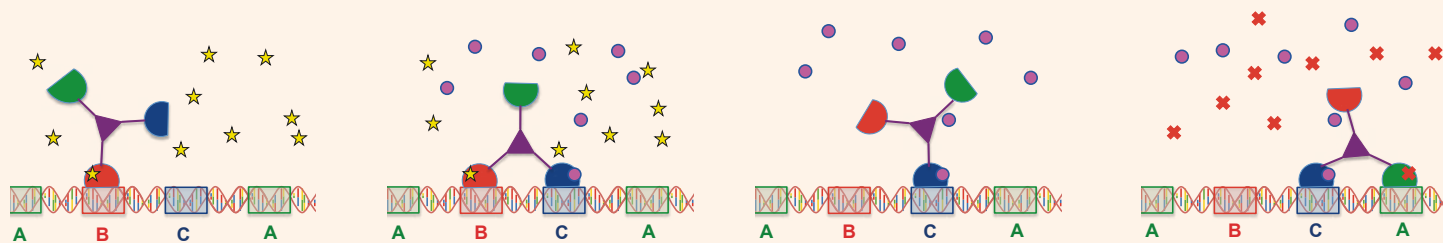
H. Linke, B. Höcker, K. Furuta, N.C. Forde, P.M.G. Curmi: Synthetic biology approaches to dissecting linear motor protein function: towards the design and synthesis of artificial autonomous protein walkers. *Biophysical reviews* (2020), 12, 1041-1054. DOI: 10.1007/s12551-020-00717-1.

AUTHOR



■ Prof. Dr. Birte Höcker is the Chair of Biochemistry III - Protein Design at the University of Bayreuth.

■ Fig. 1: Model of a "clocked walker"
(Source: H. Linke et al., see recommended reading).



Ancient poetic art, romantic poetry, typographic aesthetics

It was above all Herder and Goethe who, in the 18th century, aroused interest in the poetry of the Greek poet Pindar, who was born around 520 BC and was highly esteemed in antiquity. His odes exerted a particularly strong influence on the hymn poetry of Friedrich Hölderlin, who studied the Greek texts of the ancient model so intensively. These include nine fragments of Pindar, which Hölderlin translated in 1804 with the intention of faithfully reproducing the difficult, sometimes dark verses in word and syntax. He concluded each translation with a short interpretation into which he inserted his own poetic thoughts.

The translations inspired the artist Josua Reichart, who is internationally renowned for his typographic works, to create an unusual installation. On three display panels he superimposed Hölderlin's translations of three fragments with the lines of the Greek originals – similar to a palimpsest, except that here it is Pindar's historically older verses printed on the glass surface that form the colourful foreground. Since the year 2000, these panels have been in the foyer of the Faculty of Engineering at the University of Bayreuth.

Pindar
(ca. 520-445 BC)



VOM DELPHIN
DEN IN DES WELLENLOSEN MEERES TIEFE
VON FLÖTEN
**τον μεν ακυμονος
εν ποντου
πελαγει
αυλων
εκυησαν
ερατον μελος**
BEWEGT HAT LIEBENSWÜRDIG
DER GESANG
Der Gesang der Natur, in der Witterung der Musen,
wenn über Blüten die Wolken, wie Floken,
hängen und über dem Schnees von goldenen Blumen.
Um diese Zeit geht jedes Wesen seinen Ton in seine Treue, so wie eines
in sich selbst zusammenhängt. Nur der Unterschied der Arten macht dann
die Trennung in der Natur, daß also alles mehr Gesang und reine Stimme ist,
als Accent des Bedürfnisses oder auf der anderen Seite Sprache. Es ist das
wellenlose Meer, wo der bewegliche Fisch die Pfeife der Tritonen, das Echo
des Wachstums in den waichen Pflanzen des Wassers fühlt.
PINDAR
HÖLDERLIN

Das Unendliche
**ποτερον δικας τειχος
υψον η οκολιας
οπισθεν αναβας
το εμαινον ουτω
περιφραζας
διαβιω
διχα μοι
νοος ατρεκειαν
ειπειν**
Ob ich des Rechtes Mauer
Die Höhe oder Kränze der
Ersteig' und so mich selbst
Und hinter mich als
Mich lebe, darüber
Ob ich nicht die Mühe der
Gemüth, genau es zu sagen.
sollte ihn
nicht größer werden, als Schwanken und des
Sich zwischen Rechts und Klugheit hier sich
den Zusammenhang aufzulöse, der nicht ihnen selbst,
sondern auch drittes in sich selbst werden muß,
wodurch die drittes in sich selbst zusammenhängen,
darum hab ich ein zweideutig Gemüth.
PINDAR
HÖLDERLIN

das alter
**ος αν δικαιως και οσιως
τον βιον διαγαγη
γλυκεια οι καρδιαν
ατιταλλοισα
γηροτροφος
ξυναορει ελπις
α μαλιστα θνατων
πολυστροφον
γνωμαν
κυβερνα**
wer recht und heilig
das leben zubringt,
süß ihm das herz ernährend,
lang leben machend,
begleitet die hoffnung, die
am meisten sterblichen
die vielgewandte meinung regieret.
PINDAR
HÖLDERLIN

Eines der schönsten Bilder des Lebens, wie schuldlose Sitze das lebendige Herz erhält,
woraus die Hoffnung kommt; die der Einfalt dann auch eine Blüthe giebt, mit ihren
mannigfaltigen Versuchen und den Sinn gewandt und so lang Leben macht, mit
ihrer eilenden Weite.

Friedrich Hölderlin
(1770-1843)

