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INNOVATIONS FROM NATURE

NEXT GENERATION BIOPRODUCTION

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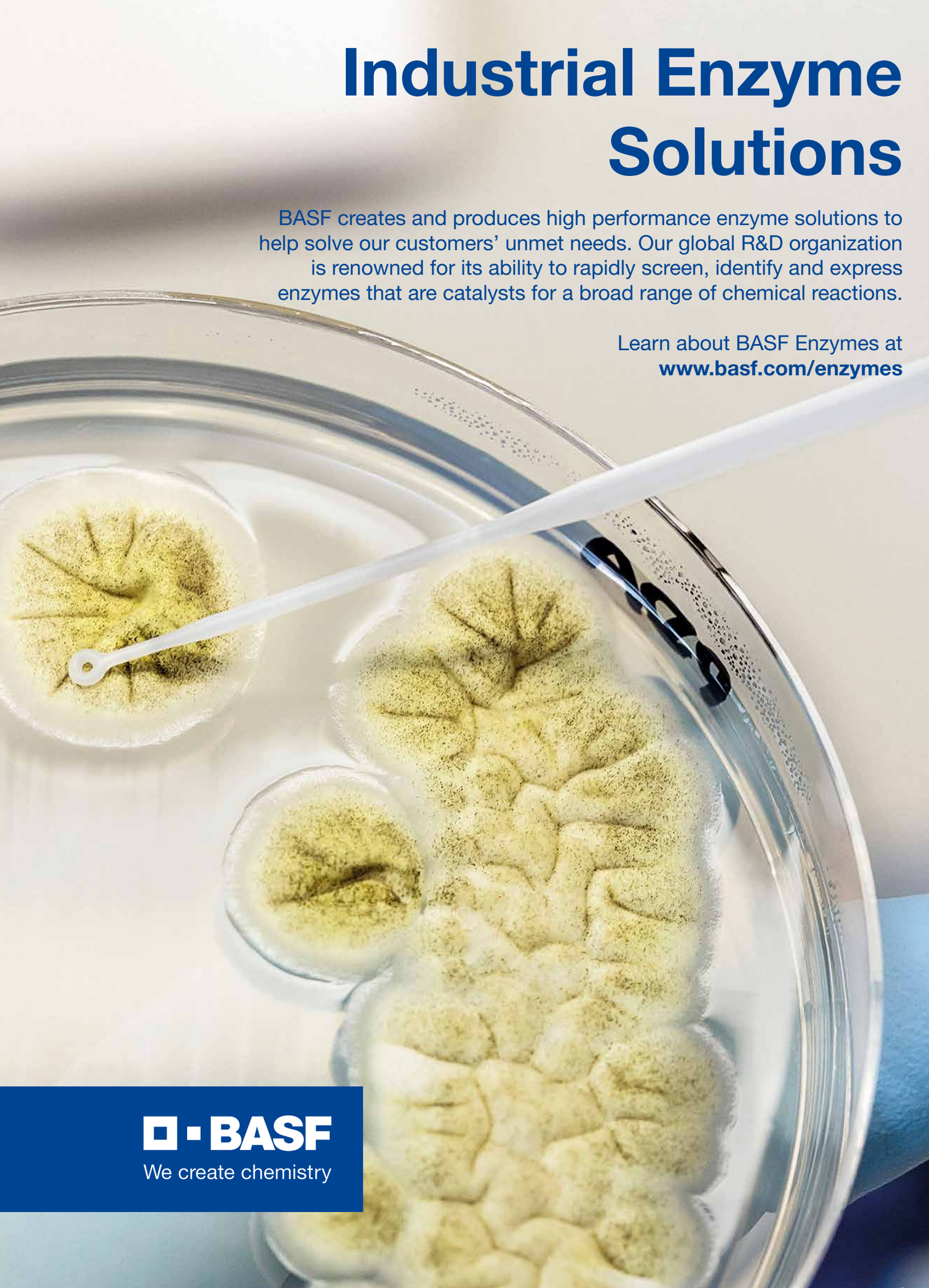

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Next Generation Bioproduction

Climate change, dwindling resources, pollution of our environment, food security, pandemics – we are facing many challenges that need rapid solutions. Industrial Biotechnology with its modern tools and processes in the field of Next Generation Bioproduction will play a key role for a successful bioeconomy and efficient bioproduction. Therefore, acib and its network bundle their competences and know-how – to enable scientific results and provide technologies that will allow a safe, healthy and bright tomorrow.

We are living in a time, where threats such as pandemics, the climate crisis and the increasing pollution of our environment are the major challenges that we and generations to come are facing. To ensure that temperatures aren't increasing further, the global economy has to undergo a rapid change from relying on fossil energy sources to renewable solutions. Methane and CO_2 emissions have to be reduced. Ecosystems must be preserved and better protected. And last but not least, it is important to reassess consumer behavior as well as whole food chains.

How are we going to meet these manifold challenges? Industrial Biotechnology is one of the most promising approaches when it comes to a transition towards a healthy planet and sustainable bioeconomy – by producing and using biological resources, by creating valuable products in the food and feed areas and by resorting to bio-based chemicals and materials and bioenergy. With its numerous modern tools and processes Industrial Biotechnology is indispensable for the further development and success of bioeconomy as a whole and is going to play a key role in efficient bioproduction. For this, it has to undergo a transformation itself, to enable promising scientific results and provide technologies that benefit us all.

Therefore, the Austrian Centre of Industrial Biotechnology (acib) bundles its competences and know-how in the field of Next Generation Bioproduction.

The goal: Enabling a paradigm change towards the application of synthetic biology by integrating various engineering disciplines and concepts of modularization and digitalization applied at all stages of bioprocess design and development.

Our comprehensive research activities create the basis to address urgent needs of the biotech industries to promote growth and sustainable developments in the markets of tomorrow. On the one hand, flexible process technologies enable our international network of scientific and industrial partners to establish better predictable process developments and faster times to market. On the other hand, new markets and market opportunities will emerge, creating and providing new applications and services that will allow a safe, healthy and bright tomorrow.

During the past years we have developed a comprehensive scientific portfolio together with our 200 international partners, from science, industry and and spin-offs within the acib network. To give you an overview of a selection of topics we proudly present the second edition of our Biotech Success Stories under the common thread "Next Generation Bioproduction".

acib – Innovations from Nature

The Austrian Centre of Industrial Biotechnology (acib) is an internationally active biotech research institution with the vision to replace traditional industrial technologies with new economically beneficial and ecologically friendly methods. Thus, products can be developed, which are based on natural processes and using tools from nature. acib combines the expertise of 150+ highly qualified employees from all fields of industrial biotechnology, with the know-how of our international scientific partners to meet the needs of biotech, pharma and chemical companies worldwide.

acib is jointly owned by the University of Natural Resources and Life Sciences, Vienna, the Graz University of Technology, the Universities of Innsbruck and Graz and JOANNEUM Research. As a non-profit organisation according to EU-definition acib is based on public and private funding for research. acib has been founded as a competence centre in the framework of the COMET program and is funded by BMVIT, BMDW, SFG, Standortagentur Tirol, Government of Lower Austria und Vienna Business Agency. The COMET-Funding Program is managed by the Austrian Research Promotion Agency FFG.

With more than 25 years of experience in biotechnology, acib is the perfect research partner for improving industrial production methods. As an excellent hub, we bridge the gap between academia and industry by translating academic knowledge into new industrial applications and products with higher values, lower costs and an optimized environmental balance. It is our mission to provide solutions for pressing future topics such as climate change, pharma, health and life sciences, waste management, recycling and renewable resources, the development of bio-based materials and energy sources and providing nutrition and feed technologies. Innovations, that benefit us all.

We are highly grateful to all partners who allowed us to create this brochure.

picture by comfreak (pixabay)

Key for citric acid production discovered

acib researchers found the responsible transport gene that allows the production of citric acid in large quantities. A milestone!

Citric acid is – in terms of quantity – the most important microbially produced natural substance in the world with an industrial production capacity of approx. 2 million tons per year. A number of everyday products would be inconceivable without this versatile acid: It is used to acidify and conserve foods such as marmalades and desserts, as well as in cosmetics, cleaning agents, detergents and life-saving medicines. The growing demand for citric acid causes production volumes to rise by three to four percent a year. For the industry it is a challenge to ensure ever higher product yields with consistently high quality.

HUNDRED YEARS OF PROCESS – COMPREHENDED FOR THE FIRST TIME

"Whereas until the beginning of the 20th century citric acid had been produced from lemons, for more than a hundred years the filamentous fungus *Aspergillus niger* has been regarded as an industrial fermentation vehicle for citric acid and fulfils this task very efficiently", says acib researcher Matthias Steiger. To this day, however, research has puzzled about how the process works in molecular biological detail – and how it can be optimized. Together with a research team from acib and BOKU Vienna, Steiger found a new transporter that for the first time revealed to biotechnologists which protein enables the fungus to release citric acid from the cell. This mechanism is the basis for producing citric acid in large quantities. The research results have been published in the renowned journal "Metabolic Engineering".

PRODUCTION OF CITRIC ACID IN DETAIL

Steiger explains the production process: "Today so-called 'submerse processes' are used in the biotechnological production of citric acid. The fungus Aspergillus niger is cultivated in closed bioreactors to produce the substance as requested in a nutrient solution containing sugar. In order to make the fungal cells produce citric acid in large quantities, or in other words to over-produce it, the acid must be transported out of the cell. The gene which encodes this transport protein has now been discovered: "This protein has the ability to secrete the citric acid produced in the cell via the plasma membrane. We were able to show that we could start or stop the production of citric acid by switching the gene on or off. This transport mechanism is the key building block for understanding the metabolic pathway that takes place in the organism", says Steiger. After further purification processes, the acid is available to industry as a raw material.

BETTER MARKET PRICES FOR FINAL CUSTOMERS

The better understanding of this process means improved stability for production conditions and a fivefold production yield compared to production with wild strains, which corresponds to approx. 100 g citric acid per litre. According to the statements of the researchers, these insights give manufacturing industry a significant edge in the future. acib key researcher and BOKU-scientist Michael Sauer comments: "By better understanding the individual process steps and process conditions, we hope not only to increase production but also to make it more robust. This, so the prognosis, could set new yardsticks in the quality of products and lead to price advantages for final consumers.

Continuous production of Virus-like particles

There are a multitude of challenges associated with the production of next-generation biopharmaceuticals and vaccines. The Austrian Centre of Industrial Biotechnology (acib) and partners developed a new platform that promises faster, more economic and safer production of modern pharmaceuticals – from gene therapies for neurodegenerative disorders such as Parkinson's or Alzheimer's, to cancer therapy and modern preventive vaccines against influenza, HIV, dengue, zika or in the future even the Coronavirus.

Modern biopharmaceuticals are often based on the mass production of designer proteins, such as virus-like particles (VLP) for gene therapy or for the development of vaccines, to support the organism in producing antibodies against various pathogens. Imagine the immune system as a memory match player busily identifying the surfaces of any virus that appears and developing resistances as soon as it gets into contact with the virus. VLP make use of this principle: they imitate the surface of the virus and feign an infection without damaging the body, because the dangerous genetic material inside the virus envelope that is responsible for infection, has been removed.

Since the surface proteins of VLP can be tailored to various applications, this technology is becoming ever more interesting for industry. However, the production of this specialized biomolecules calls for improved and above all, more robust production procedures.

CONVENTIONAL PRODUCTION PROCEDURES HAVE SIGNIFICANT DISADVANTAGES

For fifty years, vaccines have been produced by means of seed viruses. These are living pathogens that multiply in cells from chicken eggs. Seed viruses are used, for example, to produce approved influenza vaccines. The rule of thumb "one vaccine dose per egg" means that the number of vaccines is limited to 150 to 200 million available eggs worldwide. Formerly used alternative platforms – such as vaccine production in cultured cell lines of eukaryotic organisms such as yeasts and insects – have the disadvantage of instability.

NEW VIRUS-FREE INSECT CELL LINE

In a joint project, the Austrian Centre of Industrial Biotechnology (acib) and the Boyce Thompson Institute (BTI) at Cornell University investigated a platform technology for the optimised production of diverse proteins. "This has become possible thanks to a cell line developed by BTI that for the first time is free of a certain type of insect virus that has been an issue for these cells in the past", explains acib researcher and project manager Reingard Grabherr.

The process is tested on pilot-plant-scale by acib. Using a sophisticated fermentation process, the genetically optimised insect cell line is stimulated to grow and produce protein in a bioreactor, before the scientists introduce the genetic information for the generation of designer proteins, which are purified from the insect cells after several days of production.

"Through cooperation with acib, BTI researchers are able to observe the new cell lines under conditions that normally prevail in commercial production. Testing the new technology in these conditions is novel for the university environment", said Paul Debbie, Director of technology transfer and licensing at BTI, who is pleased about this opportunity. Remarking on the value of collaboration for scaling up, Debbie said, "acib's capabilities are far beyond anything that we have here at BTI where we are mainly working at laboratory scale".

MAJOR POTENTIAL FOR BIOPHARMACEUTICAL INDUSTRY

Researchers aim to prepare the pilot-production platform for industrial application, but to do so they must first carefully observe how the scaled-up process has affected the cell lines at a genetic level. “To achieve even higher process reliability and prevent losses, we carry out transcriptomics analyses and check how the 15,000 different genes of the cell behave”, Wolfgang Ernst, researcher at acib, explains. “As a new platform technology, the process entails great potential for the pharmaceutical industry”, Alois Jungbauer explains. He is area leader at acib and researcher at the BOKU and has already established contact to interested international companies.

A wide range of next-generation biopharmaceuticals could be produced with the new technology in a few years and in a much faster, simpler and safer manner. Improved production of VLPs and other designer proteins will open the doors to a promising future of gene therapies for neurodegenerative disorders including Parkinson’s or Alzheimer’s, cancer therapy, and long-awaited preventive vaccines.

Real-time Monitoring of Biopharmaceutical Production

While currently most production processes for biopharmaceuticals are assessed by laborious and time-consuming off-line analytics, the process development by acib-researchers enables the monitoring of such processes in real-time.

The share of marketed drugs that have been biotechnologically produced has nearly doubled in the last decade. These biopharmaceuticals include drugs for the treatment of diabetes or rheumatoid arthritis as well as vaccines and cancer therapeutics. Such biotechnological processes make it possible to produce therapeutics for the treatment of diseases that were considered incurable just a few years ago. Compared to the chemical synthesis of medical agents, biotechnological processes in living cells are much more flexible and are conducted under more gentle conditions. With annual worldwide sales of several billion euros, the biopharmaceutical industry is also an economically significant industry with important locations of international and national companies in Austria. Continuous production and quality control of manufacturing processes in real time have become state of the art in the automotive or food industries and have been shown to improve product quality and production efficiency. Although the competent drug regulatory authorities have been demanding the introduction of such real-time control in the pharmaceutical industry for years, these strategies have so far found little application.

SAVING TIME AND COST BY ALSO ENHANCING QUALITY STANDARDS

Biopharmaceuticals, which are mostly produced in bacteria or animal cells, are very challenging both in their structure and in the complexity of related impurities. The regulatory requirements for the purity of these products require multistage purification processes and a high degree of process understanding. Product quality is currently being reviewed through continuous sampling throughout the processes and subsequent analysis. As such quality controls are usually very time-consuming, the results are obtained hours or days after completion of individual process steps. This delayed analysis only allows a determination of the quality, but has no active impact on it. In collaboration with two international industry partners acib researchers have developed a system that enables the in-process control of complex purification processes of biopharmaceuticals in real time. While previous methods often only provided information about one quality characteristic of the product in the ongoing process, the newly developed method delivers information about the product quality and quantity as well as about present impurities in a matter of seconds. This is made possible by the combination of a panel of sensors and the development of mathematical models that correlate the measured signals with important quality criteria. The consortium also developed a user interface, which allows the monitoring of the system and the visual presentation of the collected data as well as a feedback of the system control information. After testing for three years, the system was put into operation at both companies. In addition, a patent was filed in Europe and the US.

A NEW ERA FOR MANUFACTURING PROCESSES IN INDUSTRIAL BIOTECHNOLOGY

The in-process control allows to detect product quality by knowledge-based process management. This significantly reduces the risk of batch failure, the overall process duration and the number of the necessary analyses. The processes become safer, faster and more efficient and thus save time and capacities for other products or additional batches of a product, thus eliminating product bottlenecks. This results in reduced manufacturing costs and saved resources, which in turn contributes to a cost reduction of these high-priced drugs. Technologically speaking, the use of in-process quality control in real time is the indispensable prerequisite for the establishment of continuous processes. From this point of view, the developed process makes our company partners fit for the next step, giving them a clear innovation advantage.


BEST COFFEE

Plastic bags that cannot breathe

Many bio-plastic bags have no place in the garbage. They dissolve too slowly in oxygen-deficient environments like biogas plants and when incinerated they are a burden to the environment. A research project at the Austrian Centre of Industrial Biotechnology (acib) hunts for enzymes, which accelerate degradation and avoid emissions. The aim is to reduce plastic mountains and replace conventional packaging by bio-based polymers.

Only very few know it and we all do it, but bio-plastic bags have no place in organic waste collection bins. According to DIN standard EN 13432 bio-degradability means that, after a fixed period of time, 90% of a material have degraded to water, CO_2 or biomass under defined temperature, oxygen and humidity conditions in the presence of bacteria or fungi. Lately, part of the bio-waste in plastic bags has been introduced into biogas plants where anaerobic conditions (oxygen-deprived environment) generate biogas as a valuable energy source. Under these circumstances bags from certain polymer types can only be degraded very slowly. The bio-waste cannot be set free and the process is disrupted. A team of acib scientists in Tulln addressed the question if the decomposition of plastic labelled as bio-degradable such as customary bio-waste plastic bags, food packages or mulch foils could perhaps also work in fermentation plants.

To address this topic, the scientists did some in silico research and screened thousands of entries in an enzyme database to identify those able to degrade plastic.

BOTOX IN WASTE

The bacterium *Clostridium botulinum* whose proteins are also present in Botox is present in small quantities in bio-sludge. In order to enable the enzymes of these, and other, bacteria to degrade plastic under anaerobic conditions in a large area, considerable engineering efforts are necessary.

In cooperation with ETH Zurich acib produced an optimised enzyme variant, which was introduced into a biogas testing plant. Up to this time there has been no information on how enzymes from this anaerobic microorganism work and so the scientists developed a method to measure the degradation process of polymers. The enzymes optimised in the lab scattered on the polymer layer and stimulated the degradation process.

They cut the long polymer chains in shorter and shorter pieces until only monomers, the smallest molecular parts, are left. These monomers are then metabolized by micro-organisms. Thus, the plastic bags can completely be degraded and converted to valuable biogas together with the bio-waste.

LONG TERM GOAL: PLASTIC-FREE PLANET

Since about 12% of the worldwide plastic waste (about 45 million tons per year) are incinerated, this new process could mean a turning point for the permanent degradation of plastic.

The new method is, however, only an intermediate step on the eco-sensitive route to a plastic-free life. As long as biologically degradable plastics cannot be recycled and reused properly the most reasonable solution is to gather them in biogas plants together with biogenic waste. Thus, the generated energy can at least be used for electricity, heating or bio-methane. In the long run the project results are expected to replace conventional packaging by bio-based polymers, which degrade within some days.

This would mean to close the carbon cycle and to avoid plastic waste.

Testing COVID-19 drugs

A collective research project between acib, the biotech company Innophore and the Medical University of Graz focuses on the identification, evaluation and pre-clinical testing of medical compounds in a high safety laboratory to fight COVID-19.

A collaborative acib-research project focuses on the identification, evaluation and pre-clinical testing of a certain group of active ingredients, combining faster availability with high effectiveness. These so-called antiviral drugs have been used in the fights against many viruses e.g. HIV, MERS and SARS. They can inhibit the multiplication rates of enzymes or prevent virus particles from invading cells and consequently avert possible infections. This makes them effective tools against COVID-19.

FASTER PATIENT TREATMENT DUE TO DRUGS ALREADY AVAILABLE ON THE MARKET

Many of these antiviral drugs are already available on the market, approved for other purposes. This makes it easier to repurpose them for a variety of applications, for example the treatment of COVID-19 patients. However, first these substances have to be identified as potentially effective. Therefore, the Graz-based Biotech company Innophore has been screening more than two billion active substances that might be active against COVID-19. In a next stage the most promising candidates are tested in a BSL-3 laboratory at Medical University Graz providing the highest available safety standards in Austria. There, these substances are optimised for further use and tested in-vitro in order to clarify their suitability for potential clinical trials.

SAFE ENVIRONMENT FOR HIGHLY INFECTIOUS VIRUSES

The in-vitro tests at Medical University Graz comprise three steps: First, toxicity tests are being conducted to eliminate potential cell damage and to determine the right substance concentration. For this, OC-43 isolates from the Charité Berlin as well as COVID-19 virus strains from 17 Styrian patients containing different virus variants were cultivated.

Different chemical compounds are tested to investigate the disruption of the SARS-CoV-2 replication. Among these compounds are inhibitors for replication enzymes as well as inhibitors, which can block essential viral transferases. For this, the virus will first be introduced into cell systems of Vero cells, derived from apes, and subsequently reproduced. In a next step, scientists infect the cells – with and without adding the drug in different concentrations. The infection process is monitored by different assays and quantitative polymerase chain reaction (PCR) to determining the titre of the virus and to learn if the drug can successfully be used to prevent virus replication.

CELL CULTURE MODELS REDUCE ANIMAL TESTING

In the second phase, the scientists precisely monitor and study the absorption rates, effects and possible side effects of the drugs outside the human body using so called human organoids. These cell groups, grown in the laboratory, mimic the structures and characteristics of the human body. The more information can be gathered in these petri dishes about how substances might work in the human body, the less animal testing is needed, shortening drug development time significantly.

DEVELOPING NEW CLASSES OF DRUGS

In the last phase, the scientists test the suitability of different drugs for clinical use, mainly focusing on the pre-clinical phase. The more extensive and promising the data, the higher the possibility that the industry will further investigate and develop these drugs for their use in humans. We still don’t know when it will be possible to develop a suitable drug but in the end a combination of various different concepts ensures better treatment of COVID-19.


Coronavirus : Covid-19
VACCINE

Faster research against COVID-19

Together with the University of Innsbruck and BOKU Vienna, scientists from acib developed a revolutionary platform technology for the pharma industry, enabling a faster search and production of potential SARS-CoV-2 drugs in large quantities as well as providing efficient antibody tests.

Since the virus is constantly evolving, when a promising vaccine or drug is found new detection and screening methods have to be developed in order to indicate which drugs are effective against the virus and which are not. These developments will be important for the treatment of other viruses as well.

Together with Austrian universities and industrial partners scientists from the Austrian Centre of Industrial Biotechnology (acib) developed a crucial and highly innovative high-speed technology in the fight against Covid-19: “Our platform technology BOSS (Biotechnological Optimizations by Selection Systems) enables us to link the survival of bacterial cultures in the laboratory with the presence of certain anti-viral compounds, so that due to their rapid growth we are able to identify new, potential drugs out of millions of variants without much effort – and this overnight”, explains project leader Rainer Schneider, Key-Researcher at acib and professor at the Institute of Biochemistry at the University of Innsbruck.

Next to the detection of new, potential drugs and the prediction of their effects and activity in the use with new viruses, BOSS as a platform for different processes could allow the industry to establish faster and optimised procedures for producing a variety of biopharmaceuticals such as antibodies or vaccines, insulin and interferon or tumour therapy drugs.

THE SARS-COV-2-VIRUS SWITCH – FROM ON TO OFF

In order to reprogram the bacteria, the scientists used a certain strategy: “We linked the bacterial growth to the protein that the virus needs for its reproduction. Within the SARS-CoV-2 virus, the protein called Mpro-Protease is our target, the Achilles’ heel so to speak”, says Schneider. Proteases are control modules. Similar to tiny molecular scissors, they cut the long sequences of long-chained amino acids that consititute the building plan of proteins. The position of the cut determines the particular function or activity of the macromolecule. In the human body, these activities control the metabolism or digestive functions; for a Coronavirus they are the key to its reproduction.

“The trick of the BOSS technology is to modify an essential growth protein of bacteria so that it can be detected by the virus protease and in a next step cut it and destroy it. After that, the bacteria will no longer be able to reproduce unless they are treated with a substance, a drug, that inhibits the activity of the protease. Now it is possible to identify and select in a very short time a variety of substances which possess the desired properties and are potential weapons against SARS-CoV-2”, Schneider explains how the BOSS technology works. BOSS, so the scientists agree, could accelerate drug-based solutions in different fields of industrial biotechnology against the fight of Covid-19 and hopefully could help to save lives.

When biotechnologists follow their noses

It is grey, waxy, smelly and very expensive: Ambra, one of the world's rarest organic substance, could only be found in the digestive tract of sperm whales. The compound is highly sought after by the perfume industry due to its fragrance fixative properties and distinctive aroma. Biotechnologists found a new biosynthetic pathway to produce the precursor of Ambra, named Ambrein, exactly as it occurs in nature. The findings could revolutionize the perfume industry by making different products eco-friendly.

Ambra is considered as one of the rarest, most expensive natural aromatic substances in the world. Depending on its quality, one kilo could cost up to 55,000 dollars. Due to its quality as a fixative, enabling scents to last much longer, it is highly sought after by the perfume industry.

As a main resource of Ambra serves Ambrein, a triterpen alcohol which is formed in the digestive tract of less than five percent of sperm whales. This mostly solid, waxy substance of dull grey or blackish colour is known to get to the surface of the oceans by vomiting, where it can drift for many years before it is washed onto the shore. By contact with saltwater, air and sunlight and through oxidation, the odorous substances Ambrox and Ambrinol are produced, which are responsible for the well-balanced, earthy and rich aroma.

As a result of the natural limitation of Ambra, the high industrial demand as well as the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), prohibiting the trade with endangered species and sperm whale product, Ambra nowadays is chemically synthesized.

CHEMICAL PATHWAYS EXPENSIVE AND NOT EFFICIENT

Most pathways of chemical synthesis use diterpenoids from plants as a starting material, e.g. Scareol from *S. sclarea,* also known as common clary. This method has some huge disadvantages: First, the correct synthesis of these complex molecules is very expensive and effortful. Many individual steps are necessary in order to achieve a yield of only about four percent. Moreover, most of these production steps require the controversial use of environmentally unfriendly toxic chemicals, high process temperatures and pressure. Besides, the synthetic scent lacks the complex and opulent fragrance mixture. As a result, different high-priced perfumes still contain various amounts of natural Ambra.

GREEN PERFUME INDUSTRY

A new biosynthetic pathway could turn these disadvantages to opportunities for environmentally friendly and cheaper products. The Austrian Centre of Industrial Biotechnology (acib) found a way to produce the natural precursor of Ambra, called Ambrein, with a new metabolic pathway in the yeast *Pichia pastoris*. This means that the scientists are able to display the whole fragrance spectrum of natural ambra in unprecedented quality, large quantities and for the first time. Compared to other enzymatical processes, a new optimised enzyme enables a seventhfold increase in yield, using a simple source of carbon such as glycerol or sugar.

The scientists are now focusing on bringing the patented innovation to industrial scale. The new production pathway has the potential to revolutionize the perfume industry, making it eco-friendly and green.

Precious sugars in breast milk

Breast milk contains the optimal mix of nutrients for a healthy development of the baby. Certain complex carbohydrates known as human milk oligosaccharides are among the most important contributors. The Institute of Biotechnology and Biochemical Engineering at the TU Graz is researching together with the Austrian Centre of Industrial Biotechnology (acib) how these might be produced industrially.

When it comes to the healthy development of a baby, breast milk and its ingredients are without rival. In addition to lipids, carbohydrates and proteins as genuine nutrients, it also contains countless immunological as well as prebiotically and probiotically active substances. These include large amounts of so-called human milk oligosaccharides (HMOs) So far, more than 200 different HMOs have been identified and are increasingly in the focus of science. This is because the results of clinical studies indicate that they are beneficial for human health in numerous ways. As prebiotics they support the development of the intestinal flora by feeding beneficial intestinal bacteria, stimulating their growth and increasing their activity.

Another advantage for the intestinal flora is the antibacterial effect of some HMOs. Their "docking points" are the same as those of the mucosal cells in the gastrointestinal tract where infectious bacteria attach in the first step towards infection. Bacteria entering the body are unable to distinguish between the docking points of HMOs and those of mucosal cells. Offering their docking points as a lure, HMOs proceed to capture the bacteria and ultimately excrete them. HMOs also enter the bloodstream and circulate in the body. It is assumed that this allows them to provide protection against infections in other parts of the body and the lung. Finally, certain HMOs are important building blocks for the neuronal development of the baby.

HMOS FOR BOTTLE-FED BABIES

In terms of concentration and sheer variety of HMOs, the milk of cows and other mammals cannot replace human breast milk. Although industrially manufactured baby food nowadays often contains plant-based oligosaccharides with a certain prebiotic effect, their structure and complexity differs considerably from that of the oligosaccharides in human breast milk. So how can we make sure that bottle-fed babies also benefit from the positive effect of HMOs? The reconstruction of HMOs by means of large-scale chemical synthesis was found to be both difficult and costly. Isolating HMOs from breast milk is not an option because of the limited availability of the resource for industrial volume production.

THE BIOTECHNOLOGICAL APPROACH

This is where biotechnology comes into play: Bernd Nidetzky and his team of researchers at the Institute of Biotechnology and Biochemical Engineering at TU Graz are searching for possibilities to synthesise human milk oligosaccharides in the laboratory by biotechnological means. In cooperation with the Austrian Centre of Industrial Biotechnology (acib) they focused on two groups of HMOs that occur in high concentration in human breast milk – fucosylated oligosaccharides and sialylated oligosaccharides.

Their aim is to find out how to produce a sufficient amount of the enzymes that catalyse the linking reaction between the individual oligosaccharide components (glycosyltransferases) with the aid of microorganisms, and how to effectively use them. "The good news is that all human milk oligosacharides are based on just five basic sugar building blocks that can be linked by enzymes to form complex structures", says Barbara Petschacher from Bernd Nidetzky's team who is investigating this particular subject.

The researchers at TU Graz and acib already reached a major milestone in the past. They succeeded in modifying an enzyme from the group of sialyltransferases so that it is able to produce two different HMOs. Both HMOs consist of sialic acid and lactose but these are linked at different molecule positions. "This is notable in that the enzyme is normally very specific. If unmodified, it will only connect the molecules in one way", explains Katharina Schmölzer from acib, the leading partner in this study.

The results of the research at TU Graz in cooperation with acib, supported by the Austrian Competence Centre Programme COMET, are not only significant for the production of baby food but also for the development of functional foods for older children and adults. As an example, synthetically produced HMOs could be used in therapeutic foodstuffs that support the treatment of severe diseases and reduce the infection risk with multi-resistant hospital germs.

Author: Ulrike Keller, TU Graz

Unlocking the full potential of Chinese Hamster Ovary (CHO) cells

Because CHO cells are the most popular vehicles for making valuable therapeutics, the genome scale data and predictive models developed within the Austrian Centre of Industrial Biotechnology (acib) enable the development of cheaper and more effective therapies.

Over the last years, the biologics market has been growing at an ever-increasing rate, with monoclonal antibodies emerging as the leading products. Today, CHO cells are by far the most important mammalian cell line used to produce more than 70% of therapeutic proteins currently on the market. They are thus an indispensable part of modern medicine, mainly because CHO cells are able to synthesize proteins with characteristics similar to those of humans.

INCREASING YIELDS AND RELIABILITY

After having contributed to the generation of a reference genome from the Chinese hamster and subsequently compared the genome of several CHO cell lines, the working group of Prof. Nicole Borth at the Austrian Centre of Industrial Biotechnology (acib) focused on an even deeper understanding of these cell lines. By studying the gene transcription dynamics, they discovered new levels of CHO cell regulation that are based on epigenetic changes. These epigenetic modifications control the expression of individual genes and provide cells with the ability to assume different behavioural patterns from the same genome sequence. In the hamster, this enables the development of, f.i., nerve or liver or skin cells, all containing the same genome but characterised by different gene expression patterns. In CHO cells, these epigenetic changes determine the precise phenotype and process behaviour of individual production clones. For example, the pattern of DNA-methylation around the transcription start site clearly indicates whether a certain gene is expressed or not and thus serve as an ON/OFF switch. Histone modifications on the other hand modulate the relative expression level of genes and thus help the cells in responding to changing substrate concentrations or culture conditions. In addition, long non-coding RNA (lncRNA) transcripts are expressed in large numbers, in fact more than protein-coding genes, and they also play an important role in regulation of expression. Together with acib's work on establishing full gene knock-out libraries using CRISPR, this detailed knowledge of how CHO cells really function is invaluable and can be used to engineer and select improved cell lines. "Now that we understand better how these cells work, we can adjust them to the desired requirements", explains Borth, thinking about faster development, higher yields and improved product quality.

BETTER AND AFFORDABLE PHARMACEUTICAL PRODUCTS

So far, a major problem in cell line development for production processes is the time required to identify cells that are able to produce the recombinant protein efficiently, with the required high quality and with high genomic stability of the cell line. By solving this challenge, acib considerably contributes to shortening the time until biotherapeutics hit the market, which is of tremendous value to the patients. And, most importantly, it "will lead to more efficient and cheaper production of therapeutic agents at prices that any average health system can afford", says Borth.

The future of Intelligent Process Sensors

It's been 16 years since the FDA first released its Process Analytical Technology (PAT) initiative. It calls for in-line process sensors that can move a measurement from manual sampling and laboratory instruments to automated control of critical process parameters.

Intelligent "Arc"-sensors from Hamilton talk directly to the PCS without a transmitter. They not only send a compensated measurement value used to control processes, but also send a host of diagnostic data that is automatically recorded on the sensor in tandem. This reduces effort and risk of error. Communication from Arc sensors was designed to be flexible enough to fit the needs of all users, so they can also be configured and monitored with PCs and mobile devices. The automatic GMP-conforming documentation maintains the history of each sensor so that operators can tell when it has been used, calibration errors or warnings, interface errors (e.g. out of span 4-20 mA signal), and hardware errors (e.g. glass impedance). The information may be used immediately, as in the case of a process deviation, or for a future decision, such as when to calibrate or replace the sensor.

Hamilton is continually working on ways to simplify PAT compliance, from introducing new measurement parameters to progressing data management. With more and more data available, a variety of new and retrospective analyses will be possible and could yield continuous improvement and new ideas for improving batch quality. Quality-by-Design is the ultimate goal of those in the biopharmaceutical industry looking to reach a level of the smart factory of the future. Hamilton's "Arc"-sensors enable the manufacturers to ensure a high quality, efficiency and yield already today.

www.hamiltoncompany.com/process-analytics

acib-services for sustainable success

The Austrian Centre of Industrial Biotechnology (acib) offers not only excellent scientific research or serves as a hub between science and industry: It is also strong in providing various services e.g. in business development, funding, scientific communication, technology scouting and Open Innovation. It is our approach to fulfil the needs of partners from different backgrounds of industrial biotechnology – by inspiring to new ideas, enabling close collaboration within manifold project-opportunities and offering tools and services for your sustainable success.

1. BUSINESS DEVELOPMENT AND FUNDING

acib can provide companies with a technological advantage over their competitors not only by targeted contract research, but also by partnering in international funding programmes. We have in the past participated in several successful European projects (from FP7 to H2020, but also BBI, IMI, ERA-NET, etc.) and have been valued as a very reliable and innovative partner.

ACIB SERVICES FOR INDUSTRY:

+ Contract research in all areas (from R&D to production and analysis)
+ Extensive literature studies and IP search
+ Technology scouting
+ Consulting for funded research
+ Professional project management for (funded) projects
+ Professional dissemination activities
+ Organization of events and conferences
+ Training courses (theoretical and 'hands-on')
+ Partner search
+ Looking for technologies
+ acib task force – solving problems for companies at their place
+ Flexible and tailored solutions for the industries needs

ACIB SERVICES FOR ACADEMIA:

+ Reliable and innovative partner in EU-projects
+ Taking care of the communication & dissemination work package in EU-projects
+ Partner in other (inter)national funding schemes
+ Using our large (industrial) network for finding additional project partners
+ Providing fee-for-services
+ Mutually beneficial media-sponsorships

BUSINESS DEVELOPMENT
Dr. Martin Trinker | acib GmbH
martin.trinker@acib.at

2. DISSEMINATION AND COMMUNICATION

Science communication to different audiences and stakeholders through a variety of communication channels is becoming more and more important. Efficient dissemination and communication measures are mandatory in the majority of funding programs in order to maximise the impact of a project. To manage the dissemination and communication tasks of EU-projects in a professional manner, acib offers different, targeted services.

OUR SERVICE

+ Concept development of tailor-made dissemination & communication work-packages for your research project
+ EU compatible plan for dissemination & exploitation of results (PEDR)
+ Visual identity (Corporate Design, Logo) to ensure sustainable positioning and high recognition of the project
+ Website (general project information, central platform for information)
+ Maintenance of Social media activities and eNewsletter
+ Videos, podcasts, blogs, newsfeeds
+ Webinars
+ Classic media activities and public relations (press releases, press conferences, journal articles)
+ Flyer and leaflets, factsheets, promotional material
+ Event organization, e.g. European Summit of Industrial Biotechnology (esib), Stakeholder Workshops, Training Workshops (Business courses, science communication, IP etc.)
+ Application for Awards and Prizes

DISSEMINATION/EU PROJECTS
Mag. Katrin Weinhandl | acib GmbH
katrin.weinhandl@acib.at

3. OPEN INNOVATION PLATFORM

The virtual Open Innovation Platform of acib enables interested people, companies and research institutions to participate in idea finding processes easily and independent from their location. This is a method to generate new ideas and offers the possibility to participate in Open Innovation projects in all areas of industrial biotechnology. All Open Innovation services are free of charge.

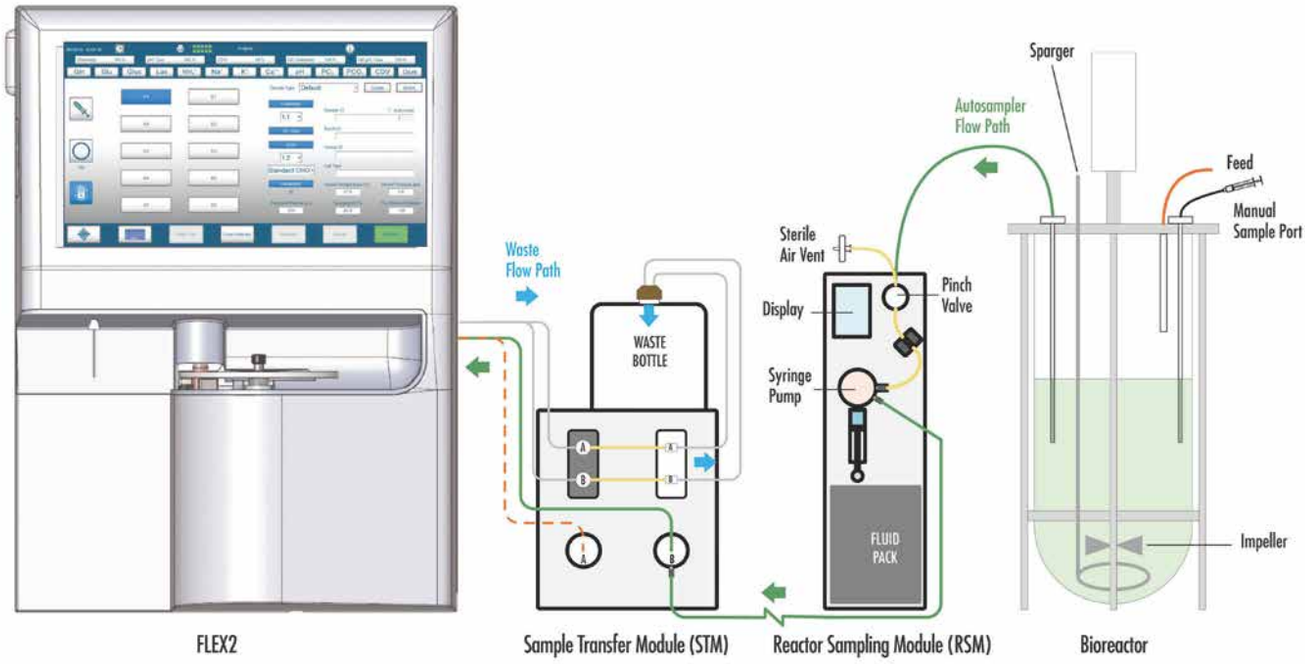
SERVICES OF THE OPEN INNOVATION PLATFORM

+ "Ask an Expert" is a low-threshold offer to ask questions related to biotechnology. The questions are directed by the business development team to scientists of the centre to be answered.
+ In the "Virtual Idea Lab", ideas can be discussed in the community in an open forum environment.
+ Co-Creation Centre
  When ideas start to become real projects, they can be further developed collaboratively in the Co-Creation Centre. Here, acib also offers information regarding biotechnology entrepreneurship and funding and founding of spin-offs.

OPEN INNOVATION
Dr. Matthias Slatner | acib GmbH
matthias.slatner@acib.at

acib says thank you

We want to thank all our scientific and company partners for collaborating and making this brochure possible. We are looking forward to create new ideas and work on innovative projects and solutions for a better future and – new success stories to tell.



BioProfile® FLEX2 (Nova Biomedical®) offers scale-independent automation capabilities from micro and mini bioreactor systems (like Sartorius ambr® 15/250) to large-scale production vessels.

acib funding

As a non-profit organisation according to EU-definition acib is based on public and private funding for research. The Austrian federal COMET-programme builds a sound basis for acib's activities. Additional funds are provided by FFG, EU and other funding organisations. Furthermore, acib relies on increasing shares of industrial funding – more than 50% of all activities are financed by industrial partners. Private donations and investments are welcome.

Further information about the COMET-programme: www.ffg.at/comet

acib owners

GRAZ UNIVERSITY OF TECHNOLOGY

Graz University of Technology was founded 1811 and pursues teaching and research in the fields of science and engineering. With 12,000+ students and 2,300+ employees she is a leading university regarding research agreements with business and industry from basic research to industrial implementation.
www.tugraz.at

UNIVERSITY OF GRAZ

At the University of Graz, which was founded in 1585, 4,000+ employees instruct 32,000+ students at 6 faculties and 76 institutes. The University of Graz regards itself as being a nationally and internationally sought-after partner for young scientists. Six Nobel laureates have taught and researched at the University of Graz.
www.uni-graz.at

UNIVERSITY OF NATURAL RESOURCES AND LIFE SCIENCES, VIENNA (BOKU)

The University of Natural Resources and Life Sciences, Vienna perceives itself as a teaching and research center for renewable resources, which are necessary for human life. The BOKU was founded in 1872 and educates 10,000+ students.
www.boku.ac.at

UNIVERSITY OF INNSBRUCK

The University of Innsbruck was founded in 1669 and actually comprises 28,000+ students and 4,500+ staff as well as faculty members. It offers a wide range of studies at 16 faculties; from natural sciences, humanities and social sciences to theology and technology.
www.uibk.ac.at

JOANNEUM RESEARCH

With a focus on applied research and technology development, the business oriented Joanneum Research plays for more than 30 years a key role as a technology provider in transfer of technology and know-how in Styria.
www.joanneum.at

acib partners

+ 3M
+ Aarhus University
+ AB Enzymes
+ AbBcn
+ ABM
+ ACSI
+ AENEAM
+ AGES
+ Albert-Ludwigs-Universität Freiburg
+ aliplast
+ Amsterdam University
+ ARIC
+ ASA Spezialenzyme
+ ASSO-BIO
+ Ava Biochem
+ AWI
+ Axiom
+ B. Braun Melsungen
+ BASF
+ Baxalta
+ bio-ferm
+ Biopox
+ Biotenzz
+ Biotrend
+ BIRCV
+ bisy
+ Bitop
+ Boku
+ Brain
+ CASCAT
+ CNA
+ CNR Italy
+ CNRS
+ COBIK
+ CSIC
+ DAM
+ darwin
+ Data How
+ DFK
+ DSM Food
+ DTU
+ ECOEMBES
+ Elicityl
+ EMBLEM
+ enGenes
+ EnginZyme
+ EQ
+ ETH Zürich
+ Evercyte
+ Evon
+ feyecon
+ Fraunhofer
+ FZ Jülich
+ G.L. Pharma
+ GALAB
+ GlycoDiag
+ Glycoselect
+ Greiner
+ HAW Hamburg
+ Heineken
+ Henkel
+ HFP
+ HHI
+ Humboldt Berlin
+ HWWI
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+ MMU
+ MUG
+ MUL
+ NanoMyp
+ nB nanoScale
+ Nordisk
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+ NP
+ NPZ
+ Organobalance
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+ University of Ljubljana
+ University of Minho
+ University of Pavia
+ University of Trieste
+ University Wien
+ University of Zaragoza
+ University Bremen
+ University Coll. Cork
+ University of Leicester
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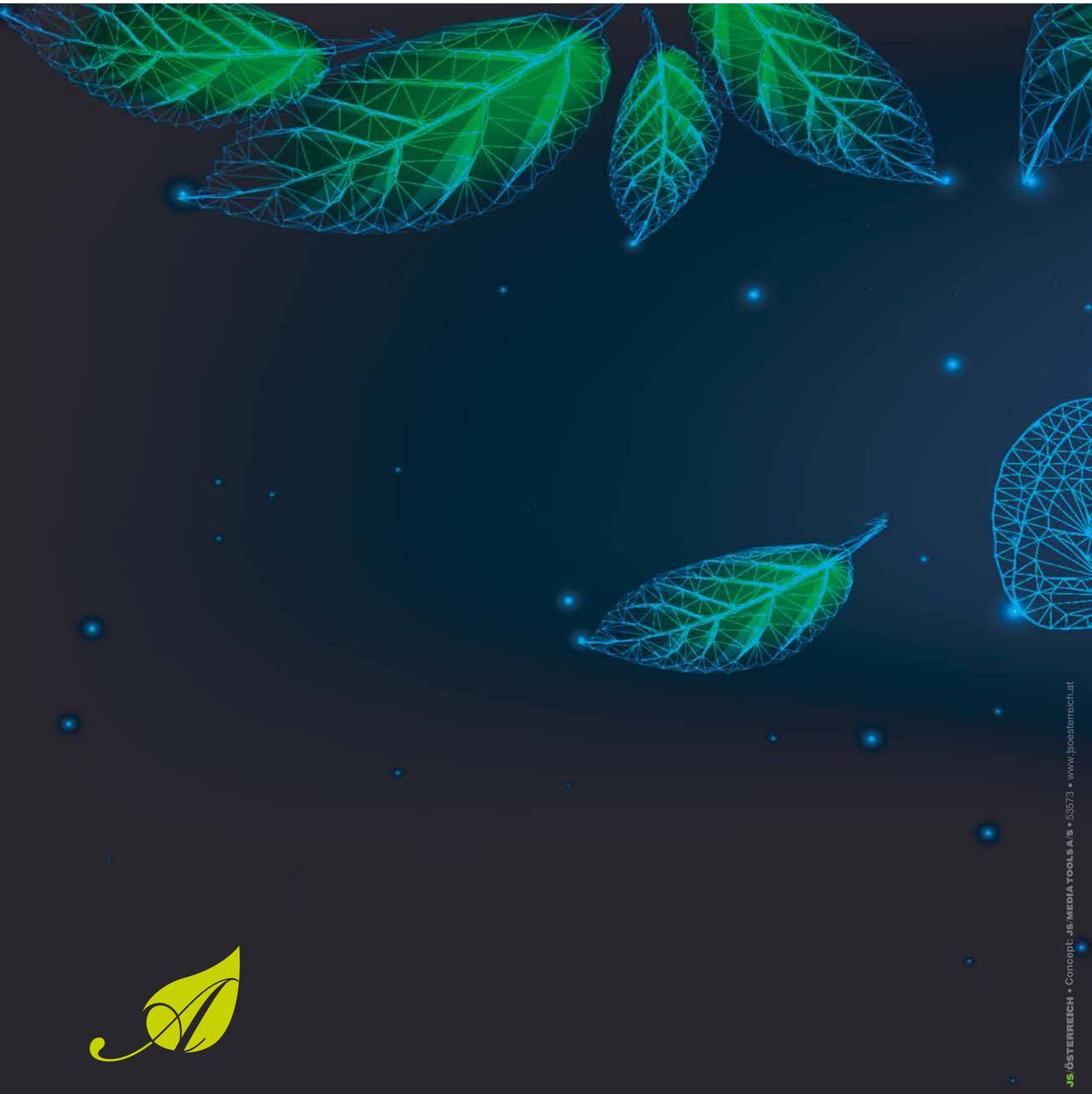
INNOVATIONS FROM NATURE



www.acib.at

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