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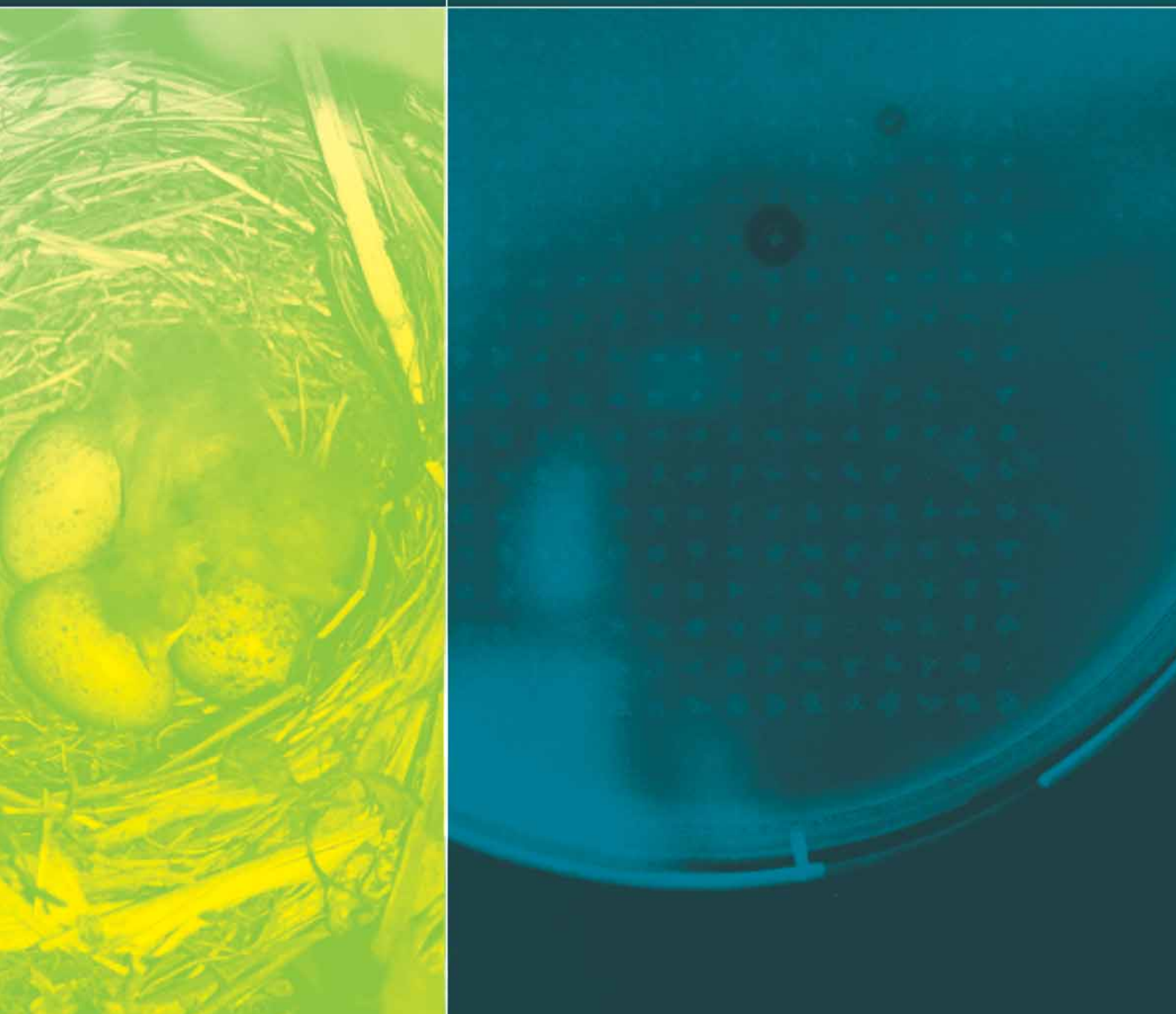

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Enzyme engineering

By enzyme engineering enzyme activity, stability and substrate specificity, and thus yields of industrial bioprocesses can be optimised – current limitations and outlook.

TEXT | ROLAND WEIS

Over millions of years nature has evolved a broad diversity of enzyme catalysts to guarantee the survival and reproduction of living organisms. However, natural evolution needs a far longer time to adapt enzymes to new challenges than a dynamic market situation demands. Enzyme engineering accelerates evolutionary events and can bring relief to existing bottlenecks in enzyme activity, stability and substrate specificity, thereby creating new useful catalysts which were not existing in nature before.

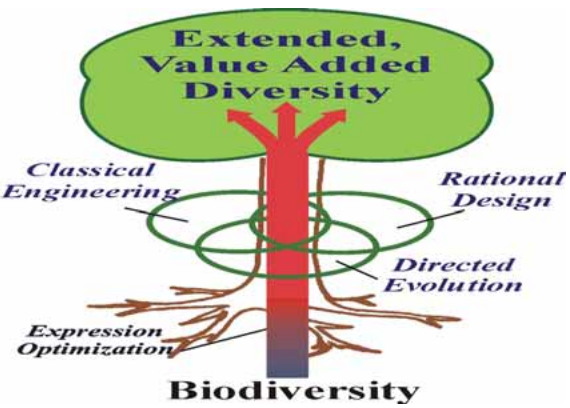

Figure 1: Nature provides a broad diversity of interesting enzymatic activities. Efficient enzyme expression is a prerequisite for the engineering to industrial catalysts.

Cloning the genes and recombinant enzyme expression is an indispensable step for intended biocatalytic applications on large scale and opens the way for cost-effective production. The availability of a gene allows for recombinant protein expression in suitable host organisms. Moreover, the gene at hand is a prerequisite for enzyme engineering on a molecular level, resulting in protein production in high yield and quality. Can engineered muteins have higher activity than natural enzymes with their most preferred substrates? Recent reports indicate that the climax of enzyme activity has by far not been reached by natural evolution yet[1]. Can enzymes only work under conditions which are found in the natural environment of the host organism? Engineering proved that proteins from e.g. extremophiles, that exist at extremely high or low temperatures, can be well active under reverted conditions, too[2].

There are many questions like these and in principle most goals can be reached by the two main strategies for enzyme engineering. Since *de novo* introduction of new enzymatic functions in existing scaffolds was rarely resulting in efficient enzymes, it is generally accepted that biodiversity offers a good starting point for enzyme development and discovery. If at least some enzymatic activity is present, structure-guided design and directed evolution can be regarded as powerful strategies to improve enzyme fitness and enzymes which can be readily expressed in *E. coli* can be trimmed to surprising technological fitness. However, both approaches are finally depending on powerful expression of the improved mutein. Limitations in protein production belong to the main reasons why successful examples of difficult-to-express muteins such as enzymes from Archeae, Actinomycetes and eukaryotic organisms are rarely reported.

Remedies for limitations

Several companies try to escape from this dead end road by establishing several expression platforms for bacterial enzyme discovery and engineering. This allows efficient enzyme discovery even from uncultured organisms. In the Research Centre Applied Biocatalysis in Graz, the enzyme production host *Pichia pastoris* is also employed for direct enzyme engineering and screening. This provides an optimal platform for the development of engineered eukaryotic muteins, whose production can further be easily scaled up. Special cell growth and expression protocols have been established within the highly interdisciplinary strategic research program of the Research Centre[3]. Using 96-deep-well plates, uniform growth and expression as well as low standard deviations of the results from well to well were achieved by optimisation of the cell viability. Thus, protein engineering approaches for eukaryotic enzymes can be performed directly in the subsequent production host *P. pastoris*. Thereby enzyme development cycles are shortened and results are more reliable for industrial scale up.

Cloning and expression of almond HNL

The recently published cloning,

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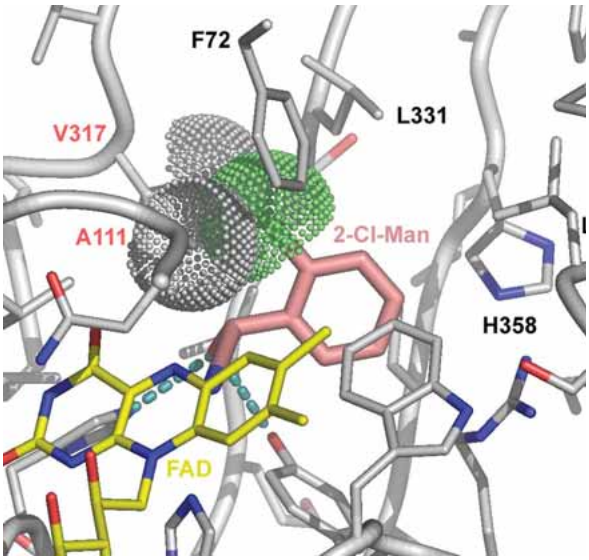

Figure 2: Substrate docking experiments with computer modelled enzyme structures give indications for possible steric clashes and guide mutagenesis experiments as shown for 2-chloromandelonitrile within the active site of hydroxynitrile lyase from Prunus amygdalus[5].

heterologous expression and comprehensive engineering of the hydroxynitrile lyase isoenzyme 5 from the almond tree (*Prunus amygdalus*) represents one of the few successfully performed developments of eukaryotic enzymes. This enzyme catalyses the (*R*)-selective addition of HCN to aldehydes and ketones resulting in enantiopure cyanohydrins. These can be further hydrolysed to alpha-hydroxy acids, which are important intermediates for the production of active pharmaceutical and agricultural compounds. The coding gene sequence was gained by PCR-splicing of genomic almond DNA and reclone for expression in *P. pastoris*[4].

Comprehensive enzyme engineering

The leader sequence for secretion was changed from the native plant signal to the alpha-mating factor signal sequence from baker´s yeast. Combining this signal sequence exchange with the stabilisation of the N-terminal region, a 4 to 4.5 fold increase in secretion efficiency was achieved, irrespective of the production scale (500 µl to 4000 l)[3]. Hence, the relative expression behaviour remained constant in all scales although important parameters as e.g. oxygen consumption rates or induction conditions were totally different.

Substrate-oriented protein engineering for enhanced turnover frequency was carried out for the difficult conversion of 2-chlorobenzaldehyde[5]. The investigation of the modeled enzyme structure after substrate docking into its active site revealed steric clashes between side-chains of active site residues and the big chloro-substituent of the substrate (See Figure 2). Consequently, a size reduction of the amino acid alanine 111 in the active site of the enzyme by mutagenesis to glycine facilitated binding of the substrate and led to a more than 6-fold increase in enzyme activity. The efficient combination of a target-oriented, fast and reliable protein engineering by structure-guided design for enhanced enzymatic activity on a specific substrate with expression engineering directly in the final production host resulted in an excellent new enzyme for industrial applications within a few months after defining the need for such a catalyst.

A further successful example for eukaryotic enzyme engineering was reported for the (S)-specific hydroxynitrile lyase from *Manihot esculenta*[6]. The active site of this enzyme seems to be accessible from the surface only through a short channel. This narrow channel is capped by a bulky tryptophan residue (W128), which limits the substrate transport efficiency to the enzyme's active site. Thus, low catalytic efficiency for the conversion of aldehydes with bulky substituents was observed. By replacing this tryptophan with smaller amino acids such as alanine or glycine, large substrates can enter and bind to the active center efficiently. This resulted in higher product yields within shorter time.

Outlook

Nature provides a vast diversity of proteins for biocatalysis. Depending mainly on smart enzyme analytics, these enzymes can be adapted to the challenges of industrial applications on non-natural substrates. By pulling enzyme development out of the context of natural evolution surprising enzyme features could be obtained. The tools to create these designed enzyme catalysts are available and simple to use. However, in many cases efficient enzyme production remains one of the bottlenecks and still much work has to be done to obtain a new and more efficient enzyme. Only interdisciplinary research teams are able to fulfil all the demands for enzyme developments from laboratory scale to applications on large scale and to create more than just «interesting» scientific reports.

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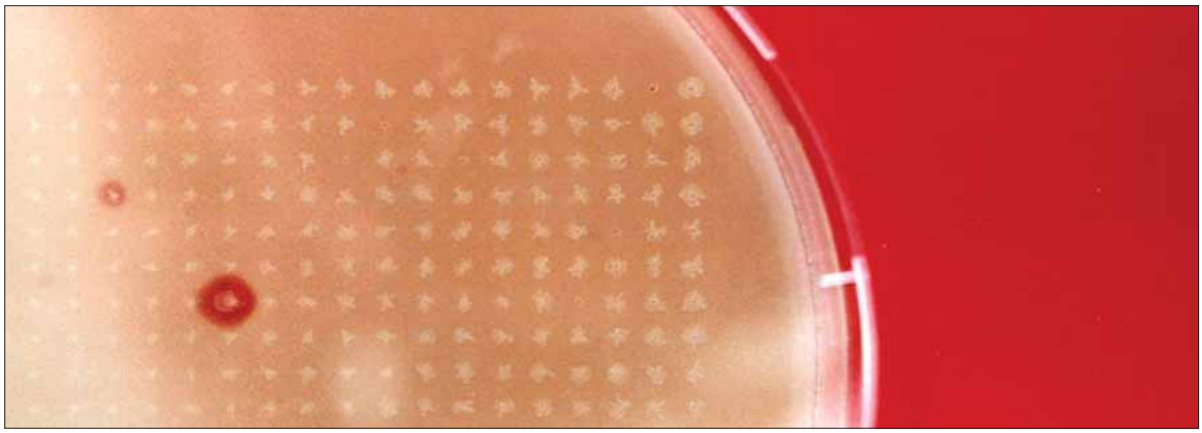

Figure 2: Expression screening of industrially relevant metagenomic enzymes (esterases) encoded on environmental DNA fragments cloned in *E. coli* . Halo formation indicates enzyme activity on tributyrin.

Metagenomic resources for novel enzyme templates

Metagenomics, the technologies involved in genetically accessing all microorganisms in a habitat irrespective of their cultivability or taxonomic affiliation, is becoming accepted as one of the single most important leaps forward in harnessing natural diversity for biotechnological application [1].

TEXT | PATRICK LORENZ, HOLGER ZINKE

These technologies were developed as it became clear that the overwhelming majority of bacteria and archaea, even from apparently ordinary sampling sites, resisted standard cultivation attempts. Indeed the direct extraction and sequence analysis particularly of 16S ribosomal DNA genes revealed that cultivated microbes typically accounted for no more than 1% of the species present. This meant that historically at least 99% of all microbial biodiversity had evaded scrutiny. It is this treasure trove of molecular diversity – enzymes, biocatalysts and bioactive small molecules – that microbes have to offer biotechnology.

The fundamentally different approaches to obtain natural biocatalysts, either from the relatively few cultivable microorganisms or from the metagenome by direct cloning are illustrated in Figure 1. Whereas cultivation often allows for the use of the native organism to produce an enzyme that optionally could also be expressed recombinantly, heterologous expression in surrogate hosts like *Escherichia coli*, *Streptomyces lividans* or *Bacillus subtilis* is mandatory with metagenomics, as the donor organism of any fragment of metagenomic DNA usually is unknown and uncultivable.

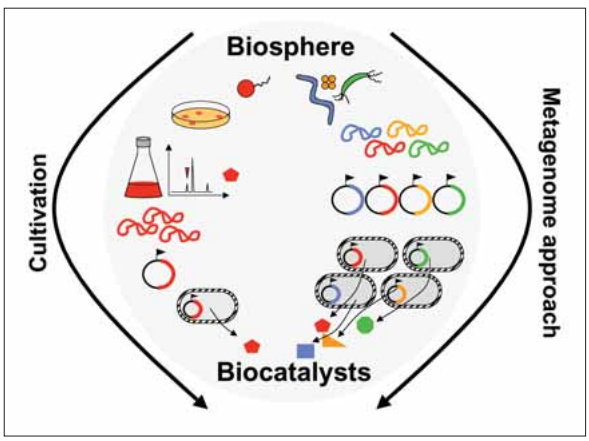

Figure 1: Conceptual difference between classical cultivation and the metagenome approach for the isolation and expression of microbial enzymes

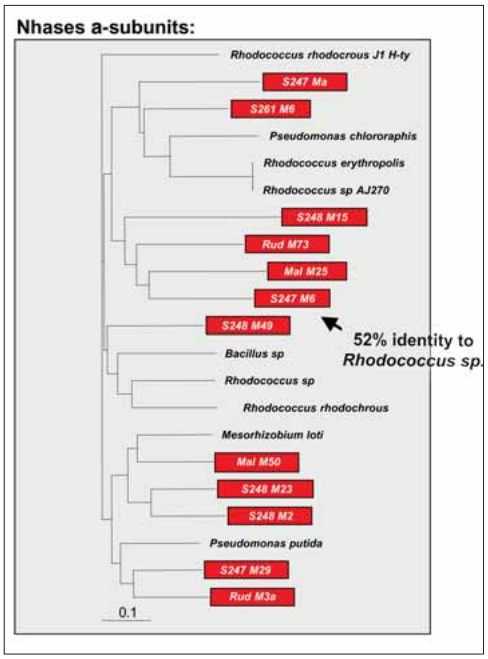

Figure 3: Tree representation of sequence diversity of novel metagenomic nitrile hydratase alpha-subunits (highlighted in red). The sequence space represented by known reference sequences of cultivated microorganisms (in plain) is substantially extended by metagenomic sequences. Scale bar: horizontal distance on tree representing 10% sequence dissimilarity)

Genomic DNA is directly isolated from an environmental sample, fragmented and ligated into appropriate genetic vectors like plasmids or cosmids. The resulting constructs are then transformed into the recipient host (e.g. *E. coli*) that transcribes and translates the metagenomic information into functional biocatalysts. This already points to one of the great challenges of putting metagenomic genes to work recombinantly in biotechnological applications: heterologous gene expression. Obviously from the wealth of molecular scaffolds extracted from nature, only those that can be expressed with the limited set of expression systems available, will be of utility. But the failure to express a certain metagenomic enzyme gene, sampled either randomly by expression screening (Figure 2), or identified and retrieved through its sequence similarity to a known active homologue, can be compensated for by the tremendous number of candidates available. And the dimensions involved here are really remarkable. It has been shown that an average sample of soil may contain several thousand different microbial species harbouring the corresponding complement (millions) of diverse genes. Over one million novel protein encoding genes were identified in DNA fragments cloned from samples prepared from bacterial microplancton of the mid-atlantic ocean [2]. What does the enzymatic diversity look like and can it be put to work? Published examples of collections of synthetically relevant metagenomic biocatalysts exist e.g. for nitrilases [3] converting nitriles to the corresponding carboxylic acids and nitrile hydratases (Nhases) [4] to produce the corresponding amides. Typically such metagenomic enzymes are very diverse and have sequences with limited homology to entries in gene databases like GenBank or Swissprot as illustrated for nitrile hydratases in Figure 3. In fact, sequence novelty is one of the key drivers for the interest in the metagenome approach in commercial applications as an important impediment for the implementation of enzymes in key processes may be conflicting sequence-based intellectual property (IP). Defining novel functional sequence space by tapping into metagenomic resources therefore may be an important way to tackle this issue.

Although the diversity of enzymes to be expected from uncultivated biodiversity is enormous, generally these enzymes will have gone through billions of years of biological evolution, i.e. mutation and selection for functionality to provide an advantage for the organisms that express them. Selective pressure will have been exerted along biophysical and biochemical parameters and through competing life-forms in the natural environment. It is not very likely therefore, although not impossible, that natural biocatalysts exist that perform perfectly well in harsh artificial environments very different from those that they were selected for in nature, like, for example, in some biochemical reactors. Here *in vitro* evolution technologies are valuable to adapt metagenomic enzyme templates and fine-tune enzyme properties to suit substrate/product-defined process conditions, leading to «ideal biocatalysts» [5].

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Dr. Patrick Lorenz (1962) is biologist and head of B.R.A.I.N.'s Enzyme Technology Unit

A Soup Kitchen during the General Miners Strike circa 1926, Walsall Wood, UK

Challenges in whole processed, batch-produced foods

Nowadays the food processing industry is faced with an ever-increasing demand for safe and minimally processed food with a high degree of wholesomeness and a fresh-like appearance. This has resulted in a number of challenges ranging from farm to fork in the food chain.

TEXT | **STANLEY BRUL**

Prof. Dr. Stanley Brul (1964) is a biochemist. He is Senior Scientist at the Department of Microbiological Control, Unilever Food Research Centre, and full professor of Molecular Biology and Microbial Food Safety at the Swammerdam Institute for Life Sciences

Evidently foods need to be fully safe for consumption and free of spoilage at all times during closed and open shelf-life. The main challenge for the food manufacturer is to come as fast as possible to the optimal balance between microbiological food stability and enhanced food quality through the use of fresh products and minimal processing techniques. Thus on the one hand new processing technologies have been and are being evaluated, the latest one being high-pressure processing at sub-zero temperatures for 'cold' pasteurisation purposes. On the other hand the rigour of defining process settings and operations in the supply chain is also being further strengthened. This is made possible for a significant part through new investment in biological research that aims at capitalising on the genomics revolution. Over 200 microbial genomes are known and various contemporary analysis techniques are rapidly gaining terrain. Understanding how many microbial food-borne pathogen and spoilage microorganisms use their genomic potency to respond to environmental stresses can assist through the development of biomarkers (DNA / protein based) in lowering the time-to analysis in the food chain and enhancing specificity of the results obtained. The latter will be instrumental in devising new process management systems where the level of detail of the microbial inactivation / growth model is compatible and in line with the requirements of the process model that assesses food taste, flavour and texture.

A case study on spores from spoilage Bacilli

In the manufacturing of Savoury products such as soups and sauces a recurrent theme is the need to lower process temperature treatments in order to improve product quality. While this is practice at the same time sufficient care has to be taken to ensure microbiological product stability i.e. absence of growth of spoilage organisms. Typically though ingredients used such as many herbs and spices often contain heterogeneous high loads of bacterial

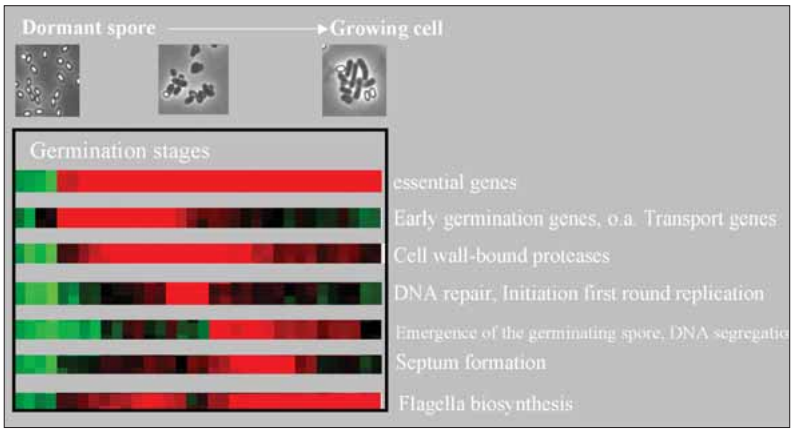

Figure 1: Application of genome-wide transcript analysis to non-injured germinating Bacillus subtilis spores. Schematic representation of transcriptional events during the transition of a dormant B. subtilis spore to a actively growing vegetative cell. Top figures show phase contrast images of morphological changes of the germinating and outgrowing spore. The images in the lower part of the figure show the expression of genes during the specific developmental stages in spore germination and outgrowth. Red indicates presence and green a absence of transcripts. RNA was isolated from germinating spores essentially as described by Oomes and Brul 3 and modified by Keijser et al. (manuscript in preparation).

endospores. Furthermore it is unfortunately observed that increasingly so many of these true 'wild-type' spores are extremely heat resistant1. Such spores will survive process conditions reaching 3-7 minutes 115-121°C making it very challenging if not impossible to reach the original goal of minimising thermal process treatment to optimise / maximise product quality while ensuring sufficient microbiological stability of the process and end-product.

The above translates to a requirement of knowing what the types of microbial spore formers are that are present in ingredients of Savoury products i.e. understanding their microbial ecology at a high level of detail. In these studies it is obviously key to assess the outgrowth behaviour of process surviving spores as that is what finally causes problems to the manufactured foods. Thus stress survival and repair processes will have to be analysed. Such an approach allows us to improve the predictive models for microbial, here bacterial spore, behaviour and therefore provides the possibility to start applying 'Systems Biology' approaches to the field of Food Microbiology. In addition the occurrence in ingredients has implications for the whole food chain where it is important to be able to trace and track such unwanted microorganisms as efficiently (rapidly and specifically) as possible based on the insights gained in their molecular physiology2. Contemporary developments both in the EU (IP Good Food started January 2004) and the US (national USDA programs) show that tracing and tracking microorganisms in food is (again) on top due to an increasing emphasis on 'Food Defense' (i.e. ensuring fully traceablity and toxicologically / microbiologically robustness against bioterrorism).

Currently the state-of-the art is that for this particular case we have analysed sporulation behaviour coupled to gene-expression under conditions where spores of varying thermal resistance arose3. In this way we identified candidate genes that might serve as biomarkers for high heat resistance. In addition we analysed germination behaviour of spores at the molecular level to identify genes key to the process both in non-thermally injured spores (see figure 1 next page) and in thermally injured spores (factory trial currently being analysed see figure 2 next page for the principles of such a trial set-up).

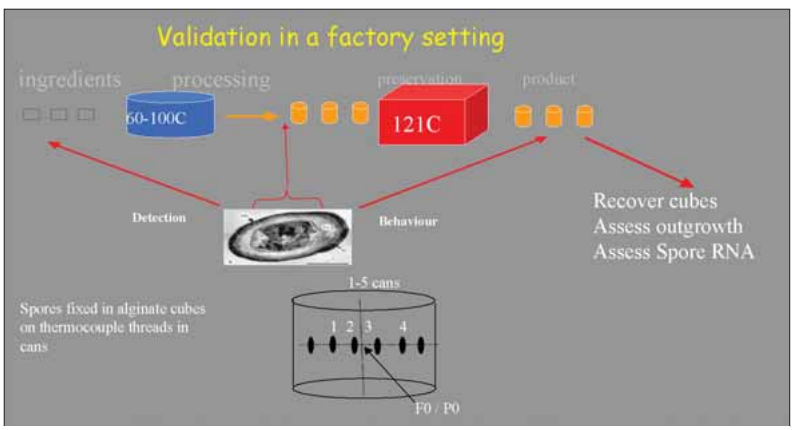

Figure 2: Principles of a factory trial in real product of process survival in-can in an industrial setting for soup manufacturing.

The current studies were performed, however, only in the well-known laboratory strain and in one food product isolate producing high thermal resistant spores. Further work on the ecology of the ingredients is planned. Fundamental issues on how such an ecology is formed and what in other food products, in particular Chilled products may, be expected are research questions awaiting answers. This gets more relevant as Chilled products is a growth segment of the market.

Acceptance of the new tools in Society

The new methods of analysis enhance flexibility in the food chain and can help consumer confidence regarding the food they eat. The flex-

ibility will allow the producer to arrive at what may be called precision processing that ensures a microbiological safe food process, while doing away with overprocessing to ensure a fail safe process. This aid in quality assurance management will benefit both the consumer as it allows improvement in product organoleptic quality and nutritional value at an as before always guaranteed microbiological food safety level.

In regulatory terms the devlopment of the technology should allow enhanced time to analysis in the food chain of benefit to tracing and tracking in case of incidence. In addition studies on microbial ecology in the food chain will be facilitated. This is currently creating a state of the art framework for the production of safe foods against the background of continuous microbial evolution and thus challenge to the industry. In order to arrive at these benefits it is crucial that scientists, regulators, consumers and the industry have an open dialogue on the newly emerging technologies. Such a dialogue has been started by various organisations e.g. the Dutch Genomics Initiative in the Netherlands as well as at various levels in the European Union. Constant feedback is necessary to make sure that sound scientific information is provided, interpreted in a correct manner and that concerns raised by consumers are answered in a thorough and comprehensive manner.

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Cost-effective feedstock collection and storage, energy integration, production of valuable co-products and large production facilities are the key factors to feasible biomass utilization.

Biomass conversion to fermentable sugar

Plant cell wall material, or lignocellulosic biomass, has the potential to provide a renewable feedstock for the production of fuels and chemicals, currently produced mainly from petroleum. Growing concerns over the political, economic, and environmental costs have led to a renewed interest in tapping petroleum alternatives. Here we give a summary of the state of the art in the conversion of lignocellulosic biomass to fermentable sugars.

TEXT | **JOEL R. CHERRY, KEVIN WENGER**

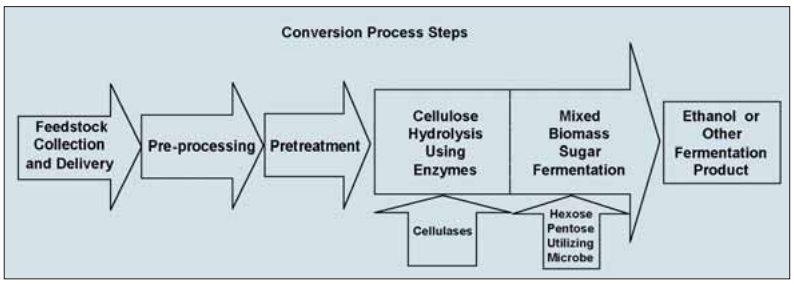
Dr. Joel Cherry (photo) is a biochemist and Research Director, at Novozymes Inc.. He manages the BioEnergy Project. **Dr. Kevin Wenger** is a Chemical Engineer, with Novozymes North America, Inc. He manages fuel ethanol R&D.

It is most likely that feedstocks will initially consist of agricultural and wood processing materials that are already collected at a processing facility (e.g. sugarcane bagasse, rice hulls, corn fiber, pulp and saw mill wastes) or urban wastes that are collected for a fee (e.g. municipal solid waste, urban plant trimmings) since their conversion potentially alleviates disposal issues and generates revenue. Utilization of agricultural residues (e.g. corn stover, wheat or rice straw) or dedicated energy crops like switchgrass or hybrid poplar, will require establishment of an infrastructure for collection, transportation, and storage be established before they will be available for economically feasible conversion.

Pre-processing of feedstocks generally includes removal of foreign, non-plant material and physical size reduction by chopping or milling. In the case of on-site processed materials, this step has already been completed, while remaining feedstocks will require pre-processing at added energy and equipment costs.

Pretreatment refers to a thermal and/or chemical step that increases the accessibility of the cellulose in the biomass to enzymatic hydrolysis. The result of an effective pretreatment is a dramatic reduction in the amount of enzyme (cellulase) required to convert the cellulose polymer to glucose and an increase in the yield of fermentable sugars. Both of these effects have a significant impact on the overall process economy (1,2). There are a number of promising and proven pretreatment technologies (reviewed in 3.) available at varying levels of implementation, but the method most thoroughly studied is the dilute acid method. Here the preprocessed feedstock is incubated for 1-4 minutes at 190-198 °C at 12.1 atm pressure, effectively hydrolyzing the hemicellulose fraction to monomeric, soluble sugars (4, 5) Composition of plant biomass is 30~40% in cellulose, 30~40% in hemicellulose, and 15~20% in lignin. After dilute-acid pre-treatment, the solid fracton contains ~57% cellulose, ~5% hemicellulose, and ~28% lignin, while the hemicellulose sugars are solubilized in the liquid fraction.

After pretreatment, the solid fraction is treated with cellulase at temperatures ranging from 30-50 °C to release glucose from cellulose. As a plant structural polymer, cellulose is much more resistant to enzyme action than starch, the other glucose polymer found in plant materials, requiring approximately one hundred-fold more enzyme protein to effectively break it down. In the late 1990's, cellulase for biomass conversion was the dominating variable cost in the conversion process at $4.50 to $5.50 per gallon of ethanol produced. In 2000, the U.S. Department of Energy awarded two three year contracts totaling $32 million to two major enzyme producers, Novozymes A/S and Genencor International, to reduce the cost of cellulase by 10-fold. By both reducing the costs of production and increasing the effectiveness of the cellulase, both companies have claimed reductions on the order of 20-30 fold, to the point where enzyme cost is no longer the dominating economic barrier to producing ethanol from biomass. That said, significant barriers remain.



Biomass utilization has traditionally been broken down into the following discrete steps

Barriers to the Commercial Utilization of Biomass

Despite the fact that cellulase cost has dropped significantly, overall process economics for producing ethanol or other fermentation products from biomass are higher than comparative processes utilizing starch. Capital costs for the construction of a biomass utilization plant are estimated at 2-3 fold higher than a comparative corn dry mill, largely due to the need for more unit operations, exotic acid-resistant reactor materials for the pretreatment operations as well as increased volume capacity to handle more dilute sugar streams (6). In addition, utilization of pentose sugars derived from the hemicellulose fraction of biomass requires the use of fermentation organisms able to utilize both hexose (glucose) and pentose sugars; common commercial yeast strains preferentially metabolize glucose and can only utilize pentose sugars after genetic modification. Recent progress in the genetic engineering of fermentation organisms has shown promising progress, but the efficiency of these organisms still lags behind those fed a strict diet of glucose. In the production of ethanol, or any other fermentation from biomass, overall process economics require that as much as possible of the incoming feedstock be converted to salable products, meaning that hexose and pentose sugars, as well as the lignin fraction, must be converted to products, either material goods or energy, in as efficient a manner as possible. Finally, work to date has focused on optimization of unit operations- pretreatment, enzymatic hydrolysis, and fermentation. Work performed cooperatively between the National Renewable Energy Laboratory (NREL), academia and industry has demonstrated that small alterations to the pretreatment regime can have major effects on the amount of enzyme required for hydrolysis, suggesting that a more integrated approach to an overall process optimization will be fruitful to further reducing process costs.

Path to Commercial Development

In order to overcome the barriers as fast as possible, it is necessary to develop biomass conversion technology in a stepwise fashion. Initially construction of pilot and demonstration plants can be used as a basis for techno-economic evaluations of the novel technologies. Subsequently, integrating biomass conversion into existing large-scale operations will allow the technology to develop, while reducing total investment and minimizing the overall operating risk. It is generally concluded that cost-effective feedstock collection and storage, energy integration, production of valuable co-products and large production facilities are the key factors to feasible biomass utilization. Converting cellulosic materials already present at industrial operations, e.g. seed hulls, bagasse, waste wood, is a logical first step. Integrating power generation, waste handling, and supply chain with existing operations is also an obvious advantage. Development and operation of such facilities, in addition to further research addressing the technical barriers, can make lignocellulosic biomass a significantly utilized feedstock in the future.

The speed with which biomass ethanol is commercialized will depend on a variety of interrelated economic, political, and environmental factors. The selling price of ethanol tracks closely with the price of gasoline, which is subject to fluctuations in crude oil production, regional political stability, and demand. While it is tempting to say that biomass-based ethanol will only become a commercial reality when it can compete in the global marketplace with sugar or starch-based ethanol, this may not be true for a variety of reasons. Many countries that have little starch or sugar production capacity still have an abundance of harvestable cellulosic bio-

mass (e.g. Sweden). Biomass ethanol offers a significantly more decentralized source of liquid transportation fuel and a concomitant opportunity for rural economic development. In addition, unlike current ethanol feedstocks, the utilization of biomass does not compete with food uses, which eventually will limit the growth of the current ethanol market and its ability to reduce petroleum dependence (7). Environmental concerns over greenhouse gas emissions, formalized in the Kyoto Protocol, will likely favor biomass-based ethanol production as carbon credit trading becomes a more important market driver. Together these issues will likely spur the implementation of policies that favor economic incentives for the production of biomass-based ethanol, perhaps sooner than later.

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Swiss Industrial Biocatalysis Consortium

Industrial Biotechnology is significantly gaining ground in various fields. However, the potential is by far not exploited. The Swiss Industrial Biocatalysis Consortium aims to make further use of this potential by pooling strains and expertise within it's internationally operating member companies.

TEXT | HANS-PETER MEYER, THOMAS MÜNCH

Dr. Hans-Peter Meyer (1949) is microbiologist by training and Head of Microbial Technology Development and Outsourcing, Lonza AG.

Dr. Thomas Münch (1964) is biotechnologist and Head of Ingredients Development, at Givaudan Schweiz AG's European Development Centre.

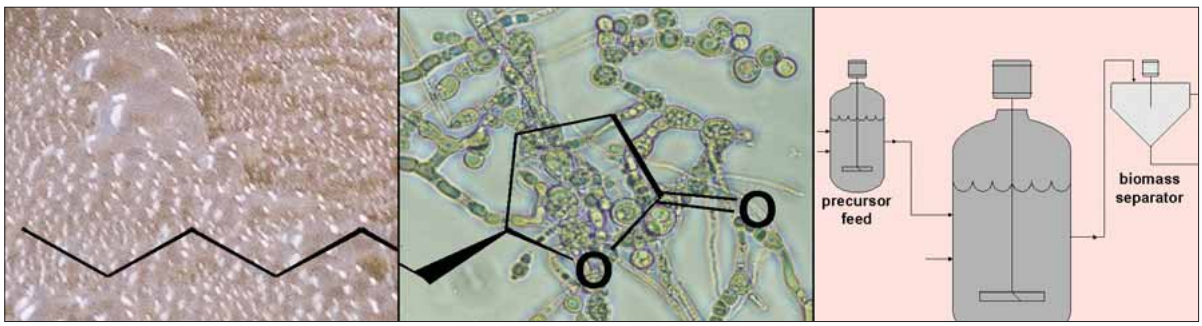

Figure 1: Biotransformation typically converts a chemically synthesised educt into a desired optically pure product. Microbial cells, as the filamentous fungus shown in the middle picture or their enzymes are applied. In this example, a carboxylic acid ester is regio- and stereoselectively hydroxylated and lactonized to yield the above peach lactone. Since the organic chemicals used as educts or precursors are often inhibiting, so called fed-batch fermentation is the state of art, where the precursor is fed into the bioreactor vessel, to keep concentrations below inhibiting levels.

Today, one can easily notice a great deal of renewed interest and activity with regard to 'industrial biotechnology' (IB) or 'white biotechnology' as others call it. IB describes a wide variety of industrial products and services that use micro-organisms and their respective enzymes for the manufacturing process. The renewed interest in IB started early in this new millennium. This maybe due to the wide regard of industrial biotechnology as one countermeasure to the negative effects of using fossil fuels, such as green-house effect and atmospheric pollution. A bio-based economy using renewable feed-stocks is also one desirable long term scenario for replacing non renewable oil based resources, as the limits of the exploitable oil reserves become reality in a not too distant future.

However, IB is still in its infancy, even though biotechnology has been successfully established in certain industrial sectors. Biocatalysis is typically regarded as a success story, since biocatalysis or biotransformation are well established in several cases of large scale production of fine chemicals, especially for the manufacture of optically pure compounds.

However, the potential of biotechnology is not yet fully realized even in established areas such as biocatalysis for fine chemicals. There are a number of reasons, but the most important one is that the industry is generally lacking a broad strain and enzyme base with well characterized biocatalytic activities for its various applications. A group of scientific representatives from Swiss industries active in IB started a joint initiative to address this issue and formed the Swiss Industrial Biocatalysis Consortium.

It is important to clarify that we consider the microbial strain as the first and foremost functional element in biotransformation. However, the availability and the possibility of targeted selection among different strains for different biotransformation tasks is still missing. The limited availability of characterized strains is the greatest obstacle.

The challenge: myriads yet unknown substrates/products

To understand this we must consider a particular challenge: biotransformation processes are by far more diverse when compared to therapeutic protein production or even secondary metabolite production.

Figure 2: All kind of different organisms, prokaryotes and eukaryotes, unicellular and filamentous, recombinant and wild types, growing and resting cells etc. must be grown and then used for biocatalysis. Thus the sterile biotechnological equipment, such as feed vessels, fermentors, filtration equipment or bagging facilites etc must be extremely versatile. Consequently, biocatalytic equipment tends to be more capital intensive than fine chemical catalysis equipment. The biotechnology facilities shown here are from a pilot scale plant.

Statement for the R&D needs of industrial biocatalysis by the «Swiss Industrial Biocatalysis Consortium»

The potential of biotransformation or biocatalysis is not fully exploited for manufacturing purposes. The reason for this is that the industry is generally lacking a broad strain and enzyme basis for its various applications. «Industrial» means large scale solutions for the life science and chemical industries, and the compounds include natural and non-natural intermediates and final APIs (Active Pharmaceutical Ingredients), flavour compounds, fine chemicals, generation and modification of metabolites and natural products. In order to assess the actual burning issues and needs of industrial biocatalysis, representatives from industry met to formulate the necessary tools from their perspective. The members of the consortium, who are presently also working on a practical solution for a broad strain and enzyme basis are Volker Jungmann (Syngenta), Oreste Ghisalba (Novartis), Hans-Peter Meyer (Lonza), Thomas Münch (Givaudan), Franz Kaufmann (Ciba), Beat Wirz (Roche), Roland Wohlgemuth (Sigma-Aldrich).

First priority of academic research must be to find new strains, enzymes and reaction types. Oxidoreductases and lyases, i.e. NADH dependent dehydrogenases, monooxygenases and asymmetric C-C bond formation by aldolases and hydroxynitrile lyases have the highest priority from an industrial perspective. The following enzymes were identified and listed according to their importance.

Oxidoreductases

Dehydrogenases.

1. NADH-dependent dehydrogenases for the asymmetric reduction of ketones, ketoacids and olefins.
2. Oxidation of alcohols with dehydrogenases have second priority.

Oxygenases.

1. *Mono*-hydroxylations, especially hydroxylations of non-activated centers and of non-natural substrates are important reactions. Improve the practicability and robustness of the in vitro P-450 systems, resp. develop an FMO based alternative system.
2. Peroxidases.
3. Other mentioned reactions were transformation of ribonucleotides, stereospecific epoxidations and the oxidation of ketones to esters and lactones (Baeyer Villiger).

Lyases

1. Synthetically useful enzymes for C-C bond formation (preferably asymmetric) using aldolases and hydroxynitrile lyases.
2. C-N (aminolyases) and C-O (hydratases) bond formations. Find lyases with a broad substrate acceptance.

Enzymes with lower R&D needs. Hydrolases are of lower priority, because the technology has been implemented in industry and do not represent an academic challenge anymore. Among the hydrolytic enzymes, the lipases/esterases are mostly used, followed by proteases and acylases. Generally a higher number of available enzymes and strains are needed, and these must be more robust with a broader substrate acceptance and higher selectivity. However, this is a domain of specialised enzyme suppliers today. Epoxidases, amidases, nitrilases and nitrile hydratases are other hydrolytic enzymes of some industrial interest. With respect to transferases, transaminases may have the highest impact, followed by sulfotransferases and glucuronyltransferases (both for drug candidates). Racemases and isomerases do have limited industrial applications.

Figure 4: From nature we know that not every project is going to fly. Biocatalysis still has many hurdles for economic success. However, a combined effort will increase the chances for a commercial take-off. From a purely quantitative perspective, the theoretical chance for project realisation is probably increased by an order of magnitude, and the R&D risk is reduced correspondingly, with a consortium approach. Overall, we are convinced that being embedded in a consortium will create benefit and business opportunities for each consortium member.

Thousands of different strains or enzymes are required to fully exploit the selective biotransformation potential for the conversion of a myriad of different substrates into the desired products. But a thorough investigation reveals that:

(1) …99% of all micro-organisms have never been cultivated and their enzymes are still unkown.
(2) …thousands and thousands of new different substrates will need a corresponding characterised strain & enzyme sources.
(3) …feasibilities of biocatalysis in early stages mostly still often fail because of missing strains and enzymes.
(4) …biocatalysis typically has the best chance as potential alternative to an established process which commercially justifies the cost and time needed for the development of a biocatalysis process.
(5) …there is no consolidated information on biocatalysis strains and enzymes as exists for chemical catalysis.
(6) …therefore chemistry with their well developed tool-box typically delivers the first generation process. Biocatalyis delivers the second generation process if at all.

As a consequence, most biotransformation projects typically start from scratch, they are laborious in development and their lead times are not in-line with the time constraints of e.g. pharmaceutical products.

This is the point where the Swiss Industrial Biocatalysis Consortium wants to act. Long lead times can be shortened by the proposed consortium approach which intends to enlarge the biotechnical toolbox by bringing together the individual strain libraries and expertise of the consortium members.

The solution: a strain consortium

A majority of newly isolated and characterised strains of the individual collections are actually never used in production. The reason is, the strain or enzyme was not active or specific (enough) on the targeted substrate and reaction type of the company owing the strain. Therefore, the project died due to unsatisfactory results of process economy, clinical testing or due to changing business environment. But these same strains, which may be of no actual value for the strain owner, could in some cases be of great value for another consortium member for other products and reactions.

Industry leaders forming the consortium agree that a broad strain library is a key success factor, and to address this concern they now want to share useful information on their strain collections, according to clearly defined rules and goals. A strain data base is elaborated using the individual strain collections of the current consortium members, Ciba (Basel), Fluka (Buchs), Givaudan (Dübendorf), Lonza (Visp), Novartis (Basel), Hoffmann-La Roche (Basel) and Syngenta (Basel). With the consortium strain collections, the theoretical chances of project realisation increases by an order of magnitude, and the R&D risk is reduced correspondingly.

Overall, we are convinced that a consortium will create business opportunities for each consortium member. The different options and forms of cooperation of the consortium, legal issues and commercial aspects are completed, and we plan to finalize the data migration into the consortium data base in spring this year.

Mission to Academia

In order to deal with the expectations in R&D as well as in production, we need innovation, alignment, and collaboration. The consortium will provide a forum to facilitate interaction amongst industry as well as between industry and academia. The consortium also promotes the development of new bioprocesses and their applications, and has formulated a first statement in summer 2004 (see infobox on prvious page). □

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Adult Stem Cells Can Produce Neurons

Stem cells from adult bone marrow successfully developed into nerve cells when implanted into chicken embryos. In the embryo, stem cells have a large repertoire of potential cell types, but in adults their capacity is more limited. Within the bone marrow are hematopoietic stem cells (HSCs) that constantly resupply the body with fresh blood and immune cells. Joel Glover and colleagues from the University of Oslo found that human adult HSCs are capable of giving rise to neurons, something not normally in their repertoire. They collected HSCs from adult bone marrow, implanted these into the developing spinal cord of chicken embryos, and showed that the HSCs began to express genetic markers indicative of neurons. About 10% of these cells showed characteristics of motor neurons. The researchers therefore suggest that exposing HSCs to the same cellular signals encountered in the chicken embryo could provide a way to grow new nerve cells from a patient's bone marrow.
PNAS

Shedding Some Light on Blindness

Even modest amounts of light can accelerate certain inherited forms of blindness, according to a newly released study. Retinitis pigmentosa, which can result in blindness, is commonly caused by mutations in the rhodopsin gene. Artur Cideciyan and colleagues from the University of Pennsylvania examined the effect of environmental light on retinal degeneration in dogs carrying a mutation in the rhodopsin gene. They found that moderate light exposure caused significant damage and retinal cell death. Increasing amounts of light overwhelmed repair mechanisms and led to an acceleration of retinal degeneration, with the highest light levels leading to complete loss of photoreceptors in less than 4 weeks. The authors caution that procedures that expose the retina to moderate amounts of light should not be used routinely in patients with rhodopsin mutations, and that retinal examinations should be as brief as possible to limit light exposure.
PNAS

bilderbox

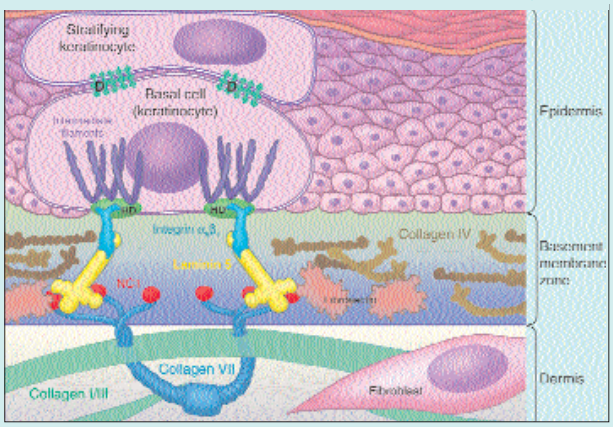
How Our Internal «Food Critic» Works

An internal «food critic» judges food based on amino acid content shortly after mammals and birds consume it, and a new study outlines the biochemistry behind this amino-acid-deficiency detector. Mammals and birds detect deficiencies in amino acids that can not be produced and must be ingested – «essential amino acids» – with a monitoring technique similar to the yeast system. The new findings could be of particular interest in areas of the world where essential amino acid deficiencies and starvation are more prevalent than in the developed world, as well as to people who must mix vegetable sources to make amino acid balances in their meals. Neurons in the «amino acid chemosensory» brain area, the anterior piriform cortex, sense amino acid deficiency and pass this information on to neural circuits that control food intake, according to the authors. In the absence of a single essential amino acid, the transfer RNAs that normally carry amino acids to the ribosomes (where the amino acids are added to growing protein chains) are involved in the early biochemical steps that produce the amino-acid- deficiency signal in the brain that eventually leads to a change in food choice. Rodents can detect amino acid deficiencies and alter their feeding behavior within 20 minutes.
Science

Skin Cancer Insights

A mutated version of collagen, a protein found outside of cells in the «extracellular matrix» or ECM, causes certain forms of human skin cancer, according to a new study. The new work helps explain why some patients with an inherited skin disorder called «recessive dystrophic epidermolysis bullosa» (RDEB) develop a deadly cancer called squamous cell carcinoma and others do not. The study also highlights the critical role of the extracellular matrix in tumor formation and suggests that proteins of the extracellular matrix may be valuable therapeutic targets for certain forms of cancer. Susana Ortiz- Urda and colleagues show that RDEB patients who develop cancer express an aberrant, truncated version of collagen VII. This collagen fragment confers tumorigenic properties to skin cells, specifically enhancing their ability to invade surrounding tissue. Experiments with human cells grafted into mice indicate that antibodies targeting this collagen fragment can block tumor formation.
Science

Science/Illustration by Taina Litwak



An adhesion complex in the basement membrane zone of skin anchors the epidermis to the dermis.

Mine's the gap

Europe's bioindustries should rather value their own differences instead to compare with the US.

TEXT | WOLF G. KRONER

In 2003, according to Ernst & Young, 198.300 employees worked for US biotechnology companies against 77.907 in Europe. Good for the US. In the same year the US counted 1.473 firms against 1.861. Good for Europe. In the US private biotech firms (78% of total) are less human capital intensive than public ones. Is this now good for Europe or for the US? If financials count, the US appears first. In 2003 revenues of US bioindustry totaled €29bn – 72% out of product sales. Meanwhile Europe's biotechnology industry earned €5.5m.

Ernst & Young: Refocus. 2004: 35.

Region	2003			2002			2001			2000		
	N	%	%	N	%	%	N	%	%	N	%	%
US-EU	7	78		5	45		21	60		16	53	
EU-US	2	22		6	55		14	40		14	47	
Transat	**9**	100	**23**	**11**	100	**38**	**35**	100	**64**	**30**	100	**56**
EU-EU	29		74	13		45	15		27	22		41
Other	1		3	5		17	5		9	2		4
Total	**39**		100	**29**		100	**55**		100	**54**		100

European Biotechnology Mergers & Acquisitions

The Gap as Artifact

Although, these financial figures of course, reflect only part of the story, it is an everlasting argument in EU politics to bolster demand for a variety of measures including more funding of life sciences research, stop brain drain, introduce branch specific fiscal reductions, or, to foster a European identity of biotechnology industries in the various nation of the continent.

While the intentions may be valuable in itself, the instrument to advance these solutions entails its own problems. Thus, the economic gap between a European and a US biotechnology industry is an artefact as long as the origin of national industry's revenues is not taken into account. Ernst & Young data are the best that is currently available, however financial figures are in general aggregated from what is published by the mother company. This reflects accurately decision making power (i.e. where to invest), but it introduces a US bias. Undoubtedly, the biggest biotech companies of the world have their headquarters on the other side of the Atlantic, but current figures for biotech industry hide the fact that considerable value is created outside of the US. A case in point is Genzyme Corp., in Cambridge, Massachusetts. In 2003 Genzyme had $1,7bn revenues. 56% of these are realized in the US and 31% in Europe where Genzyme has research, production and distribution operations in 24 countries. Similar figures may be obtained from Amgen, Biogen and others out of the 8 big US biotech companies whose revenues make up for a large part of total income within this industry segment. The available industry data are further idealized by political considerations. Thus, Genentech total revenues are counted as part of the US industry's total income and not as part of Hoffman La Roche's consolidated financial statement. While consulting firms or economic promotion agencies sponsoring such stock-taking cannot be blamed, it is noteworthy that official authorities and funding agencies rely on these data in their decision-making instead of commissioning impartial studies. Given the huge sums, EU pumps into Life Sciences and healthcare, it is astonishing that sound data are lacking on what should be counted as «biotech industry» and how added value from such endeavours could be measured.

Beginning 2000 an OECD working group (among them France, Germany and Canada) started a project on quantifying biotechnology industry with the intention of introducing a new sub-category into official national statistics and providing impartial data to policy-makers. Interesting enough, Eurostat, the EU's statistics office never really took up this initiative. In a similar vein, OECD has suggested not to count as separate patents filed and granted by EPO or US PTO. It argued, that by looking at patent families, as well as origins of inventors and assignees an «innovation gap» between the US or Europe simply might disappear into the air. In the end, reflection about improving industry condition might be more advanced, when starting from Ernesto Bertarelli's observation (Ernst & Young 2004:9): «European-based companies can compete effectively in the global environment, including in the U.S.»

Value difference

A European biotechnology industry in the sense of shared interests does not exist. The difference becomes sensible when looking at the variation among clusters and trade associations. While some clusters are truly global in reach driven by strong financing and advanced scientific

research, others are serving home markets with me-too products. Both types are successful within their niche. Or, associations. Some of them have organically grown bottom-up from industry with a broad spectrum of activities being tied to international discussions. Others, may be synthetic trade organisations, founded top-down, some being initially but one-(wo)man entities, some focusing just on national political lobbying, some focusing on local economic promotion, some on personal networking. Unifying this multiplicity requires first to take stock of this variety and value each approach on his own terms.

A sustainable identity of a «European biotech industry» cannot be fostered by pointing outside Europe. What may work within one country might not be of use in another. For example, France has a tradition since the days of Alexis de Tocqueville in rallying its compatriots for action by comparing itself with the United States. However, outside of France trumpeting «Le défi américain» is often not understood as invitation to a benchmarking exercise and reflecting about it's own. For example, some representatives from German biotech industry feel, they should emulate the US by promoting and exporting the German industry model. By contrast, UK's or Ireland's biotech industry shrugs upon the «US vs. Europe» talk. The question here is to compete with Asia, especially in the stem cell domain. For others on the continent, a contrast between Europe and the US is irrelevant, it is more a cleft between East and West. Mid-march local discussants at Biotech-World Moscow wondered why so few Westerners show an interest in internationally recognized scientific achievements of Russian biotechnology. For these discussant constraints of their own mobility and red tape are so much part of their daily life that a simple answer did not come to their mind: Language apart, access procedures to Russia are deterring even well-minded visitors: In addition to a visa they need an invitation from someone within the country. A visa cost between 80$ to 120$. You won't get it, if you cannot tell the authorities, where you stay preferably in an authorized (and costly) business hotel. Depending on your contacts you have to allow in between 3 to 10 days to get this visa. Return in time is not assured. The reality in this corner of Europe is not «look at the US», but a «love it or leave it» approach to attract interest and investment. Meanwhile, Greek biotechnologists or others from some Eastern European countries may be seen to exercise gap rhetorics. By contrast, Scandinavia's bioindustry or the one from the Iberic peninsula remain conspicuously silent in this area. Within each of these regions biotech industry is rather concerned in intensifying interactions with the US. The winds of change can be seen even in the EU. Commission president Barroso, himself coming from Portugal, is known of not invoking much the «Lisbon goal», i.e. fostering competitiveness of Europe by setting it against the US.

Transatlantic Economic Relations: An Asset

According to economist Joseph Quinlan (2003) US and European economies are heavily intertwined. The backbone of transatlantic economic relations are foreign direct investments and not trade. Quinlan documents that sales of US or EU-affiliates[1] exceed by far the volume of imports and exports. In 2000 sales of US-affiliates in Europe amounted to $1.438,6bn against US exports into this region were only at $283,7bn. EU affiliates sold in the US goods worth $1.420,1bn while EU exports to the US were worth $336,9bn. In 2001 firms from this side of the Atlantic invested a total of $946,8bn, 72% of all foreign direct investments by European industry while US industry invested 50% ($725,8bn) of all foreign investment in Europe. Second to manufacturing were European investments in the US chemical industry ($119,2bn) while at 3rd place $76bn were channelled from the US into European chemical industry.

European and US biotechnology industries, too, are more interrelated as gap rhetoric make us believe. Instead of brain drain, we witness today what Saxenian (2000) calls «brain circulation». Many in the biotechnology industry work on both sides of the Atlantic and the choice of the country is more a matter of business opportunities, research interest and lifestyle than of political considerations. Prominent examples of Europeans in the US are Dutch Henri Termeer, CEO of Genzyme, French Jean-Jacques Bienaimée, CEO of Genencor, or German Norbert Riedel, CSO with Baxter.

Figures of European mergers and acquisition activities in biotechnology (Ernst & Young 2004) provide a further flavour of the strong industry ties. Since 2000 between 23 and 56% of all European mergers and acquisitions in biotech were transatlantic ones, and only 3% to 5% are outside Europe and the US. Over the years initiatives came more form the US than from Europe, however with good access to capital markets (e.g. in 2000) this trend became balanced. These transatlantic economic relations are an asset for the industry not to be sacrificed for gap rhetoric.

Interest organisations and other stakeholders

While the US industry has its own identity at home and takes a Pro-European stance the same cannot be said of all biotechnology industries in Europe. There may be several regional biotechnology associations across the Atlantic, but they face an overall similar regulatory and economic environment which in turn shapes their common identity. This is why, US BIO is able to formulate

1 Affiliates are those commercial enterprises whereby a firm (US or European) owns or controls at least 10% of the affiliates' voting securities (Quinlan 2003: 4).

coherent positions on political, educational, economic or research issues, a task which is very difficult to achieve for its counterpart «EuropaBio». The latest effort will be in April at BioVision, Lyon. However, differences in strategy and instruments persist within the bioindustries. Trade associations alone cannot make up for the lack of unity across national borders within Europe or between the continents.

Today, more than ever there is a need for transparency and open, cross-border platforms for the industry. It is good to see that networks driven by industry not politics develop where gap rhetorics is substituted by an interest to learn from each other wherever biotech business is done on the globe. □

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BIO's new president…

TEXT | **WOLF G. KRONER**

On January 5th, former Congressman Jim Greenwood became the new president of Biotechnology Industry Organization (BIO), replacing Carl Feldbaum who had presided over BIO since its creation in 1993. Greenwood now heads the powerful trade organization with over thousand members worldwide, more than hundred employees and a budget of $45 million. Greenwood will earn approximately $650,000 annually in his new job.

BIO

Keynote speech at CEO & Investor Conference, New York February 23, 2005.

BIO's new president comes from the political field and is an experienced legislator with 24 years of experience in the state and federal legislatures. From 1993 through 2004 he was a delegate for the 8th District of Pennsylvania in the House of Representatives, which is the US parliament. From 2001-04 Greenwood chaired the Energy and Commerce Subcommittee on Oversight and Investigations where he dealt with a broad spectrum of issues from corporate governance to bioterrorism. Greenwood was actively involved with introducing healthcare legislation, including a bill to limit indemnities in medical liability suits. He has a reputation as a moderate Republican able to work with colleagues in both political parties.

Jim Greenwood worked closely with BIO while in Congress. In 1998 he was named BIO's «Outstanding Legislator of the Year» for his steady support of US bioindustry's positions in Congress particularly with regard to human cloning, a controversial issue in domestic policy and also within the Bush administration. He has been a staunch advocate of somatic cell nuclear transfer, introducing a bill to allow therapeutic cloning while banning reproductive cloning.

Prior to his service in the state legislature, Greenwood was social worker. He lives in the suburbs of Philadelphia, Pennsylvania with his wife and three children. He is 53 years old.

BIO's new president has experience with foreign legislatures having served as President of Global Legislators Organization for a Balanced Environment (GLOBE) International, but is not much known outside the US. In a survey by BioWorld *EUROPE*, some representatives of the biotechnology industry on this side of the Atlantic showed scepticism if Greenwood would continue Carl Feldbaum's course of not forcing the US perspective on Europe's bioindustries. As one put it, «I hope Mr. Greenwood will not export the view that what is good for US biotechnology is good for the rest of the world.» This fear may well prove unsubstantiated. Friends close to Jim Greenwood describe him as a person who listens well and is quick to learn. He is currently touring the US visiting BIO chapters and key member companies in order to better understand their needs. In April, Greenwood will address European biotechnology at BioVision at the invitation of EuropaBio. BIO's new president is expected to address the need for biotech industries on both sides of the Atlantic to learn from each other and, maybe, to tell the audience what he learned from his visit to take home. □

…first reactions from Europe

EuropaBio welcomes Mr. Greenwood in his new function. The board has opened all doors to BIO and the new President. We organize a European Track at this year`s BioVision and invite Mr. Greenwood to step over the atlantic in order he may see for himself the dynamism of the European biotechnology industry. This will also be an occasion to address European biotechnology and meet with Mr. Feike Sijbesma, EuropaBio's chairman, and other members of the board. I am very pleased to congratulate and welcome the new colleague from BIO. The Challenge of representing an industry that is perpetually innovating, improving, creating and growing is invigorating. I wish Mr. Greenwood to experience this in the same very positive way as I felt it since March 2004, when I started at EuropaBio.

Dr. Johan Vanhemelrijck, Secretary General EuropaBio

Assobiotec hopes that the future activities of Bio will furthermore increase collaborations with the European biotech context, and in particularly with Italy. Italy's performance in the European biotech-derived drug development pipeline is quite remarkable, especially when compared to the overall size of its biotech industry. In fact, Italian companies have 16 innovative drugs at advanced development stage – more than Germany which has four times more companies – 6 of which were granted Orphan Drug status by the EMEA (most of these by FDA as well). In fact, the position reflects more the rank of our pharmaceutical market size rather than the current dimensions of our red biotech industry: it should be remembered that the Italian pharmaceutical market has reached the fifth to sixth position worldwide in size, with a very strong public healthcare system. We are sure that in the next future Bio will increase its attention towards emerging biotech realities in the European area. We look forward to a more tight collaboration to the benefit of an overall growth of the biotech sector.

Dr. Roberto Gradnik, President Assobiotec – Associazione nazionale per lo sviluppo delle biotecnologie

After the huge development BIO experienced during the last decade under the leadership of Carl Feldbaum being appointed as BIO President is a big challenge. James Greenwood was chosen after a long and thoughtful recruiting process therefore we are confident that he is the right man for the job. We hope he can continue to contribute to the development of BIO and therefore the all biotech scenario namely taking into account the key role of biotech to increase sustainability in underdeveloped countries. We expect that his political experience would be of great importance in order to balance the interests of the emerging small companies with the positions of the larger ones. We wish him all the best in his challenging role and look forward to have the opportunity to work with him.

Dr. Luis Amado, Executive Director of Associação Portuguesa de Bioindústrias (APBio)

At the light of the US successful example, we wish US-BIO helping the European BIO-Organisations with the education of their respective federal governmental systems for appropriately funding early stage biotech programs. Moreover, we are looking forward that BIO and its new president will work closer with European BIO-Organisations in order to develop more globally oriented strategies. BBA strongly supports efforts demonstrating the unique advantages and the necessity of a single biotech market like the US one which is in contrast to the handicap carried by Europe due to its multiple marketplaces. I personally hope that Mr. Greenwood as president of BIO will de-emphasize spotlights on biotechs surfing the actual bioterrorism wave. In my view, such a move would be for the benefit of those innovative compound developments from biotechnology which enable to fight worldwide «tsunamis like tuberculosis, malaria or cancer.

Dr. Michel Baijot, Chairman Belgian BioIndustries Association (BBA)

The German Association of Biotechnology Industries (DIB) welcomes James Greenwood as new president of BIO. He has a proven track record in engaging for the interests of the biotechnology industry. These are not limited to the US but quite similar on the European side of the atlantic as many US-European biotech companies document, especially in Germany. Carl Feldbaum, co-founder and former BIO-president, and me, we are good friends. I am looking forward to develop such a friendship with James.

Prof. Dr. Peter Stadler, President German Association of Biotechnology Industries (DIB)

On behalf of EBIO, I would like to wish to the new president courage to make strong and far-reaching decisions that lead the American and European biotech industries towards more efficient trans-atlantic cooperation. It is clear that all regions must rely on their strenghts in the global competition and cooperation of different regions is the key factor of success. Every region, small or big one, must find and provide its unique features to be play a role in a of such global network. I am sure that Estonia is able to provide academic excellence and industrial wisdom to such a partnership.

Dr. Erki Mölder, President Eesti Biotehnoloogia Liidu (EeBio)

We welcome James Greenwood as the new BIO President. We hope that BIO will facilitate the further development of the industry by increasing the awareness in the governments and in society of the enormous potential in terms of improving health, curing of diseases and protection of our environment. Not the least in Europe the support of basic life science research and education and support of entrepreneurship is needed.

Dr. Søren Carlsen, Chairman Foreningen af Bioteknologiske Industrier i Danmark (FBID)

…

NBA has very good experiences from attending the three last BIO Conventions. We therefore recently decided to join BIO as an affiliate member. We hope that BIO continues to be the strong voice of the biotech industry, in the effort to increase public awareness and the contribution to quality of life. In addition, BIOs annual convention and exhibition should maintain its position as the most important international meeting place. We are looking forward to elaborate our contact with BIO and Mr. Greenwood.
Odd Magne Rødseth, Chairman Forum for Bioteknologi (NBA)

France Biotech expects BIO`s new president to generate more data on the impact of biotechnology on duration and quality of life. We would also welcome BIO`s support in helping to define, what the 2020 goals should be to guide academic research priorities. More US biotech companies should come to France to benefit from the «0 tax» status for French companies up to 8 years old and from under utilized academic and clinical research. I personally wish Mr. Greenwood, that he may have no need for biotech drugs neither for himself nor his relatives.
Dr. Philippe Pouletty, Chairman France Biotech

The global biotechnology industry becomes increasingly conscious of the lucrative offerings of developing and emerging biotech countries, particularly in red biotech as Phase II success continues to present a bottleneck for approvals. Support of preclinical research and aggressive screening, discovery and optimisation chemistries could present exciting opportunities and remarkable IRRs in the future. As representatives of the Greek biotech scene, we wish to encourage increased funding for applied research, participation of American VC firms and closer collaboration with American pharma and mature biotech firms to nurture and guide a competent and highly skilled Greek scientist pool, who unfortunately remain trapped in academic short-sightedness. Looking forward to a successful collaboration, to meeting you in Philadelphia and our sincere wishes for a productive and innovative year as president of the American BIO.
Ms. Maria Tsampoula, Chairwoman Greek Biotech Association

IBEC's Irish BioIndustry Association (IBIA) congratulates James Greenwood on his appointment as President of BIO, IBIA Chairman, Dr. Cormac Kilty wished Mr. Greenwood the very best for the future saying that IBIA looked forward to their continued partnership with BIO in the future. Ireland has always had strong links with the USA and looks forward to further US investment in Life Sciences in the country following from significant recent investments made by Wyeth and Centacor.
Dr. Cormac Kilty, Chairman Irish BioIndustry Association (IBIA)

The Hungarian Biotechnology Association would like to congratulate James Greenwood as new president of BIO. As a new member of BIO we would like to strengthen collaborations between US and Hungarian biotech firms and hope to put Hungary on the world biotech map.
Dr. Ernö Duda Jr., President Magyar Biotechnológiai Szövetség

Niaba, the Dutch Biotech Industry Association congratulates James Greenwood on his appointment as President of BIO. Niaba Chairman Dr. Rob van Leen wishes Mr. Greenwood a lot of success in strengthening the position of the biotechnology industry even further. International cooperation within the industry is of growing importance for the coming years.
Dr. Rob van Leen, Chairman Nederlandse Biotechnologie Associatie

It is important that Mr Greenwood continues BIO`s work to promote the biotechnology industry on both a US and international level. He must strenghten the public and governmental confidence in the biotechnology industry to promote health and fight diseases. SwedenBIO, representing a research intensive EU country with strong track-record in biotechnology, sees good collaborations with the US and BIO as absolute crucial
Hans Nyctelius, CEO and President SwedenBIO

The Swiss Biotech Association wishes James Greenwood that he may have similar success in his new task with BIO as his predecessor Carl Feldbaum achieved. Swiss biotech companies have heavily invested in the US during the last decades. Thus the recent success story of - – for example – Roche cannot be divided from Genentech, not to name the capital investments in many small and medium Swiss companies from US companies in Switzerland and vice versa. Global biotechnology lives from personal interaction. I am looking forward meeting James to discuss possibilities to organize joint events of mutual interest to our associations, new tools to enhance cooperation in technological fields and opportunities to foster venture capital exchange across the ocean.
Dr. Reinhard Glück, President Swiss Biotech Association (SBA)

«The issue is harmonization.»

An interview with Henri A. Termeer, Chairman, President and CEO of Genzyme Corporation.

When you think of US biopharma operations with Europe, what should be done to improve business transactions with Europe?

The most important reason why biotechnology industry has developed so fast during the last thirty years is that it could relate to the markets. Now, an environment grows where for biopharma cost of drugs or other products is the only issue and this is a barrier to the adoption of new therapies. Today, biopharma is duplicating an incredible amount of work during development, whether it concerns clinical trials, working with institutions and patients, documentation, rules for manufacturing and so on. A further costly issue are the differences in the so-called Phase IV, post-marketing. In other words, there are many regulatory agencies each doing the work that needs to be done, but these agencies are not coordinated, rules not harmonmized and as a result of that there is very costly duplication for industry. So, I think, there is a massive opportunity for policy-makers – and this actually is the moment to do this – to influence the regulatory development of this industry by first looking at markets and by making adoption of new therapies much more welcome. The issue is harmonization.

Regulators would fully agree, but harmonization efforts on each side of the Atlantic are different. How can it be sped up?

By having strong personalities to run these agencies and not giving up until the right result has been achieved.

That sounds good…

We talk too much about the discovery phase of biotechnology. It's exciting to read about scientific breakthroughs, proof of principles and on how great the world is because of all of this. If you think about stem cell research – we are many decades away from any impact on the patient. Look at BioVision, Lyon, how much time do we spend in that meeting on discovery issues and how much on the financial impact of healthcare innovations or on how to train physicians to cope with pharmacogenetics? We shy away from the reality of creating markets.

And Europe?

Europe is a very important market for US biotechnology companies. In fact, seen from a commercialization point of view, Genzyme is with some products more successful in Europe than in the United States.

What can US biotech healthcare companies learn from their European counterparts?

Europe is a rich resource of talent and a very large sophisticated market. Europe is a critical market to participate in.

European biotech suppliers are looking for pharma deals. Is US Pharma different from Pharma in Europe?

Novartis and Merck Sharp & Dohme may be different companies, but they both look at a biotechnology partner to give them a global deal. Thus biotech companies need to look at their potential pharma customers in Europe through the same eyes.

Interview: wk

NEWS | **THE RNAi CONSORTIUM**

Eleven leading biomedical organizations have formed a unique $18M, three-year public-private consortium to create a comprehensive library of gene inhibitors to be made available to the entire scientific community. Based on the method of RNA interference (RNAi), this library will give scientists worldwide the tools to knock down expression of virtually all human and mouse genes, accelerating the growth of basic knowledge of gene function in normal physiology and disease.

Called The RNAi Consortium (TRC), the collaborative effort is based at the Broad Institute of MIT and Harvard, and includes six MIT- and Harvard-associated research institutions and five international life sciences organizations.

The goal of TRC is to use the recently discovered RNAi mechanism to create widely applicable research reagents composed of short RNA hairpin sequences carried in lentiviral vectors. These can be used in a wide range of cellular and animal studies to discover the key genes underlying normal physiology and diseases - including cancer, diabetes and immunological responses. TRC will not only create and validate these reagents, but will make them available to scientists worldwide through commercial and academic distributors.

TRC is based on a scientific collaboration among principal investigators at six Boston-area research institutions: Nir Hacohen (Massachusetts General Hospital, Harvard Medical School); William Hahn (Dana-Farber Cancer Institute, Harvard Medical School); Eric Lander (Broad Institute); David Root (Broad Institute); David Sabatini (Whitehead Institute for Biomedical Research [WIBR], Massachusetts Institute of Technology); Sheila Stewart (Washington University, formerly at WIBR), and Brent Stockwell (Columbia University, formerly at WIBR).

TRC also involves five member organizations: Pharmaceutical companies Bristol-Myers Squibb, Eli Lilly and Company, and Novartis; research product manufacturer Sigma-Aldrich; and a Taiwan government-sponsored academic consortium, Academia Sinica-National Science Council. Each of the member organizations will contribute $3.6M over three years to support the effort. *sp*

Too few companies, me-too products and negligible markets?

Eastern Europe's Bioindustry suffers from bias and low visibility.

TEXT | **WOLF G. KRONER**

Conventional stock-taking in Europe's bioindustry in general leaves out Eastern European countries. They belong to the category «other countries». Experts from the West who track there the evolution of commercial biotechnology swiftly concede that leaving out is less a matter of scientific performance than of matching established performance criteria for the industry in the West. The verdict then is clear: Eastern Europe has too few biotech companies, mostly with me-too products and services exploitable only on a local basis. A look on site appears to support these views. Enterprises are in general chronically underfinanced, with outdated equipment within buildings and access routes which are not inspiring investors' trust. Moreover, the Western view is widely shared among indigeneous commercial biotechnology in Eastern Europe. In addition to outside views, soft pressure continues to be put on entrepreneurial researchers. They are frowned at «making profits from science» by peers from academic environments. While it is true that funds are lacking, markets do not live up to the liberal model and science is differently organized, there is a certain lack of understanding by Westerners.

Jihomoravské inovacní centrum

New Inkubator at the Technical University, Brno

Foreign direct investments on the rise

Facts collected on site contradict persisting biases. A case in point is the Czech Republic (CZ) and undoubtedly one economic key driver is the integration into the EU. According to a study by A.T.Kearney, the country ranks fourth worldwide in offshore location attractiveness on equal with Malaysia ranking third. However the availability and skills of workforce has to be improved compared to other Eastern European countries like Poland or Hungary. For some time foreign companies like Baxter, Eastman Chemicals or Lonza have invested in CZ, but mostly in manufacturing facilities. From there they are serving international markets. Swiss Lonza, for instance, produces L-Carnitine in various forms for food and feed. In 2003 sales abroad were €31m which makes the company one of the large export companies in the Czech Republic. Second to the automotive sector, the chemical sector (including plastics and biotechnology) received the largest part (33%) of the cumulative inflow of foreign direct investments (FDI) between 1993 and 2004 totaling €21,5bn. The results are already visible in the economic statistics. A study by the Vienna Institute for International Economic Studies (2004) found that FDI in Eastern Europe was highest in the Czech Republic with €4.020 per capita against €3.997 in Estonia. Figures from Czech Invest, a state agency exclusively processing applications for investment incentives, show that between 1993 and 2003 about 80% of FDI mediated came from Europe, mainly from Germany (€12bn), the Netherlands (€5bn) and Austria (€4bn) with the US accounting for 7% of total sums committed. Out of the investments in the chemical sector his agency dealt with in the last eleven years about 9% went into biotechnology, says Tomas Novak who currently is for Czech Invest in the US. Growth rates of FDI in this segment are above expectations. In 2003 11% went into R&D (manufacturing 70%, business support services 19%). While analysts point out that the transaction volume is driven by a comparatively small number of investing foreign companies, the build-up of infrastructures cannot be overlooked. First, manufacturing facilities are constructed or geared up

Wolf G. Kroner

New generation of science managers in the East. Prof. Jan Slovak

to the latest worldwide industry standards. Second, local added value is installed. Lonza invested €117m in its production plant at Kourim, Central Bohemia. Until 2010 the company plans to invest another €86m there including a biotech R&D centre. It is clear, that this adds to increasing local knowledge and fostering the development of innovative biotech suppliers in their vicinity.

Infrastructures changing quicker than mentalities

There is a wind of change in Eastern European bioindustry and undoubtedly EU funding programs have helped the turn from communist to market economies. At Brno, the second largest town in CZ Masaryk University builds a 20 ha life science park with a €95m credit by the European Investment Bank. This autumn a vital part called «Integrated Labs for Biomedical and Environmental Technologies» (ILBIT) will be opened. A complementary infrastructure at Brno will be MEDIPARK whose finalization is projected for 2008, an Incubator linking to ILBIT will be installed there in 2007. A first incubator (see photo) has already been installed at the Technical University. This investment greatly supports local reformers like Jan Slovàk, vice rector for strategy and development at Masaryk University, a mathematician and a promoter of commercializing research. «In the Czech Republic we are still struggling to overcome a rather peculiar heritage from communism. At that time politics regarded researchers as unreliable scientists which should not meet students», he says. «Therefore the bulk of funding went to research within the Academy of Science, but universities could not build appropriate labs and support their own scientists.» This has led to an unhealthy split among national research which turned into a problem when Czech scientists had to compete internationally after the fall of the Iron Curtain. Language is another problem that has deterred other than researchers from CZ or Slovakia to come. Nevertheless Slovák puts some hope into the new science park, special university language courses for foreigners, the low cost of living, and an environment that is secure and friendly to foreigners. Another hope are philanthropic support form sponsors like the Isabel and Alfred Bader foundation from Milwaukee, USA or the Gregor Mendel Trust, Wien/London. Meanwhile, competitive biotechnology is boosted by the efforts of many at Brno. The Institute of Biophysics has developed for Siemens biochip detection technology. With an advanced project for supercomputing the National Centre for Biomolecule Research has been established and its work has received much credit internationally.

Results are poor, however, when it comes to commercialising research. In 2003 the European Patent Office registered only 1 Czech patent application out of the relevant C12 to C14 class with none granted there.

What is a «small» biotechnology industry?

The evolution of Czech bioindustry is dynamic. Jirí Vanêcek, project manager with Technologické centrum, counts today some 25 biotech companies in a more restricted sense. About 10 of them are developing medical diagnostic kits and offering bioanalytic services. About a fifth do preclinical and clinical testing, and the same number is engaged in environmental biotech. Counting registered companies in the Republic actually hides more than it reveals. There are quite some academic endeavours with an eye on commercialization. Thus, at the beginning of this decade several Prague academic institutes and hospitals formed a consortium to do stem cell research. This initiative is today but visible as basic research, because partners within the consortium cannot really commercialize their findings within the country. They hope that a law on stem cell use will provide them a safe legal harbour from where to operate.

Courtesy by: Publisher Medizinische Genetik

Gregor Mendel with fuchsia (3rd from left) with other friars at St. Thomas Abbey, around 1860

Also, biopharma has kept a low profile. The fact is, that APIs, vaccines or food ingredients are exported abroad to well-known customers not very interested in pointing to the origin of intermediates or pre-finished products. There are now about 10 to 15 pharma companies in the country with links to biotechnology. Bioindustry in the Czech Republic by far exceeds organizations registered as for-profits. Many academic institutions and hospital laboratories increase their income by selling custom made monoclonal antibodies, reagents or other bioproducts. Their numbers are increased by private individuals often working in these institutions but acting on their own account by selling analytics, patient recruitment or consulting services. Modern biotech methods are used for quite a time inhouse in the country's brewing and food industries – without much advertising. Thus, a closer look supports Vanêcek's description of bioindustry: «Biotechnology and pharmaceutical research in the Czech Republic has reasonable standards. Some labs have achievements comparable to the leading European labs.» And what looks first as a negligible number of biotech businesses with me-too products turns at second glance into an emerging industry that might well attain a hundred big and small life science companies. No doubt, there are competitive bioindustries emerging in Eastern Europe, which await to be understood in the first place, and then discovered. □

Prospects of Biotechnology in the Czech Republic

Inertview with BIOTRIN president Jaroslav Drobník.

INTERVIEW | WOLF G. KRONER

Doc. JUDr. Jaroslav Drobnik, CSc. (1929) was part of the Ministry Commission for Registration of Medical Devices and became 1990 Director of the Institute of Biotechnology at Charles University. In 1998 he retired, but continues to have functions in several national and international advisory bodies to government and OECD on GMO and biosafety. Since 1998 he is president of a non-governmental association, BIOTRIN, which engages in raising public awareness for biotechnology especially for transgenic crops.

Two bills important for the Czech biotech industry are now in parliament. What will happen next?

There are two proposals waiting for decision, one on human embryonic stem cells, the other on coexistence of organic farmers with those cultivating GMO crops. The proposed stem cell legislation will allow collecting surplus embryos from the reproduction clinics and use them for research, in other words for the preparation of embryonic stem cells. The other bill concerns an amendment to the law on genetically modified organisms already in place. Now the political situation is somewhat complicated. Both proposals are waiting for decision since last September. The first reading has taken place, but now the bills are with the commissions. With respect to the implementation of EU legislation on coexistence, individual member states do not have much freedom to introduce their own approach. This is not the case with stem cells. The EU refuses to regulate this field and gives quite some freedom to the member states to introduce the legislation they think suits best their needs. We want to benefit from this situation, and here our country is quite supportive to biotechnology.

When do you expect a decision in parliament?

It appears that the new law on stem cells will take much time as Czech politicians have turned to other priorities. By contrast, in the case of the amendment, this is, in a way, routine. The Czech Republic is adopting the existent EU regulation. I think the amended law should be voted by parliament in April. In any case, it should be in place in spring this year, as we near seeding time.

… the corn borer is here and really has an important … impact.

Does this mean, that bt corn can be planted here for the first time?

Exactly. This is very important for our country, because the corn borer is here and really has an important economic and ecological impact. For instance, in order to extinct the corn borer, each year about 10.000 ha of corn fields are sprayed with chemicals.

Do you expect Czech farmers to switch to cultivation of transgenic crops?

The situation in our country is very similar to the general one in Europe. Food is available in abundance, and consumers see no real value in buying GM-products. Czech Farmers would readily use agricultural biotechnology, but most of the crops are exported to Austria and Germany. There consumers would refrain from buying it.

Agricultural biotechnology needs to switch to non-food GM crops

But farmers in Romania cultivate large fields with GM crops –

– also farmers in Bulgaria do it, those in Spain as well. It depends on to which countries you export.

What should be improved?

There is too much concentration on GM food products. Agricultural biotechnology needs to switch to non-food GM crops. In other words, we should develop specific crops that can be used in the production of chemicals, for feedstock, or for energy production. Therefore we should establish research on generating specific crops for this purpose. Moreover, this is not new to our country. We already convert rape seed to biofuels. This should be augmented. At least 5% of the current gasoline consumption by cars should be substituted by ethanol.1

We should also work closer together across borders. I do not know how legislation on genetically modifieds organisms further will evolve. I am looking forwards to a meeting in Ceské Budjovice next September. There, we will discuss issues in plant biotechnology for an entire week with colleagues from many other countries.

How do the scientists from former Czechoslovakia work together?

Most of the scientific societies are still binational, for instance there are still Czecho-Slovak Societies of Microbiology and of Biotechnology. But once it comes to the practical application of research, particularly in the agricultural field, this unity breaks up.

Is commercialization of research easy?

Quite to the contrary. While legislation may be supportive to protect IP or start your own company, practice is much different. Universities and academic research are strictly focused on publications and then report the impact factor. There is no patenting done. Moreover, there is a lack of support with these institutions. Think of Charles University at Prague. It has 42.000 students and several hundred professors and researchers, but no patent office and no one to help a scientist write a patent. Universities do not encourage spin-offs. I have been at Montreal, Canada. McGill University offers its facilities for one year to researchers willing to start their own company. Here, this is still unthinkable. Infrastructures and taxes should be adjusted to help this new technology play the expected economical role for the country. □

NEWS **HUNGARY**

A study released by scientists at the Katholieke Universiteit Leuven (KUL) reports that the adoption of biotech maize, sugar beet and oilseed rape would generate an incremental 36 million euros annually, with most of this being earned by farmers. The study is the first to assess the potential impact of biotech crops in Hungary. According to the report, even in a smaller country like Hungary, with only 4.7 million hectares of arable land, the adoption of biotech crops would positively impact farmers by generating incremental income. Maize, a key crop in Hungary accounts for the largest increase in value.

The study titled «Potential Impacts of Biotechnology in Eastern Europe: Transgenic Maize, Sugar Beet and Oilseed Rape in Hungary» by M. Demont, E. Tollens and J. Fogarasi is available at:www.agr.kuleuven.ac.be/aee/clo/wp/demont2005a.pdf

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«Wha's like us»

Scotland speeds up for smart and successful life sciences.

TEXT | **WOLF G. KRONER**

There is more than sheep, ships and spirits to commercialize in the Nothern part of the British isle. The taxi driver is proud of being Scot. No one matches a Scot and he cites famous countrymen inventions as e.g. telephone. Economic promoters are proud that it were Scots doing the first bone graft, discovering insulin, penicillin, interferon, or ß-blockers, inventing MRI scanners and cloning sheep «Morag» from embryo cells and «Dolly» from adult tissue. Pride is taken in that Scottish genius was there all along history, from the 15th century onwards. However, industry success does not come by with bright brains alone, with more Graham Bells, John McLeods or Alexander Flemings – the latter early biotechnologist, if this denomination would have existed in their days. Indeed, their scientific and commercial success was built on a receptive R&D community, investors and politicians who were rarely present within Scotland those days. So success was achieved elsewhere for most of the part and quite a long time.

Can do culture

In the wake of receiving autonomy Scottish industrial policy changed beginning 2000 orienting to building critical mass and foster competitiveness. In 2003/04 Scottish Enterprise (SE), the responsible non-departmental policy body, invested £107,3m (€155m) in growing businesses and £22.4m (€32m) in R&D. The promotion strategy centers on establishing an international distribution network, streamlining education to interlink with the outside research and business, installing advisor and commercial management teams for local focus enterprises and creating seed funding. Today more than 90 projects are run with life sciences as a priority area with IT and energy. Today there are 12 offices of SE in Scotland, 1 in London and 5 others on the continent with Düsseldorf as a strategic subsidiary for Eastern Europe, 4 in the US and 8 in Asia. They help Scottish companies to operate internationally and are complemented by a soft «globalscot» network of some 700 members to harness the support of prominent Scots and supporters of Scotland all over the world. A 6-year proof-of-concept fund with currently £33m (€48m) aims at closing the pre-seed funding gap between inventions in labs and leading it to industrial exploitation. Currently 52 life science projects are run worth over £9.2m (€13,3m). A Scottish co-investment fund £45m (€65m) has been set up which complements private investments with up to £2m (€2,9m) per deal. A business growth fund provides loan and equity investments to SME's up to £100.000 (€144.000). Policy aims at growing life science SME's.

Central bottleneck for Scotland life sciences are not «brain drain» and lacking monies, but a critical mass of companies where evolution might take its toll while not jeopardising the whole industry, and the structure of venture funding. Unless other UK regions Scotland still lacks a broad base of core biotechnology companies. Experts estimate that about 1/5 of UK companies are there, amounting to some 60 biotech firms in the stricter sense. By contrast, SE counts 215 life science companies along the value chain in a broader sense. However, it appears, that much of them are not yet actively venturing into this field and official counts include interrelated companies organized in separate legal entities. According to official Scottish figures there was a 37% increase in so-called high-growth start-ups in 2003/04 against the previous period, however in all industry sectors spin-outs from companies and academia decreased considerably by 23%. Flag ship companies like PPL Therapeutics commercialising were liquidated in 2004 while founding of others were delayed to adverse capital markets. Most of the VC capital invested into biotech companies in Scotland still comes from business angels, says Tom Shepherd, CEO of CXR Biosciences, a pharmtox company in Dundee. BAs typically invest up to £2m (€2,9m) which means that biopharma companies (currently 6)

Courtesy by Trustees of the National Museum of Scotland

Dolly and Morag (right side) immortalized at the Royal Museum, Edinburgh

in general have to look elsewhere to raise larger sums. While small funding is of valuable benefit in creating a bedrock of biotech industry in Scotland SME's are in need of outside albeit not large monies, it nevertheless hampers full exploitation of biotechnology commercial potentials. A recent Department and Trade Report said that in the entire UK biotechnology firms raised €676m (2002) against €6.7bn in the US and it warned that firms would have to move their operations to the US in order to raise capital. Thus, in recent years, some US companies as Invitrogen or Geron have acquired Scottish companies as a useful backyard to fill up their pipeline and exploit it at home.

New Terms for Auld Alliance

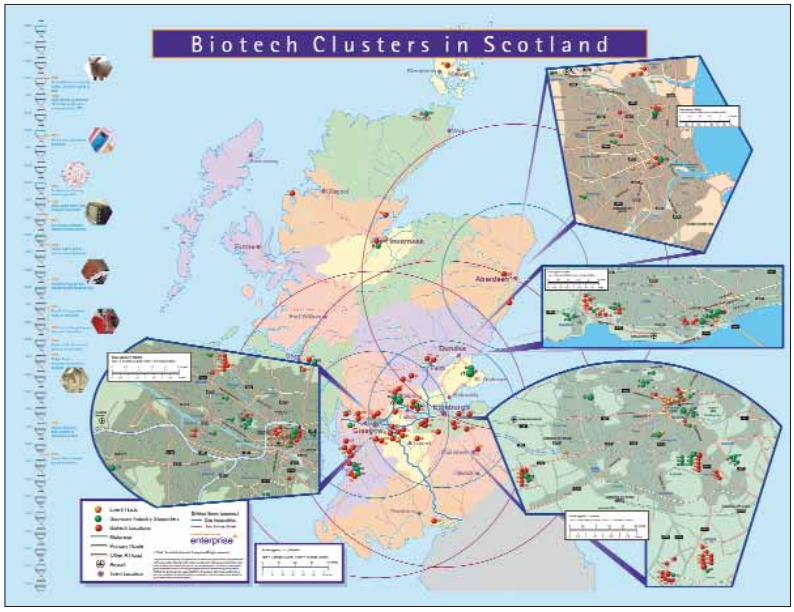
Until 1560 when Mary the Guise died at Edinburgh Castle Scottish policy espoused pro-continental attitudes, with strong ties to France within the Auld Alliance. For many centuries thereafter Scots were known to share reservations with fellow islanders about closer adherence to continental Europe. Quite recently, with increased political autonomy from Westminster Scots' Euro scepticism is turning into rapprochement. Nowadays the Auld Alliance is built on new terms. The EU is expected to show its interest in Scotland in the first place. And the Scots apparently benefit from a pro-European attitude. Infrastructures are modernized with EU monies. In the accounting period 2003/04 Scottish enterprise received EU-funding of €39,6m (over 100% increase against the previous year). Part of it flows to regional implanted life sciences. Prestigious research institutes like Roslin near Edinburgh receive today non-negligible EU-funding, accounting already for 9% of it's total income. In addition, European Framework 6-research funding goes to stem cell projects which in turn foster development of companies allowing to build up global competitiveness.

«When Scots accept the challenge…» says John Ward, chairman of Scottish Enterprise, «…there are none more determined, more resourceful or more enterprising.» One of the levers to put political vision into practice is Intermediary Technology Institutes Ltd. (ITI), a 100-per cent government enterprise, set up to spot independently of individual companies and academics market opportunities for IP and existing products. For the next ten years the biotechnology arm, ITI Life Sciences has £15m (€21,7m) to spend each year to push transfer from early business projects by academia and provide incentives for companies to internationalize and invest more in R&D. ITI's business model is built on market foresighting, creating a research portfolio prospecting different ways of product development and only in the end opting for the appropriate means of commercialisation as founding companies, licencing etc. Second to the stem cell area, ITI has launched this february a three-year-programme funded with £3,7m (€5,3m) to develop 3D cell-based assays with fluorescence lifetime detection technology. Key is to turn an already existing loose network into a virtual project company of three Scottish enterprises, CSS-Albachem, Edinburgh Instruments and Hannah InterActions. During project course this will be stepped up into a non-virtual focused working relationship.

The need for cell-based assays is clearly there. Analysts say that last year this market earned world-wide €975m with 20% projected growth over the coming years. Dundee is one of the centres for development of these assays. Peter D. Downes, dean of faculty of Dundee University, says that almost 2/3 of the total budget (£23m, or €33m) comes from external funding with large income from developing assays and reagents for industry. One of the Dundee companies to commercialize this research is former Upstate Group acquired for $205m by Serologicals Corporation last year. Within Europe the Dundee cluster will have to compete with similar initiatives at Regensburg, Germany, and Lyon, France.

One of the challenges the Scots face is to easen the heavy dependence of its biotech industry on academic research, a recent DTI report says. Successful exploitation of ideas also requires developing the distribution sides, i.e. strengthen marketing and opening up further distribution channels, which means much more than organising knowledge transfer. Meanwhile, biotechnology leaders from other parts of Europe are travelling to Scotland to look for themselves at a booming biotech industry. The latest one mid-march when Peter Stadler, CEO of Artemis Pharmaceuticals and chairman of German Association of Biotechnology Industries seized the occasion of the BioDundee meeting to discuss international trade policy issues with his colleagues. □

courtesy by Scottish Development International



Biotech Clusters in Scotland

New industrial biotechnology platform in Germany

During a stakeholder meeting at Berlin a German national platform was founded in order to promote the visibility of «white biotechnology» in the public, catalyze academia-industry interaction and provide an interface for EU funding.

TEXT | **WOLF G. KRONER**

Currently, the platform is formed by personal adherence as organisations' consent could not be obtained on short notice. The initiative was put into life after DG Research's Christian Patermann opinioned in his talk that white biotechnology might be boosted by forming national alliances instead of remaining at the European level only. Founding Members of the new platform are Stefan Buchholz, Head of Degussa's ProFerm Projecthouse, consultant Gunter Festel, Ricardo Gent, Managing Director of the German Association of Biotechnology Industries, Stefanie Heiden from Deutsche Bundesstiftung Umwelt (DBU), a national environmental foundation, and Holger Zinke, CEO of B.R.A.I.N. AG, which is one out of few German biotech companies with a larger stake in this area.

Wolf G. Kroner

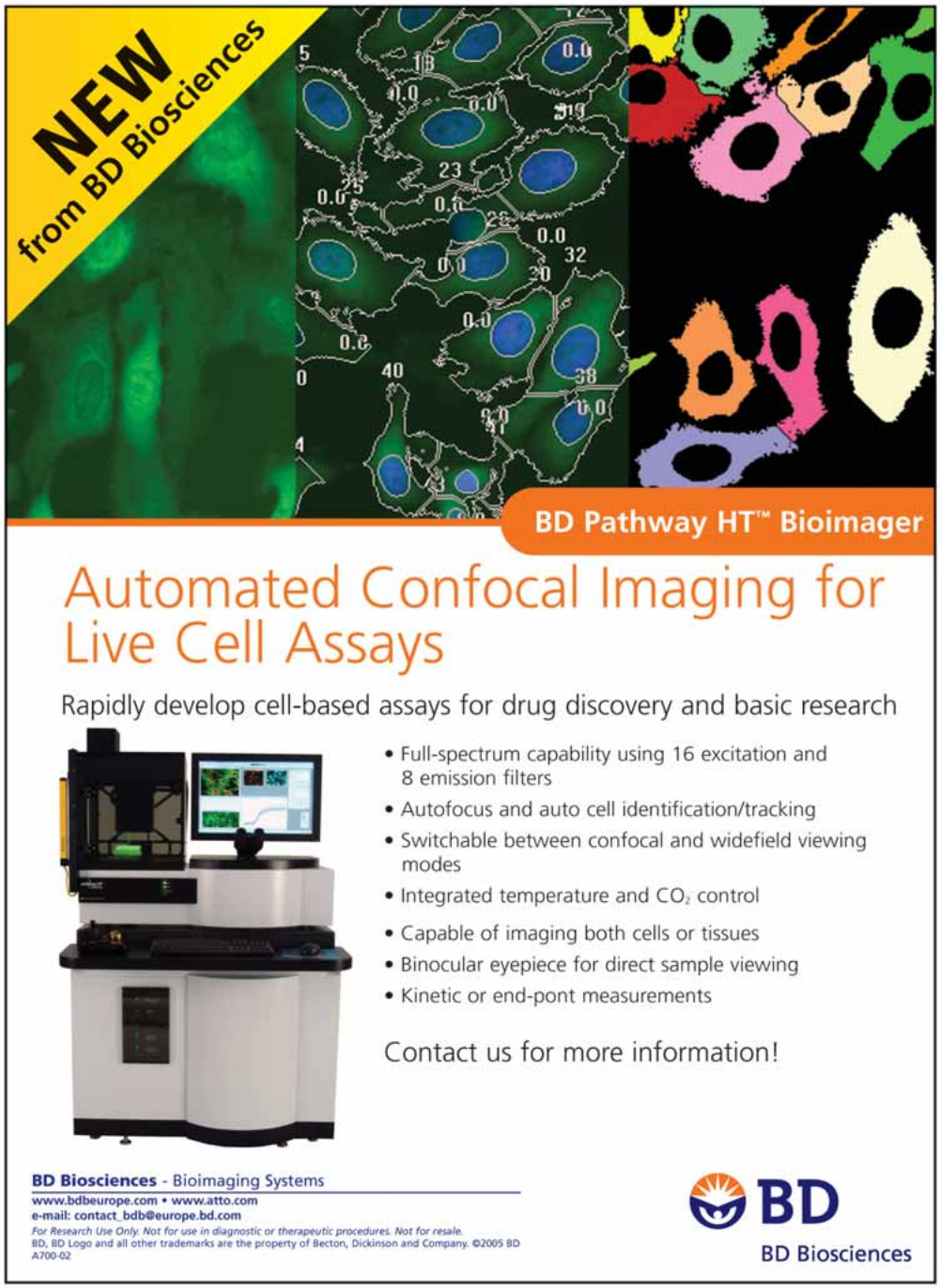
German Platform for Industrial Biotechnology. Founders: (left to right) H. Zinke, R. Gent, S. Buchholz, S. Heiden

At the moment, organizers are still preoccupied with securing a common meaning for «white biotechnology». Stefanie Heiden said that she did not want white biotechnology to become mixed up with engineering of transgenic plants in the public debate, while Jürgen Hambrecht, CEO of BASF equally promoting the subject pleaded not to take apart the «white-green-red biotechnologies-triangle». The initiative comes at a time, when similar platforms are being created in other European countries, and large European chemical companies are looking to spend more on industrial biotechnology projects near their homegrounds. German biotechnologists feel they are facing serious disadvantages by their national government's policy on genetic engineering as well as through fragmented research initiatives. They say that SME biotechs as well have to reach a concerted effort in order to benefit from the increasing demand. «We are late starters in Germany.» said Holger Zinke referring to the new platform. «Industrial biotechnology companies have sold themselves absolutely under price.» As a first step, platform founders intend to consult widely the industry in order to draw up a common action plan on the national scale. A concomitant objective is to tie better in to initiatives on the European level like the European Technology Platform for Sustainable Chemistry formed last july by EuropaBio, Cefic and the European Commission's DG Research.

Regulatory hurdles persisting

In contrast to genetic plant engineering industrial biotechnology is not expected to run into greater problems of public acceptance in Germany. However, for some applications transgene plants may be needed in order to produce intermediates (e.g. industrial sugars), and in some cases production will not be economical within contained systems solely. German industry sees a looming threat for reaping the benefits of «white biotechnology» in the country's genetic engineering law. DIB's Ricardo Gent said, that regulatory bodies should increase professional interaction across organizational boundaries, instead of stalemating

each other politically. He referred to a situation in Germany where authorities under the jurisdiction of the research ministry foster uses of biotechnology, and those under jurisdiction of the consumer ministry do their best to counter that. At Berlin, signs of support for industry's position came from the German Minister of Economics and Labour. Government policy is under continued industry pressure to produce results in improving the ailing German economy. Several large trade associations outside the chemical and biotechnology industry have stated in the past that they consider positive development of the national biotech industry as one of the yardsticks for government performance. □



Stimulation of innovations by R&D spin-offs

The spin-off of R&D activities from established companies into new companies with an independent management has increased significantly during recent years. This article will describe how academic and corporate R&D spin-offs can support the innovation strategy of established companies by creating flexible R&D structures. It is based on an actual market study performed by Festel Capital and on several discussions with industry experts.

TEXT | GUNTER FESTEL , SARAI KÖLLE

Dr. Gunter Festel (1967) is chemist and economist. He is independent management consultant and owner of Festel Capital.

Sarai Kölle (1976) studied economics with focus on biotechnology and currently works at Dechema.

There are often innovation hurdles in companies with established structures (bureaucratic thinking, fear of cannibalism, not invented here syndrome). R&D spin-offs can overcome these hurdles by accelerating R&D projects. All the energy of the new spin-off's management team can be used for the commercialization of the R&D activities. R&D spin-offs can more easily pick up impulses from outside. For example, competencies from other companies or top-class scientists from universities or public research agencies can be brought together to form the best team. One important aspect is that the R&D spin-off is not only a separate legal entity but also has its own identity including its own name and legal units. An adequate and transparent profit-sharing model between parent company, management and employees of the new company as well as external investors is fundamental. As a rule, the management should hold a significant equity stake in the company. Also, the parent company has significant advantages. The fixed cost base and management complexity can be reduced. However, it should be mentioned as well that R&D spin-offs have disadvantages. For example, the momentum of a spin-off can lead to conflicts with the parent company, which may lose control.

The Role of External Investors

External investors were involved in most of the corporate R&D spin-offs (Fig. 1). Normally the parent company provides the necessary assets and intellectual property (e.g. patents) and an investor finances the liquidity requirements of the new start-up. The financial structure depends on the cash flow characteristics of the company. Professional financial engineering secures a sustainable financial structure through the involvement of investors with the right

G. Festl

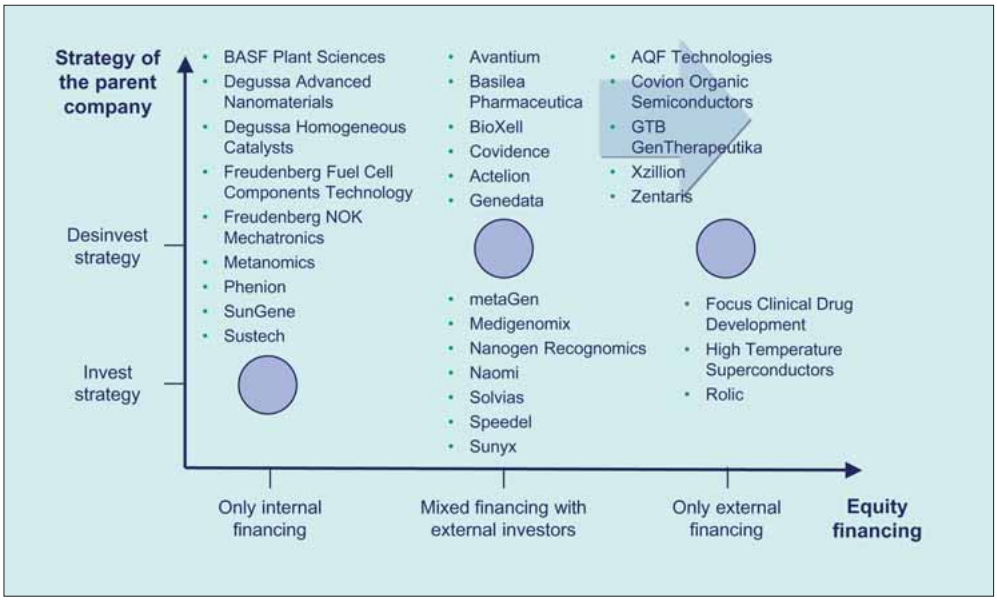


Fig. 1: External investors were involved in most of the corporate R&D spin-offs which were analysed within the market study.

G. Festl

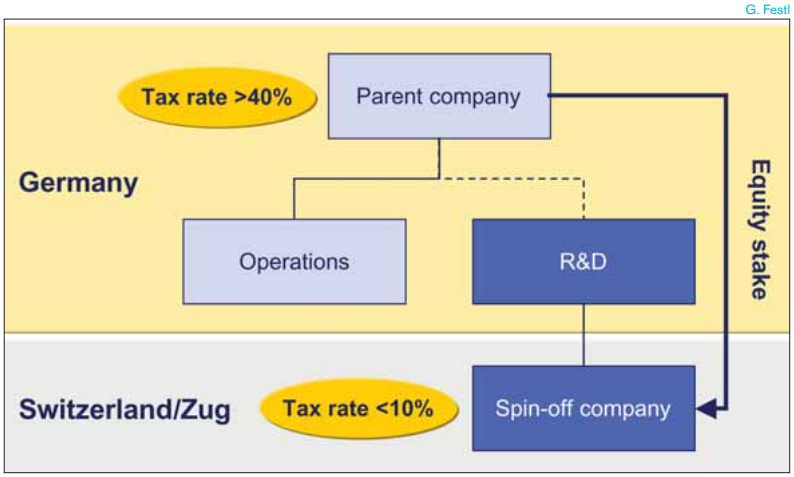


Fig. 2: The spin-off company in Switzerland would be responsible for the world-wide licensing business and pay for R&D work in Germany.

risk/return expectations. Most investors expect annual returns above 20 percent, which can be only realized after an exit. Therefore, it is this which determines the success or failure of an R&D spin-off from the investor's viewpoint. The best way to achieve an exit is an initial public offering (IPO) because the exit price is relatively high and higher returns are thus possible. However, an exit by this means was not always possible in recent years. For example, the IPOs of Rolic (technology-oriented spin-off of Roche in Basel) and Zentaris (biotech spin-off of Asta Medica in Frankfurt) were canceled. The management and the investors would be well advised to come up with alternatives like a trade sale to a strategic buyer, as was the case with Xzillion (proteomics spin-off of Aventis in Frankfurt).

The Pros and Cons of External Investors

The involvement of external investors brings both advantages and disadvantages. From the beginning, there is a strong business orientation because the external in-vestor pushes to realize profitable growth. Additional funding can be invested to meet specific targets and the investor's network can help develop the business. The main advantage is that funding the spin-off by external investors is an "acid test" for the quality of a spin-off. This means that the spin-off must be able to attract external capital. However, there are also disadvantages. A part of the value creation potential is abandoned to the capital provider and there is a potential conflict of interest concerning the exit options (reintegration versus trade sale or IPO). Frequently there is the problem that industrial companies are not willing to provide the required returns to external investors.

Sometimes the involvement of external investors is the first step in selling R&D spin-offs in a second step to a new owner. This has happened in the case of Covion Organic Semiconductors. The company develops, produces and commercializes organic light-emitting diodes for the opto-electronic industry. The specialty chemical company Avecia bought 15 percent of the equity when Covion was spun off from Celanese in 1999. It acquired the remaining 85 percent in 2001. Recently Covion has been sold to Merck in Darmstadt.

Advantages of Tax Optimization Structures

Because of the high corporate tax rates in Germany, start-ups have to consider tax optimization structures before they establish business. A comparison of tax rates shows that, for example, the Swiss canton of Zug has very low tax rates for both companies and individuals. Under certain conditions, taxes on net profit are less than 10 percent – compared with around 40 percent in Germany. It is important to note that the tax optimization structures must be implemented before profits are realized. One suitable structure could be the formation of an additional company in the canton of Zug. The R&D facilities (including all employees) could be located in Germany. The spin-off company in Switzerland would be responsible for the world-wide licensing business and pay for R&D work in Germany (Fig. 2). A concrete example from the pharmaceutical industry shows annual tax savings of about EUR 6 million based on a turnover of EUR 30 million. ⊠

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Is there venture capital for «white biotechnology»?

TEXT | **WOLF G. KRONER**

Biotech start-ups have a strategic choice: Either rise up to a full-fledged big player quoted at the stock exchange or develop into a dedicated supplier to larger manufacturers. Chemical companies follow big pharma in establishing corporate venture capital firms. One of the drivers is the increasing interest chemical industry takes in industrial biotechnology, i.e. the conversion of renewable resources and of raw materials into chemical substances using biotechnological methods. Jens Riese of McKinsey says that already 5% of chemical sales depend today on biotech. The specialties market is worth about €4,6bn with enzymes making up €2,6bn and flavors and fragrances about €2bn in sales value. «There are so many new possibilities to apply this technology, from setting new environmental standards for the manufacturing of textiles, leathers and paper to completely new products like biodegradable plastics,» says enthusiastically Steen Riisgaard, CEO of Danish Novozymes.

Reduced Return on Investment

Besides consumer acceptance and policy frameworks the opportunity to benefit from biotech critically depends on investment. In a closed EuropaBio meeting organized by Europe Unlimited at Barcelona end of last year, participants from private equity and industry discussed prospects of financing biotech applications for chemical production. The attitudes of Venture capitalists towards investing in white biotech was quite varied. There are those independent VCs who simply do not understand what «white biotechnology» is or do not bother to explain opportunities to their investors. They prefer to collect monies for «Red Biotechnology». Others who have looked into the applications are sceptical. Some organic chemists are suspicious about the use of biotechnology for producing chemicals, commented Oscar Goddijn from DSM and pointed to a potential communication problem among industry professionals. In general, representatives from private VC companies said, that industrial biotechnology falls far off the return on investment which can be realized by investing in a biotech pharma.

Corporate VC's take the lead

This view was echoed at a Berlin meeting by German Association of Biotechnology Industries and Deutsche Bundesstiftung Umwelt, a foundation engaged in funding renewable energy projects, end of february. Experts from capital markets said they did not expect in the near future that a white biotech company would come up with a market capitalization of €100m required for an IPO candidate. In Germany the best companies in the field are worth some €30m. Notwithstanding some private VCs as TVM Munich invest in companies in the white biotech field. However, the strategy there is to lead the investment to a trade sale.

In recent years large chemical manufacturers as DSM, BASF or Degussa have established corporate venture funds. Their interest is to secure early access to needed technologies by providing monies for R&D projects. The direction is two-fold, either financing a corporate spin-off, or acquiring a biotech company. However, a concern for these companies is a base too small to pick partnerships from. In Berlin Alfred Oberholz, board member of Degussa responsible for research, and Jürgen Hambrecht, CEO of BASF, both indicated that their companies are more interested in fostering a Petri dish for white biotechnology start-ups than picking out single ones before proliferation and competitive differentiation has occurred. With cutbacks on earnings and dwindling private equity investments in recent years, there are not many European biotech companies who changed from pharma to customers from the chemical industry. German BRAIN AG is one of them. Holger Zinke is happy having changed business focus in 1999, but warns to stick to the same strategy. While for a biotech engaged with pharma the issue is to enter negotiations late in development, in offerings to chemical companies it is key to discuss a project already at the idea stage and come to a deal early. This complements the view of chemical manufacturers. Part of their move to support a suitable start-up scene, they say, is the streamlining of industry-academia cooperations. Academics should not try to beat entrepreneurs, but rather concentrate on creating ideas and checking them on their feasibility. In such a way they would pave the way for start-up companies turning academic research into product ideas and offering these to industry for funding. The task of the big companies, then, is to implement product ideas in production and meet the demand for finished products. Money alone – be it VC money or public funding – will not suffice, says Zinke: «The worst a white biotech start-up can do, is drawing up a business plan from scratch to participate in business plan competitions without having at least one industrial collaboration partner.» □

Tripartite agreement

Artemis Pharmaceuticals, CXR Biosciences and Scottish ITI join forces

Negotiations since july 2004 concluded end of february in a tripartite R&D agreement between German-US Artemis Pharmaceuticals, Dundee preclinical screening platform company CXR Biosciences and Intermediary Technology Institutes Ltd. (ITI), a 100-per cent enterprise of the Scottish government managing technology transfer. ITI's Life Science Unit will grant over a three year period €7.9m (£5.5m) to the project, which means that it spends 12% of its respective total budget in a move to speed up internationalization of the Scottish local biotech industry. Artemis and CXR will jointly develop humanised in vivo model systems for ADME testing of drug candidates that will reflect more closely the human situation. In addition, the two companies will offer services to explore the drugability of so-called «sleeping beauties», i.e. substances that have failed in preclinical studies and have been put on the shelf by pharma sponsors. Artemis Pharmaceuticals claims a technology platform its own, which is a combination of proprietary gene vector design, ES cell transfection, blastocyst injection and gene switch techniques. Under the terms of the agreement the company will bring in its expertise in transgenic mice production and will design and implement the molecular biology for producing the models. CXR Biosciences will determine the target functionality that is being sought and validate the new models as well as set up practical assay systems based on them. CXR and Artemis will commercialize their joint developments together and have no other partners at present. *wk*

NEWS | **COMPANIES**

Fibrex Medical

US Fibrex Medical Inc. announced today that it has secured a US$ 10 million investment co-led by venture capital firms Global Life Science Ventures (GLSV) and Atlas Venture. Also joining the syndicate are EMBL Ventures, the venture vehicle of the European Molecular Biology Laboratory (EMBL), and Mulligan BioCapital AG. Fibrex is a bio-pharmaceutical company focusing on innovative therapeutics for the treatment of inflammation-based tissue injury. This series A financing will be used to progress Fibrex's lead candidate FX06 through proof-ofconcept studies in man for cardiac reperfusion injury. Dr. Rainer Henning will become Chief Executive Officer of Fibrex. Joël Besse, Senior Partner of Atlas Venture, and Dr. Holger Reithinger, Principal of GLSV, will join the company's Board of Directors.

Artes and AC Biotec

Artes Biotechnology GmbH and AC Biotec GmbH announce a collaboration agreement in the area of small scale cultivation and expression technologies using the companies´ proprietary technologies and genuine competencies. Within the collaboration AC Biotec will provide its core competency in the miniaturization of microbial cultivation. ARTES adds the long-term experience in contract R&D in the field of recombinant gene expression, specifically in the proven yeast system Hansenula polymorpha.

Miltenyi Biotec and Agilent

Miltenyi Biotec GmbH, one of the largest biotechnology companies in Germany and a world leader in magnetic cell separation (MACS® Technology), has been certified under the Agilent Technologies Microarray Service Provider Program. Memorec Biotec, a subsidiary of Miltenyi Biotech focused on high-throughput gene expression profiling, has also become certified.

Miltenyi Biotec's worldwide distribution grid enables the company to serve a ready market of Agilent customers around the world.

Debiopharm

Debiopharm S.A., the independent Swiss drug development company specialising in oncology, endocrinology and niche products, has purchased all the outstanding shares of H3 Pharma from Montreal-based Société Générale de Financement du Québec (SGF). H3 Pharma is a drug development company that was created in Montreal in June 2001, as the result of an equal partnership between SGF and the Debio Group. Since then, H3 Pharma has undergone an additional recapitalisation and holds shares in a German biotech company specialising in human antibodies for cancer therapy. Among H3 Pharma's portfolio of products is Sanvar® , which in December 2004 received an approvable letter for its New Drug Application (NDA) from the US Food and Drug Administration (FDA).

Cenix BioScience and Schering

Cenix BioScience GmbH (Dresden), the leading specialist in advanced RNA interference (RNAi)-based research services, and Schering AG (Berlin, Germany), one of the leading pharmaceutical companies worldwide, announced that they have signed research service agreements to accelerate the latter´s target discovery and validation efforts in several human disease programs. Both projects, which started in the last quarter of 2004, focus on the cell-based validation by Cenix of collections of candidate genes previously identified by Schering AG as possible therapeutic drug targets.

to-BBB and Biogen Idec

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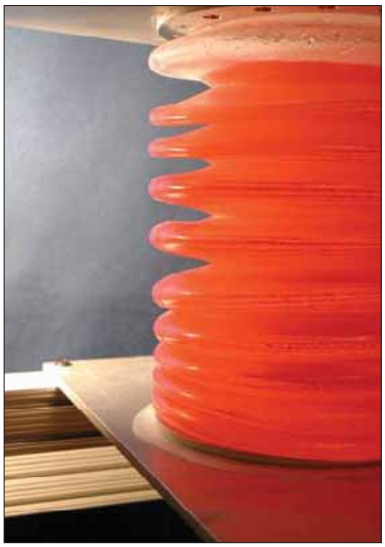
LAUNCH of the FlexMixer™



Wave Biotech and ILCDover announced today the commercial availability of second-generation disposable mixing devices. These two talented companies combined their expertise and created the unique (patent-pending) FlexMixer™. The FlexMixer™ – the first single-use mixing bag that can be used to mix materials of any viscosity or density difference – can be scaled to over 10,000 liters and does not have any internal impeller or actuator. An integral perforated diaphragm in the mixing bag is moved up and down by a simple low-cost mechanism to provide reliable, efficient and complete mixing. Applications are in the pharmaceutical, biotech, food, chemical, ink, paint and other processing industries.

Vijay Singh, the president of Wave Biotech, believes that this new mixing technology will establish disposable mixers as the preferred alternative to traditional mixing tanks, similar to the impact the Wave Bioreactor® has had in cell culture operations.

Compared to traditional mixing systems, FlexMixer™ integrates materials more completely and efficiently and eliminates the need for cleaning and/or sterilization between batches, saving companies valuable time and money.

Wave Biotech is the developer and manufacturer of innovative single-use processing solutions for the biotech industry, such as the highly successful Wave Bioreactor® and Wave Mixer®. ILC Dover specializes in the design and manufacture of flexible structures, including engineered inflatable devices and pharmaceutical powder containment systems. Among other achievements, ILC has been the sole manufacturer of NASA's space suits since project Apollo.

Contact Wave Biotech or ILC Dover for more details and product literature or visit our booths at Interphex 2005, Javits Convention Center, NYC, April 26-28, for a personal demonstration.

Wave Biotech
www.wavebiotech.com

About Wave Biotech

Wave Biotech is a research-based company that develops and manufactures innovative process equipment for the pharmaceutical and biotechnology industry. Our focus is on developing disposable bioprocess equipment for operations traditionally requiring stainless-steel tanks and piping. Key products, such as the Wave Bioreactor, Wave Mixer, and Sterile Tube Fuser, feature disposable contact materials that eliminate cleaning and validation, thereby reducing costs in operations ranging from cell culture, media preparation, buffer dissolution and thawing process intermediates to patient-specific cell therapy in hospitals. These unique, patented, devices can be installed and commissioned rapidly, drastically reducing the time-to-market for biological products. Our equipment is in use with hundreds of companies worldwide, both for R&D, as well as commercial applications.

About ILC Dover

Since 1947, ILC has been active in the design and development of products for both government and industry. Then, as today, most ILC products are comprised of softgoods materials. These products are flexible by nature and result in innovative solutions to customer problems.

Whether protecting personnel in hostile environments, containing pharmaceuticals, or developing unique inflatable devices, ILC has an enviable record of performance. By drawing from a blend of highly qualified personnel and a sound base of both proven and innovative technologies (the same attributes that helped us put man on the moon and Pathfinder on Mars), we continue to develop reliable hardware and unique softgoods to meet today's and tomorrow's challenges.

Key to ILC's success has been our focused internal research and development programs and a sense of urgency to meet new customer challenges. Our Department of Defense, commercial, and NASA customers rely on ILC's multi-disciplined technical expertise to provide innovative softgoods solutions for a wide range of applications.

Discovery Partners International chose TekCel's TubeStore™ System

TekCel, a leading innovator of sample-management and assay-automation systems for life-science research, announced that Discovery Partners International, Inc. has purchased the company's TubeStore System to manage part of the active, working samples that make up a portion of NIH's Small Molecule Repository project. TekCel's TubeStore System picks, organizes, and maintains samples in a temperature-controlled, inert environment right up to the moment they are requested for release. This prevents compound degradation and helps ensure quality results.

The National Institutes of Health (NIH) awarded DPI a multi-year contract to set up and maintain a small-molecule repository to manage and provide up to one million chemical compounds to multiple NIH funded Screening Centers as part of the NIH Roadmap (http://nihroadmap.nih.gov/). The repository is being located at DPI's Chemistry Division, in San Francisco, California. Building upon the results of the Human Genome Project, the NIH Roadmap has been established to accelerate medical research progress in drug discovery. The ultimate goal of the repository is to offer public sector biomedical researchers access to hundreds of thousands of small organic molecules, which can be used as chemical probes to study cellular pathways in greater depth.

«We are gratified to be an integral part of this important project,» said Dr. Robert J. Rosenthal, president and chief executive officer of TekCel. «Too often, the results of high-throughput screening programs are compromised due to degradation of the samples. In order to be successful, researchers must have confidence that the samples they are testing are identical, each and every time they are used. Compounds must be readily accessible, yet they must be maintained in an ultra-stable, ultra-controlled environment. That's where TubeStore comes in. We designed TubeStore as a comprehensive, automated system for the high-throughput, multi-user drug-discovery lab: all it needs to input, organize, store, cherry pick, thaw, output to the liquid-handling system, and return to storage its valuable samples – extraordinarily fast.»

The following excerpt from the NIH Statement of Work concerning this project provides further detail:

A large focus of the «New Pathways to Discovery» theme is on a class of organic chemicals, commonly referred to as «small molecules,» that has proven to be extremely important to researchers exploring the functions of the cell at the molecular level. Such molecules have also been valuable for treating everything from headaches to cancer. It remains difficult to predict which small molecule compounds will be most effective in a given situation. Researchers can maximize the likelihood of a successful match between a chemical compound and its usefulness as a research tool or its desired therapeutic effect by systematically screening thousands of small molecules. The initiative, called «Molecular Libraries,» will offer public sector biomedical researchers access to small organic molecules, which can be used as chemical probes to study cellular pathways in greater depth. It will provide new ways to explore the functions of major components of the cell in health and disease. The initiative will also accelerate the availability of promising new drugs, especially for rare diseases.

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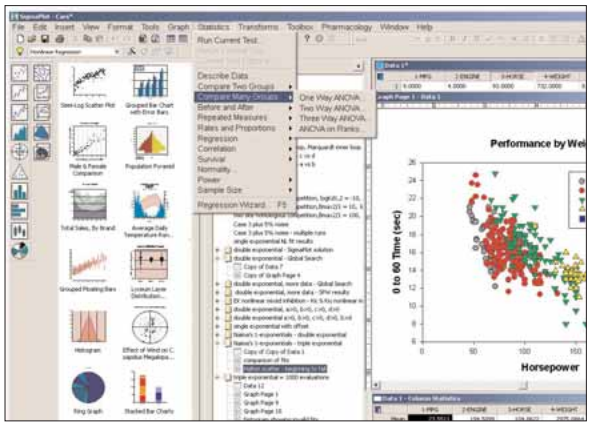
SigmaPlot 9 with extended statistics features



Systat Software, Inc., a leading developer and supplier of scientific software and services, has introduced version 9 of its data analysis and technical graphing software SigmaPlot.

Due to full compatibility with SigmaStat 3.1, Systat Software's guided statistics package, SigmaPlot 9 allows researchers to access more than 30 of the most frequently used statistical procedures including regression diagnostics, variance analysis, descriptive statistics or survival analysis directly from its statistics menu.

ODBC compliant data import and a large number of data worksheet improvements as well as the new browser-style Notebook Organizer ease data entry and navigation as well as notebook control. New export options such as PDF for graphs and reports and HTML for reports enable researchers to easily share their results with colleagues.

Further improvements include new category data format options in the Graph Wizard to show differences among groups in their data or to visualize group effects in multiple comparison charts, intelligent histograms for distribution visualization with automatic binning, added symbol types for easier differentiation of multiple groups, additional data analysis capabilities and added security features.

SigmaPlot 9.0 is available for 745 Euro (academic price: 525 Euro), the update price is 195 Euro. SigmaStat is available for 495 Euro (academic price: 395), the update price is 195 Euro. The special bundle price for SigmaPlot 9 and SigmaStat 3.1 is 999 Euro (academic price: 799 Euro).

Headquartered in Richmond, California, Systat Software is a leading developer of specialized scientific software products for data analysis, technical graphing and presentation. Its products SYSTAT, SigmaPlot, SigmaStat, TableCurve, PeakFit and SigmaScan Pro are extensively used for research, analysis and presentation in the areas of environmental sciences, life sciences, medical research, behavioral sciences, and engineering.

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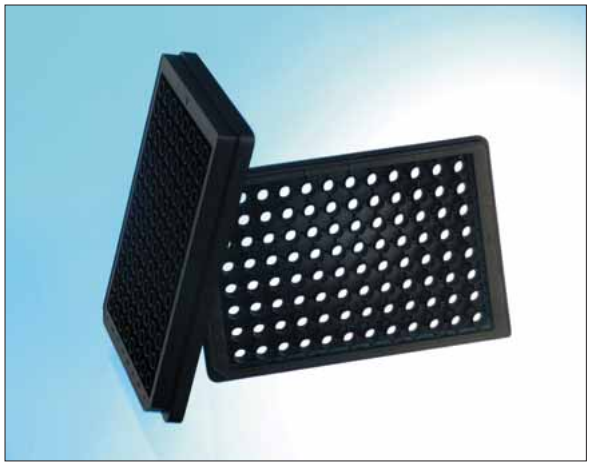
Well Half Area Microplates optimise sample volumes



Greiner Bio-One GmbH, internationally leading technology partner for the diagnostic and pharmaceutical industry and biotechnology, is bringing Half Area Microplates on the market as of February 2005, permitting a reduction of up to 50 per cent in the sample volumes in the 96 well microplate-format as compared to heretofore typical values.

For numerous applications in the laboratory the reduction of the sample volumes is an elementary criterion. In pharmaceutical active-substance screening automatised processes using high format microplates with 384 or 1536 wells are usual. But research groups in R&D as well as enterprises active in ELISA-diagnostics frequently use 96 well microplates for manual handling. The newly developed 96 Well Half Area Microplates from Greiner Bio-One are exactly optimised for these requirements: They are characterised by a standardised layer thikkness (1cm = 170µl, 0.5cm = 80µl), they can be quickly and precisely pipetted by hand and they allow a reduction of the sample volume by 50%. As suited to the individual application, laboratories have the choice between black, white, clear and µClear® Microplates in ELISA-, HTS and cell culture quality.

Greiner Bio-One GmbH
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Telefon: +49 (0) 70 22 948 - 0
Fax: +49 (0) 0 70 22 948 - 514
E-Mail: marketing@de.gbo.com

Selerity Technologies' European Customers Benefit from Dedicated Local Expertise and Support

Temperature Programmed Liquid Chromatography (TPLC) specialist, Selerity Technologies Inc has grown its distribution network to offer dedicated local expertise and support in key markets. Managed by its European partner, the Research Institute for Chromatography (R.I.C., Kortrijk, Belgium), Selerity's distribution network comprises leading HPLC specialist vendors such as Gerstel, Anatune Ltd and Da Vinci Europe Laboratory Solutions BV, who are able to support customers and potential customers across Europe and Asia.

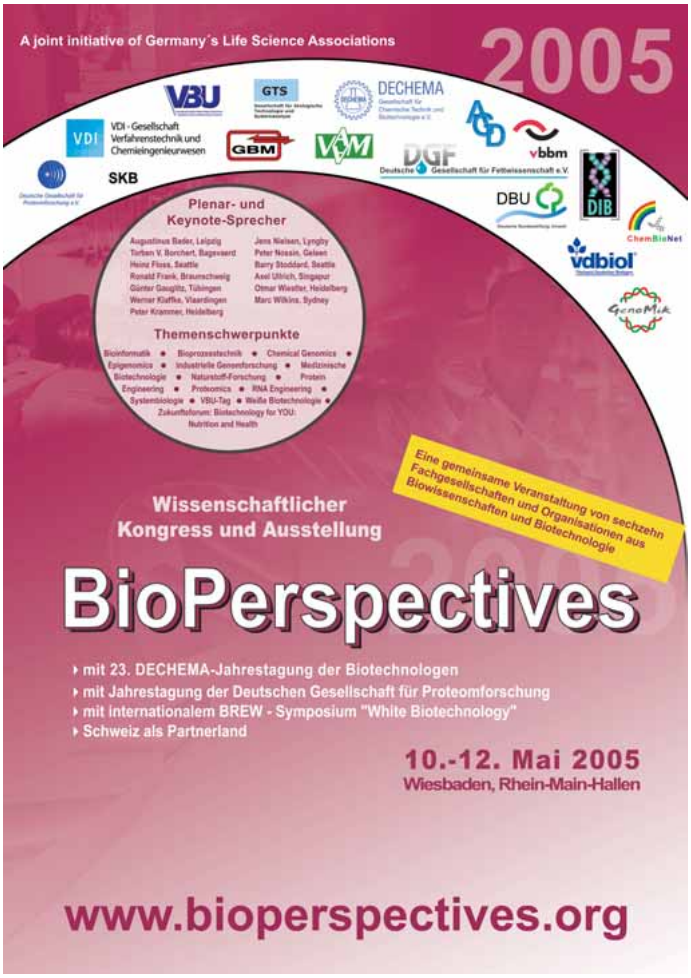
Selecting R.I.C. as the European distribution headquarters for its HLPC product line has been a stepping stone for the development of a strong, cohesive and technically knowledgeable network. There is now representation in key territories such as France, the Benelux, Germany and the United Kingdom, but also Hungary, which is enjoying very aggressive economic growth and more recently Japan. R.I.C. has facilitated this process with its strong relationships with specialist vendors and its reputation in the advancement of chromatography applications, techniques and method development.

Jody Clark, VP sales and marketing, Selerity Technologies, believes that, with most research on high temperature HPLC originating from European universities, TPLC method development is likely to be more rapidly embraced in countries such as France, Germany, the UK and Benelux. This made the appointment of a knowledgeable partner to develop these markets all the more significant. She says: «Choosing R.I.C. to proactively develop interest in our product range in Europe has been instrumental to our ongoing success. Their understanding of the market, technical expertise and focus on offering total solutions ensures that we have a reliable partner in Europe that is able to effectively manage our wider distribution network.»

Jody concludes: «With some of the most respected laboratory equipment vendors now representing our product line, we are well positioned to promote the benefits of our TPLC instrumentation to separations scientists. We are now confidently embarking on the next phase of our market development program to extend our reach to Spain, Italy and China.»

A full list of Selerity's distributors can be found at: http://www.selerity.com/main/main_euro.html

www.selerity.com
e-mail sales@selerity.com



Cascada Lab Water System

The need for purified water, so as not to impact test results, is an essential and growing requirement of research and diagnostic laboratories, especially as testing equipment becomes more sensitive and more stringent regulations are promulgated globally. To meet these demanding life science and analytical testing requirements, Pall Corporation, the global leader in filtration, separations and purification, announced that it is bringing its water purification expertise to the laboratory market with the introduction of the Pall Cascada™ Lab Water Systems. The Cascada point-of-use system provides optimum water quality to support diverse laboratory needs from the most critical, sensitive applications through general-purpose use.

«As the lab market becomes increasingly complex and demanding, customers need trustworthy providers that are deeply entrenched in water purification,» says Ken L. Harris, President Pall Life Sciences New Technology. «Pall's entry into this marketplace combines more than a half century experience in the development of the most advanced water purification technologies used by a host of industries worldwide with our in-depth, extensive knowledge and understanding of the diverse application needs of the laboratory markets we serve»

The Cascada System enables laboratories to achieve the highest purity water through a series of separation and purification steps in a single box on demand. Four polishing systems, with customized configurations to meet a wide range of sensitive application requirements for high quality ultrapure water, are available. They are:

- The Cascada BIO-water, a polishing system for demanding life sciences applications such as cell culture, in vitro fertilization, microfluidic and array systems;
- The Cascada AN-water, a polisher for demanding analytical applications such as ultra-trace environmental analysis;
- The Cascada IX-water, a polishing system for less demanding lab water applications; and
- The Cascada LS-water polisher for general-purpose lab analysis, including less sensitive life science applications.
- pretreatment system, the Cascada RO-water system is also available to protect and extend the life of the polishers, which is particularly important in cases where there is poor feedwater quality.

The Cascada Systems offer a multitude of benefits including multi-stage monitoring, data tagging, intelligent dispensing and «real-time» total organic carbon (TOC) monitoring. The systems can be comprehensively and completely sanitized. Each of the products has full FDA validation pages and traceable cartridges back to the source.

Expanding Market with Unmet Needs

«The lab water market continues to expand and rapid technological growth in regions of the world, such as Asia and Latin America, still have many unmet needs. We are confident we will be one of the leading providers of point-of-use laboratory water systems in the near future,» says Mr. Harris.

The global laboratory water systems and consumables market is estimated at $250 million dollars, growing at a rate of about 8 percent annually.
«Pall selected the best available technology for our new system to monitor and protect the quality of the output water at the least cost of ownership for academic, clinical, biopharmaceutical and pharmaceutical research laboratories,» Mr. Harris adds. «The new Cascada system is merely the tip of the iceberg for Pall in this marketplace.»
The Company plans to extend its dominant position in water purification by utilizing its proprietary technologies to continue to refine systems and lead in the growing, changing and ever more demanding laboratory water market.

www.pall.com

About Pall Corporation

Pall Corporation is the global leader in the rapidly growing field of filtration, separations and purification. Pall's business is organized around two broad markets: Life Sciences and Industrial. The Company provides leading-edge products to meet the demanding needs of customers in biotechnology, pharmaceutical, transfusion medicine, semiconductors, water purification, aerospace and broad industrial markets. Total revenues for fiscal 2004 were $1.8 billion. The Company headquarters are in East Hills, New York with extensive operations throughout the world.

Raman Spectroscopy Platform for High-Speed Polymorph and Crystal Analysis

Thermo Electron Corporation has enhanced its Array Automation software for Raman spectrometers, enabling pharmaceutical companies to dramatically reduce their polymorph and crystal analysis workload in their drug discovery laboratories.

Chris Petty, Director for Vibrational Spectroscopy Products at Thermo Electron, explains: «It has been a trend in the last few years for pharmaceutical companies to do exhaustive polymorph analysis and crystallization studies on candidate drug compounds much earlier in the drug discovery and development process. The net result has been a marked increase in the workload for the analytical groups in R&D.»

Raman spectroscopy is an ideal technique for the analysis of drug compounds. Particularly sensitive to the subtle differences found between polymorphs and other crystal forms, Raman requires no disruption to the crystalline form of a material.

Recent developments in Thermo's Raman instrumentation, such as automated well-plate, capillary tube array handling, and the MicroStage FT-Raman microscope, have enabled new high-throughput screening applications. Combining Raman's ability to determine crystalline structures with automated sample handling capabilities, the Array Automation software enables high throughput screening applications on Thermo's Nicolet™ Almega™ XR dispersive Raman and NXR FT-Raman spectrometer lines.

The Nicolet Almega XR dispersive Raman microscope permits analysis of small amounts of individual crystals, while the FT-Raman spectrometer, using Thermo's exclusive MicroStage FT-Raman microscope, eliminates fluorescence interference. Thermo's Array Automation software automates the collection of spectra from either of these formats, and performs group or cluster analysis on the collected spectra.

«Prior to the Array Automation software, spectrum-to-spectrum comparison had to be done manually. Now, work that used to take a chemist half a day can be completed in five minutes», said Petty.

The Array Automation software integrates Raman analysis into the customer site workflow by communicating with the customer's LIMS. Thermo Electron provides validation for its Nicolet Almega XR dispersive and NXR FT-Raman spectrometers. Digital signature capabilities are also available to ensure compliance with in-house requirements.

+1 800-532-4752,
e-mail analyze@thermo.com
www.thermo.com/spectroscopy

New Kit for Effective and Cost-efficient Gene Knockdown

RNA interference, a process where short interfering RNAs (siRNAs) are used to silence gene expression in a sequence-specific manner, has generated great excitement during the last years. The application of RNA interference in mammals is being widely used for the functional characterization of genes for basic research, drug discovery, and target validation, and has the potential to allow the systematic analysis of gene expression and of therapeutic gene silencing.

Roche Diagnostics' new X-tremeGENE siRNA Dicer Kit is designed for the fast and efficient preparation of high-purity pools of target-gene–specific diced siRNA for use in RNA interference applications. The resulting 21-23 bp diced siRNA is ready for transfection into cells. The Roche Diagnostics' Dicer Kit contains an optimized T7 in vitro transcription system for production of long double-stranded RNA. Furthermore, it contains recombinant human Dicer enzyme, for cleaving of the long double-stranded RNA, and a purification module yielding high-purity pools of diced siRNA.

The new kit ensures effective gene knockdown, because a mixture of siRNAs generated analogous to the in vivo process is more likely to silence gene expression than a single siRNA. Due to the high purity and the low concentration of each individual siRNA in the mixture, side effects are minimized. Using a pool of diced siRNA eliminates the need to screen multiple individual siRNAs to find an effective one, leading to savings of time and resources for the kit´s user.

www.roche-applied-science.com/geneknockdown

The promise of intelligent machines

REVIEW

ROBERT R. ROHRKEMPER JR.[1], UELI RUTISHAUSER [2]

The Promise of intelligent machines
Jeff Hawkins, Sandra Blakeslee
Times Books, 2004, hardover, ISBN 0805074562

For more than thirty years, Artificial Intelligence (AI) researchers have expected the «imminent» release of intelligent machines with abilities far surpassing those of humans [1]. Such machines would understand natural language and perceive the visual world just as we do. However, the most sophisticated machines today cannot understand language as well as a toddler and their ability to interpret a visual scene is sub-par compared to a mouse. The premise of AI was that intelligence is just a difficult programming problem. Understanding why biological systems are intelligent was thought to be nonessential. Clearly, this approach of ignoring nature's design has not been successful. Considering our distance from the goal of building intelligent machines, should we rather attempt to build machines the way biology builds brains?

A machine cannot distinguish man from machine

In his new book, On Intelligence, Jeff Hawkins, together with Sandra Blakeslee, describes how the lack of progress can be attributed to the absence of a working theory of the cortex. With a greater understanding of the hierarchal structure and predictive nature of the cortex, he says, we can build intelligent machines based on the operation of the human brain.

Starting with this promise, Hawkins motivates the reader with a definition of intelligence. He says that intelligence is not being able to pass

the «Turing Test», or even the «Chinese Room Test», which involve the inability of an observer to distinguish a machine's behavior from that of another human. He says that truly intelligent systems are able to predict complex events on varying timescales and levels of detail. At the sensory level, we predict the sensations our body will perceive when interacting with the environment. At the behavioral level, we predict how our actions will influence a result. Machines which can fool us with human-like behavior do not pass the prediction test because they do not comprehend their input. Merely following a set of rules and producing an output does not constitute understanding.

Mimicking increasing complexity

Hawkins argues that prediction evolves from the brain's hierarchal structure and connectivity [2]. Our natural environment is organized into structures of ever increasing complexity. The brain mimics this organization internally through cortical processing columns. He believes that the architecture of these columns is preserved throughout the cortex. Stimuli propagate from hierarchically lower areas until they reach a higher region with sufficient interpretation capabilities. Sections of cortex act as pattern recognition systems regardless of the sensory modality. Each area synthesizes stereotypical sequences of learned input patterns and communicates to higher-level areas. To this higher level, the synthesis may look like a familiar pattern. Thus, it will again summarize the input before referring it onward. This theory is unique because it firmly states that a common computational process occurs throughout the cortex [3]. Hawkins says that all areas of the cortex are «doing the same thing», but with different types of input.

So, if each part of the cortex is virtually equivalent to any other part, and individual neurons are very similar in other species, why is it that humans are the most intelligent? The author's answer is that we are able to predict longer temporal sequences with greater abstraction. Our neocortex, compared to other species, although very similar, is much larger and more convoluted. Dolphins have a significantly larger neocortex than humans, but it has three layers rather than six. Thus, dolphins are likely endowed with a very large memory capacity, but their ability to abstract is weak.

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2 Dr. Ueli Rutishauser is Graduate Student in Computation and Neural System at the California Institute of Technology, Pasadena, CA 91125, urut@caltech.edu

Standing on giant's shoulders

The concluding chapter acts as a summoning of scientists to work on the problem of intelligence. Hawkins says that now is the time to build intelligent machines. He makes the prediction that at first they will appear in software which runs on specially designed hierarchal computational devices. Data input to these systems may take the form of existing data, or it could be collected in real-time in quantities and spatial distributions of which humans are incapable. He says intelligent machines will be able to think at incredible rates and will converse silently many times more quickly than humans.

Sir Isaac Newton once said, «If I have seen further than others, it is by standing upon the shoulders of giants.» Hawkins also owes his wealth of knowledge to many «giants» – brilliant scientists who have laid the foundations necessary to build such a theory. Some of his theories are unsubstantiated, but are not completely novel nor subversive. Still, they provide grounds for critique and refinement of our understanding. He acknowledges that many previous frameworks have proven inaccurate, but claims that theories are important for their aide in refining our research goals and ambition to build intelligent machines.

We recommend this book, written by the inventor of the Palm Pilot, to a general audience who would like to understand an intriguing theory of human intelligence. Experienced scientists will appreciate the book for its presentation of a whole brain theory in a broader context and for the debates which it provides.

References:

[1] RA Brooks, Cambrian Intelligence: The Early History of the New AI, MIT Press, 1999.

[2] RJ Douglas and -KAC Martin, Neuronal Circuits of the Neocortex, Annual Review of Neuroscience, 2004.

[3] VB Mountcastle, The columnar organization of the neocortex, Brain, 1997

A joint Japanese-European biotechnology conference

SOZO is a new and unique bio-pharmaceutical conference which brings together Japanese pharmaceutical and biotechnology companies with their European counterparts. Speakers from some of the major Japanese pharmaceutical companies are presenting at SOZO.

Eisai, Sumitomo ,Sankyo, Tanabe,Toyama, Taisho, Meiji Seika,Sosei, Teijin, Anges and Kirin Pharmaceutical will be outlining their licensing strategies.

Japanese pharmaceuticals are having an increasing importance in the bio-pharmaceutical market in Europe through increasing collaborations, licensing and financing deals. For European delegates this is a wonderful opportunity to meet and hear from major players from the Japanese bio-pharmaceutical industry without having to travel to Japan.

Several major venture capitalists and investment banks from Japan and Europe are also presenting including Nomura, NIF, Atlas, MVM, Abingworth, Lazard, Credit Suisse First Boston, GIMV, TVM and ITX.They will be both sharing their experiences of Euro-Japanese business with the conference and also looking at new opportunities with the 46 presenting biotech companies.

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www.sozobiotech.com

BIOFORUM: A success confirmed

Feverish preparations are being made for the second edition of «bioforum», the expo and conferences on biotechnologies: where science meets enterprise. Bioforum 2005 will be held in Milan on 28-29 September at the Sede Bovisa of the Politecnico di Milano.

Following the success of the first edition (approx. 2.000 participants, 50 exhibitors and sponsors and 89 speakers), «bioforum» this year has several new goals, first among them, to extend its horizon from the national to the international scene, as well as consolidating relations between institutions, firms and research institutes.

The preparatory phase for the 2005 edition is attracting a great deal of enthusiasm, as confirmed by the fact that the project is being further enriched so as to bring together science and enterprise. It is most important to have a practical approach and the edition will be structured in six areas: health, food and agriculture and the environment, bioprocesses and bio products, bio IT, finance and services.

Participating in the bioforum represents a unique opportunity in Italy for promoting your activities and, at the same time, coming into contact with the more advanced developments in the biotech sector, all in an unmistakably business-orientated context.

www.bioforum.it/english
bioforum@iter.it
ITER, Stefano Foresti,
Tel. +39 02 2831161

2005 I MARCH

20 – 22 March
San Fransisco (USA)
BioTechnica America
www.biotechnica-america.com

31 March – 2 April
Mosbach (DE)
56. Mosbach Kolloquium 2005
www.gbm-online.de

2005 I APRIL

11 – 15 April
Lyon(FR)
BioVision/Biosquare
www.ebdgroup.com/biosquare/index.htm

12 – 15 April
Mexico City (MX)
Achemamerica 2005
www.achemamerica.de

13 – 14 April
Berlin (DE)
BioFine
www.www.selectbiosciences.com/conferences/biofine2005

19 – 21 April
Singapore (SG)
Pharmaceutical Manufacturing
www.interphexAsia.com

19 – 22 April
Moscow (RU)
Analytica Expo
www.analyticaexpo.ru

21-22 April
Padova (IT)
Bionova
www.bionova.it

26 – 28 April
Helsinki (FI)
ChemBio/BioFinland
www.finexpo.fi

2005 I MAY

7 – 10 May
Praha (CZ)
European Human Genetics Conference
www.eshg.org/eshg2005

9 – 12 May
Basel (CH)
MipTec 2005
www.miptec.com

10 – 12 May
Tel Aviv (IL)
BioIsrael 2005
www.bioisrael.com

10 – 12 May
Nürnberg (DE)
Sensor+Test 2005
www.sensor–test.com

10 – 12 May
Wiesbaden (DE)
BioPerspectives 2005
www.dechema.de

11 – 12 May
Basel (CH)
Project Management for Pharma- and Biotech Companies.
International Business Negotiation Skills: Strategies, Tactics and Countermeasures
www.scivent.com

12 May
Montreux (CH)
SOZO
www.sozobiotech.com

17 – 19 May
Wädenswil (CH)
BioTech 2005 and Swiss-Czech Symposium
www.biotech2005.ch

18 – 20 May
Leipzig (DE)
2nd World Congress on Regenerative Medicine 2005
www.regmed.org

18 – 20 May
Frankfurt aM (DE)
2nd European Conference on Natural Attenuation
www.dechema.de

18 – 20 May
Tokyo (JP)
24th International Bio Expo Japan 2005
www.bio-expo.jp

22 – 25 May
Amsterdam (NL)
Phacilitate Vaccine Forum Spring 2005
www.www.phacilitate.co.uk/pages/spring_vaccine/index.html

24 – 26 May
Genf (CH)
bioLOGIC Europe
www.lifescienceworld.com/2005/bio_CH

24 – 27 May
Basel (CH)
ILMAC 2005
www.illmac.ch

26. – 27. May
Amsterdam (NL)
Europe Viral Vectors & Vaccines
www.wilbio.com/wbe2004.html

2005 I JUNE

2 – 3 June
Frankfurt a.M. (DE)
Weisse Biotechnologie Partnering
www.dechema.de

5 – 6 June
München (DE)
Biotech Finance Forum
www.e-unlimited.com

5 – 8 June
Heidelberg (DE)
Congress on Environmental Catalysis
www.dechema.de

5 – 9 June
Harrogate (UK)
ESACT Meeting
www.esact.org

6 – 8 June
München (DE)
BioTrends
www.biotrends.de

7 – 10 June
Praha (CZ)
European Human Genetics Conference
www.eshg.org/eshg2005

10 – 14 June
Glasgow (UK)

World Congress on Chemical Engineering www.chemengcongress 2005.org

22 – 24 June
Sawbridgeworth (UK)
Medicinial Chemistry
www.scientificupdate.co.uk

23 – 24 June
Roma (IT)
Pharma Finance 2005
www.milanogroup.com

23 – 27 June
Lodz (PL)
Polish Biotechnology
www.biotechnologia.pl

27 – 30 June
Seoul (SK)
Korea-Germany Life Science Partnering Event

2005 I JULY

1 – 3 July
Delft (NL)
Biotrans 2005
www.biotrans2005.bt.tudelft.nl

1 – 3 July
Athine (GR)
2nd International Greek Biotechnology Forum
www.bionova.gr

3 – 8 July
München (DE)
Biotech Finance Forum
www.e-unlimited.com

2005 I AUGUST

21 – 25 Aug.
Kobenhavn (DK)
ECB12 – 12th European Congress
lhp@bio.auc.dk

31 Aug. – 3 Sept.
München (DE)
4th Annual Meeting of the European Tissue Engineering Society
www.tissue-engineering.net

2005 I SEPTEMBER

3 – 9 Sept.
Dresden (DE)
ELSO 2005
www.elso.org

4 – 8 Sept.

Oxford (UK)
Global Aspects of Technology Transfer: Biotechnology
www.grc.uri.edu/programs/2005/global.htm

6 – 8 Sept.
Wiesbaden (DE)
Dechema/GVC-Jahrestagung 2005
www.dechema.de

13 – 15 Sept.
St. Gallen (CH)
Nanofair 2005
www.nanofair.ch

14 – 15 Sept.
London (UK)
Pabord 2005
www.pabord.com

23 – 26 Sept.
Göttingen (DE)
2nd European Conference on Prokaryotic Genomes
www.dechema.de

28 – 29 Sept.
Milano (IT)
Bioforum 2005
www.bioforum.it

2005 I OCTOBER

4 – 7 Oct.
Milano (IT)
Expobiotech
www.assoexpo.com

5 – 8 Oct.
Zürich (CH)
European Pharma License Exchange
www.www.europlx.com

9 – 14 Oct.
London (UK)
BioPartnering/CORDIA
www.cordiaconvention.com

11 – 13 Oct.
Nuernberg (DE)
TECHNOPHARM European Congress on Life Science Process Technologies
www.nuernbergmesse.de

11 – 13 Oct.
Nuernberg (DE)
POWTECH Int. Fachmesse für Mechanische Verfahrenstechnik und Analytik
www.nuernbergmesse.de

18 – 20 Oct.
Hannover (DE)
BioTechnica 2005
www.biotechnica.de

18 – 21 Oct.
Göttingen (DE)
Conference on Prokaryotic Genomes
www.dechama.de

2005 I NOVEMBER

7 – 9 Nov.
Dresden (CH)
BioEurope 2005
www.ebdgroup.com/bioeurope

28 – 30 Nov.
Lille (FR)
9ème Carrefour Européen des Biotechnologies
www.carrefoureuropeen-desbiotechnologies.com/

15 – 17 Nov.
Montreux (CH)
NanoTech
www.nanotech-montreux.com

16 – 19 Nov.
Düsseldorf (DE)
Medica
www.medica.de

31 Nov. – 1 Dec.
Porto (PT)
European Pharma License Exchange
www.www.europlx.com

Strong exhibitor line-up for BioFine 2005

BioFine 2005, the international life science exhibition and networking event, takes place in Berlin, Germany from April 13-14, 2005, and already more than 60 exhibiting companies have confirmed their participation in the event.

Organised by avakado, BioFine 2005 is the international exhibition, conference and networking event for companies offering contract services, technologies and products to pharmaceutical and biotechnology companies involved in the discovery, development and production of novel drugs. The event will take place at Messe Berlin, offering suppliers to the life science industry the platform to generate new business leads, while maintaining and improving existing customer relationships.

BioFine 2005 will also include the MedChem Europe 2005 medicinal chemistry conference jointly organised by Scientific Update and Select Conferences, two half-day workshop sessions, site visits to the Campus Berlin-Buch biotechnology park and the R&D laboratories of Schering AG, and a gala evening, ensuring it delivers the complete solution for sector professionals.

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MedChem Europe 2005
Claire Francis
Scientific Update
Tel: +44 1435 873062.
Email:
laire@scientificupdate.co.uk.
www.medchemeurope.com

Biologic Europe 2005 – Where biotech and biomanufacturing meet

Europe's leading biotech and biomanufacturing convention now includes dedicated content for SMEs in the biotech sector, including a separately bookable pre-conference biotech strategy briefing day. Plus presentations covering: adding value in product development, getting the required expertise, outsourcing options for biotechs, the clinical trials directive, quality management for clinical trials and comparability challenges.

For biomanufacturers, there are visionary strategies and technology presentations covering biosimilar challenges and opportunities, future product opportunities, technology transfer and PAT initiatives, novel cell lines and expression systems, manufacturing facilities, challenges and solutions plus overcoming bottlenecks in downstream processing.

Who should attend?

If you are a Biomanufacturer, biotech, RDA, Government, CMO, Construction company, Equipment provider, Consultant or Venture capitalist, this is the must attend conference of 2005. More speakers and conference tracks than ever before. Huge savings and benefits for corporate groups. Over 13 hours of dedicated networking. Plus 50% discount for biotech start-ups and non-profit organisations.

This is the only conference designed to bring biotech and biomanufacturing together.

Brian Mallory or Michael Parsons
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www.lifescienceworld.com/2005/bio_CH

MipTec conference 2005 on drug discovery is taking shape

From 9 to 12 May 2005 the MipTec Conference and Exhibition will take place at the Basel Convention Center. MipTec has emerged as a leading European conference on enabling technologies for drug discovery and development. The event is entering the 8th year under the leadership of a multi-national Program Committee. MipTec has evolved broadly from its roots in high-throughput screening and related automation technologies to encompass a wide range of topics that engage those involved in creating the next generation of therapeutics. By their own admission, the organizers of MipTec assert that it is a delicate balance to cover such a diversity of topics while attracting more and more attendees each year. But it is in this diversity that reveals the uniqueness and appeal of MipTec to scientists from Biotech and Pharma alike.

In addition, for the 3rd consecutive year, there will be a one-day pre-conference specializing in one key area (Monday, 9 May). Two years ago, it was «Chemical Genomics», last year was «Oncology Drug Discovery» and this year it will be «Innovative Therapies for Neurodegenerative Diseases». Development of new drugs for neurodegenerative diseases like Alzheimer and Parkinson's disease is one of the hottest topics in many pharma and biotech companies. The conference will discuss «what's needed» and «what's hot» in preclinical and later stages of drug discovery and development.

To kick-off the main MipTec conference, Professor Alex Matter will give a Keynote Address entitled «Drug Discovery in the Third Millennium». Dr. Matter, currently Head of the Novartis Institute for Tropical Diseases in Singapore is an international legend in the world of molecular targeted therapeutics, having led the award-winning team that discovered and developed Gleevec, a drug that essentially cures a previously fatal disease, chronic myelogenous leukemia. Dr. Matter will undoubtedly discuss this success story as well as his current efforts to address unmet medical needs in the Third World.

On the last day of MipTec the organizers have arranged to have Dr. Christopher Lipinski, Emeritus Pfizer Investigator to give a closing Keynote Address entitled «The Discovery Innovation Gap: Questioning the Politically Correct Assumptions». The main MipTec Conference will cover the following session topics:

Pre-Clinical Profiling and Biomarker Discovery

This session will explore the technologies being employed to increasingly shorten the timelines from lead identification to clinical development. Infrastructure for early ADME evaluation and embedding biomarker discovery early in the discovery process are two key examples of what will be covered.

Leveraging the Power of Informatics in Drug Discovery

With the huge explosion in the number of targets and the number of compounds screened in lead-finding campaigns, informatics becomes a key component of the discovery process. Topics such as chemo-informatics, triage of HTS hits, and data-mining are a few examples of topics discussed in this session.

MipTec
The Leading European Event on Enabling Technologies for Drug Discovery

Orphan Target ID and Validation

While functionalizing the human genome, it is likely that many potential targets will be discovered that may not fit neatly into pre-defined familiar target classes or may not have known ligands. These targets may also not have the molecular epidemiology available to allow data-driven decisions. This session has been highly popular in past years, largely ascribable to the innovative biology presented. For the last two years this topic yielded the Award winner for the Best Oral Presentation: in 2004 Dr. Gail Emilsson (Yale University, US) on «Riboswitches as Novel Antimicrobial Drug Targets», in 2003 Dr. Barbara Froesch (The Genetics Company Inc., Switzerland) on «From Fruit Flies to Potential Cures for Human Diseases».

Structure-Based Drug Discovery and Chemical Genomics

When MipTec began eight years ago, computer-aided molecular modeling rarely had an impact on drug discovery, but in the new century it has had a significant impact on lead optimization and drug design. And while there are many different definitions of chemical genomics depending on who you ask, these talks have been the most provocative at MipTec, such as phenotypic cell-based screening.

Streamlining Lead Discovery: Novel Assay Technologies, Biomolecular Screening, Hit-to-Lead Process

While it has become apparent that HTS is no longer a bottleneck in the drug discovery process, innovative strategies to improve the process, lower the cost, and provide a higher quality deliverable with state-of-the art technology will never fade from fashion. This session should be very well attended and be the source of vigorous discussion.

Chips, Arrays, and Microfluidics
Whether it is SNPs analysis, Proteomics, or HTS, it seems that miniaturized technologies are increasingly leaving the realm of science fiction and entering the realm of real-world applications. This session, organized by two world-renowned thought leaders, is a perennial favorite for innovators to reveal their latest breakthroughs.

Maximizing Value from Compound and Sample Collections
In the increasingly competitive drug discovery arena, an organization's most important asset, second only to their scientists, may be their compound collection and the quality and diversity thereof. This session is becoming increasingly popular at MipTec.

More than just a Conference
While some conferences tend to treat the exhibition as an afterthought to the scientific program, MipTec unapologetically makes it a pivotal focal point, holding several events in the exhibition area and encouraging attendees to spend appreciable time interacting with the value-added partners that the technology companies represent.
The Poster Session will be held in the exhibition area, during set times visitors can discuss findings with the authors. The three best posters will be presented with the Basel Award in a ceremony in the exhibition area on Wednesday night. Posters can be handed in for review until 7 March.
The Best Presentation will be awarded by the PolyPops Development Foundation during the Closing Session on Thursday. This year for the first time, the European Laboratory Robotics Interest Group donates an award for technology innovation at MipTec. □

- **Dates: 9 to 12 May 2005**
- **Venue: Convention Center Basel, Switzerland**
- **Call for Posters until 7 March 2005**
- **Early Registration for Conference until 1 April 2005**
- **For registration and further information: www.miptec.com**

Knowledge Matters – Life Sciences Executive Courses

SCIVENT, a provider of international seminars and conferences for the Pharmaceutical and Biotechnological Industry, has created a new series of interactive executive courses for 2005. After the great success during the last years, Scivent has outlined two new courses in the fields of Project Management and International Business Negotiation. The courses will be held parallel to MipTec 2005 (May 9 – 12, 2005, Convention Center Basel, www.miptec.com) in Basel on May 11 – 12.
SCIVENT is proud to have the opportunity to work together with leading experts in the field as there are Aspiras and Paul Charlton Coaching both from Germany. Speakers from these companies will contribute to the courses. The courses are for 2 days each and limited to a maximum of 15 or 20 attendees.

Who should attend?
Courses have been developed for strategy consultants, business development and sales people, experts in licensing and financing and the drug discovery community. The courses will convince the delegates by the interactive format and close contact to the speakers.

Course 1: Project Management for Pharma- and Biotech Companies
May 11 – 12, 2005
The first course, given by Aspiras, Mainz in Germany will focus on effective project management which is essential when developing new technologies, tools and applications for drug discovery and drug development encompassing laboratory solutions as well as biopharmaceutical and clinical applications. The course is intended to provide a detailed overview on the key success factors of new product development in life sciences. In particular various tools of project management will be presented, including project-targeting, development plan, milestones and decision points, project valuation (profit & loss statement), project documentation and information and knowledge management.

Course 2: International Business Negotiation Skills; Strategies, Tactics and Countermeasures
May 11 – 12, 2005
This course, held by Paul Charlton Coaching, Germany, provides a practical and effective opportunity to learn and practice key essential concepts and skills to help ensure highly successful, mutually satisfactory, agreements in a scientific, commercial and international context. The course will provide a full set of practical tools in the effective planning and implementation of negotiation activities taking into account the subtleties of corporate and global culture and the specific complexities within technology & medical markets.

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