Based on bio

B-Basic as building block for a biobased economy

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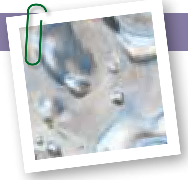






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We thank all scientists and parties involved for their cooperation

Photography

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B-Basic

Graphic design

LENS! (www.lenspuntnl.nl)

Pinter

Drukkerij Edauw en Johanissen bv

Published by

TU Delft, Department of Biotechnology (B-Basic)

Delft, April 2010

ISBN:

978-94-90370-04-6

Preface

B-Basic is a biobased experiment. It is designed to boost biobased innovation by bringing top level scientists and industry experts together, and focus on meaningful R&D and help translate that towards realities. The biobased value chain requires expertise from many disciplines - bioscientists, engineers and social scientists alike. So a public-private environment is almost a natural requirement for success. But innovation success is not automatic nor guaranteed. It requires taking people out of their comfort zones, to recognize opportunities, build trust and take (educated) risks. When B-Basic was proposed in 2002 and launched in 2004 it was one of the largest coherent programs worldwide with a collective budget exceeding 50 million euro, and over 10 partners. So B-Basic is an experiment, and a large one. It is a compliment to the partners that they dared to take part in that experiment.

The partners realized that B-Basic could not achieve it's targets by staying within the confinement of The Netherlands, but required a strong international orientation. An important contributor to that orientation was a series of B-Basic Missions to Brazil – at that moment far away. Similarly, B-Basic tried to find anchor points in Asia and US. There were many discussions with international colleagues, and the concept seemed to resonate. For example IP issues that were expected to be complex due to co-development of industry and academia turned out to be solvable due to a clear mechanism, which has been applied in many other consortia since. Also at other places, biorenewables and bioenergy research centers were created. B-Basic is an example of a global trend to bring biobased expertises together – probably the only way to develop a truly sustainable biobased economy. Now, B-Basic is part of a network of biorenewables centers, both informally but also formally as a founding member of the Global Biorenewables Research Society. So B-Basic was an experiment, and a necessary one.

This book is meant to reflect on the successes and draw lessons. For obvious reasons, the successes are highlighted. The open-ness between the partners, the attitude of better and more results to be gained jointly instead of individually was key. An important lesson was that it was not easy to create new companies where existing organizations could not absorb the many outcomes. Another lesson was that the development of a biobased economy is not driven by technology alone. B-Basic played a critical role in The Netherlands orientation towards a biobased economy, especially by focusing on the relation between economic and environmental impacts. There is a clear national strategy now – that underlines the critical importance of international orientation, advanced technology, awareness on sustainability criteria and the drive to build and invest. The Netherlands as a whole is now engaged in the biobased experiment.

With this orientation and the lessons learned, we are ready to build further. BE-Basic is launched at February 18 2010, as the 120 million euro joint effort of the B-Basic and Ecogenomics Consortia and others. International organizations are now partners in BE-Basic, anchoring the international strategy. This as well as the planned Bioprocess Pilot Facility creates entirely new opportunities and definitely also new challenges. So, the biobased experiment continues since experimenting is the only way to build a sustainable future.

Luuk van der Wielen and Gerda Lourens

24 March 2010

About B-Basic

Towards a sustainable chemical industry

The chemistry and energy sector depend strongly on finite fossil feed stocks. The challenge is to develop high-quality, chemical products and energy carriers that sustainably use our natural resources and help to reduced the greenhouse effect. Therefore we must now make the step towards on a bio-based economy.

Five years ago the B-Basic consortium of universities, research institutes and companies started research into new biotechnological processes as building blocks for a biobased economy. B-Basic, which stands for Bio-Based Sustainable Industrial Chemistry, developed fundamental knowledge and second generation biotechnology for the sustainable production of biobased chemicals and biofuels.

Security

"There were three good reasons to start industrial biotechnology quickly," says Luuk van der Wielen, Director of B-Basic and Professor of Biotechnology at the TU Delft. One of the reasons was resource security. "This includes energy security and also the new raw materials for the production of chemicals and materials. Renewable raw materials, if used sustainably, present a solution to this."

Creating new activities and jobs is another important motive for investing in a biobased economy. The new know-how and the products resulting from the research help to develop a sustainable chemical industry and to develop a new portfolio of products. This has a broad impact on the export position and the logistic sector. "We do not have a large hinterland for the cultivation of biobased raw materials but then again we don't have oil either but the Netherlands has still developed a strong chemical industry. Our harbours are the entry ports to Europe," according to Van der Wielen. A good knowledge base available for the development of a biobased economy is the third reason. The combination of Delft-Wageningen especially is greatly underestimated, thinks Van der Wielen.

"The combination of agricultural and industrial production has already been worked on for a century. This is not hype to us but a continuous investment in a field that we are good in: internationally, as well. The Netherlands leads the European platforms in the field of industrial biotechnology and environmental biotechnology."

Sustainable

The sustainable concept has several meanings within the context of the biobased economy. One is the use of renewable raw materials, as long as they are sustainably produced. "This lies a little outside our field of study," states Van der Wielen. "But by aiming at the biobased raw materials that have woody fibres (lignocellulose) as their base instead of glucose, you are able to guarantee the sustainability of a process better. It then involves waste products such as agricultural waste and leftover wood. We have developed technology for these raw products an example of which is the Delft super yeast which can convert the sugars released from waste into bio-ethanol." The other meaning of sustainable relates to the conditions under which industrial biological systems work. Chemical processes often demand more energy and damage the environment, while biological processes use lower temperatures and pressure and are more selective. In addition micro-organisms can carry out several synthesis steps in one go. Van der Wielen, "We are trying to improve these processes further so that they are also economically competitive with the petrochemical industry." We are even going a step further. By the fast development of bio-informatics and metagenomics (the analysis of all DNA that is present in for instance a soil of water sample) we are passing over the analysis and metabolic engineering stage and going straight on towards design: synthetic biology. Not by designing a new organism like Creg Venter, but by installing new functionalities, the same as in a recent breakthrough in the production of antibiotics, when the whole production route of a fungus was inserted in yeast."

Partnerships

The B-Basic public-private partnership turned out to be a success formula just like other similar partnerships according to Van der Wielen. In our country a good breeding ground for this is available. "Not only do we have strong and innovative companies but Dutch society, with a working consensus model, is the place for these public-private partnerships to flourish," explains Van der Wielen. "Moreover the strategy for a complex development such as a biobased economy is to join forces. A single company or institute no longer has the manpower to tackle the complexities of the market and the scientific and technological developments and this is becoming more and more obvious along the path to a biobased economy. In a green economy the agricultural sector and the chemical industry will have to communicate more frequently. There is no single company capable of performing all the aspects in this chain and that is why partnerships are so important. The same applies to academia. A very logical model is to bring the academic partners together to work with a large formation in a multifaceted research area."

Looking at patents

Looking back at the cooperation between academies and industry he observes that the unexpected is unavoidable. "At the moment you start a programme for five years you think you know what is important to both industry and science but you also know that this will change and we underestimated how quickly that could happen in industry. A subject greatly promoted by industry proved to be of less interest after the start of the programme, very annoying, but then you have to dare to take the necessary measures and not continue with a whole programme just to keep the peace. A research group must also get the chance to do industrially relevant work. That is the strength of good programme management."
According to Van der Wielen the programme has proven its scientific quality and quantity and nothing need be changed there. The number of patents and the speed they appear needs no other approach. The innovation workshops and the Leo Petrus Innovation Trophy have linked scientists and the industrial R&D departments and scientists and new business development organisations excellently. "As a consequence the focus on the value of research has been greatly improved. This is expressed in a significantly higher return from patents which are not obtained when the projects are finished but within one or two years of the start of the project. An obvious acceleration has occurred. What we have not yet seen is any new businesses, or at least less that we had hoped for. We will be tackling that dynamically in BE-Basic."

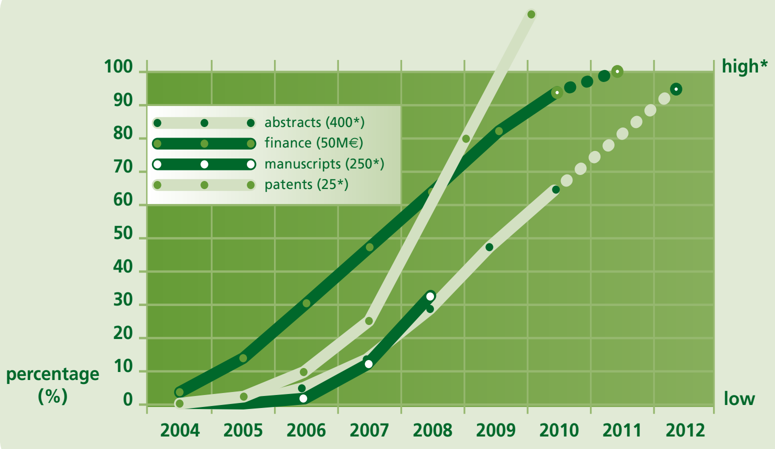
B-Basic triangle

The B-Basic Triangle stands for three goals in the research programmes:

- High yields, rates and selectivity by fermentation and biocatalysis by stress resistant, highly selective microorganisms and biocatalysts
- Low feedstock costs by novel feedstock engineering concepts
- Low investments by novel bioprocess engineering concepts

B-Basic output

Key performance indicators for scientific output and valorisation and expenses. Displayed as the actual percentage of the expected final numbers (*) after completion of the programme.



B-Basic partners

Universities

institutes

Industry

B-Basic facts:

Duration:	2004 – 2009
Budget:	50 million euro
Researchers:	
Postdocs	15
PhD students	40
PDEng students	4
Programmes:	5
Projects:	32
Scientific output[1]:	
Scientific publications	90
Theses	2
Presentations	131
Poster presentations	114
Design projects	15
Economical output[2]:	
Patent applications	31
Societal output[1]:	
Societal Workshops with stakeholders	7
Number of B-Basic staff participating in courses on public perception	2
Number of B-Basic staff participating in societal relevant symposia	43
Societal communication activities	52
Innovation output and knowledge transfer[1]:	
Annual B-Basic Symposium	4
B-Basic technical workshops	26
Advanced Courses (TUD/UL)	11
Masterclasses (RuG)	3
PDEng projects	23

[1] based on the last progress report on 2008
[2] measured until April 2010

B-Basic and ACTS

ACTS, the platform for public private partnerships in the area of sustainable chemistry within The Netherlands Organisation for Scientific Research (NWO), received a subsidy in 2004 to implement the B-Basic programme. B-Basic's objective of contributing to a sustainable future in the field of bio-based chemicals and energy fitted in perfectly with the ACTS mission: facilitating and initiating research into innovative technologies for sustainable materials and energy sources.

Besides B-Basic, ACTS accommodates four other programmes in the field of sustainable bulk chemicals: Advanced Sustainable Processes by Engaging Catalytic Technologies (ASPECT), Sustainable Hydrogen, Integration of Bio and Organic Synthesis (IBOS) and Process-on-a-Chip (PoaC).

Structure and benefits

The ACTS Executive Board was responsible for the administration of B-Basic and the ACTS office for the support of B-Basic's programme committee. In addition, the ACTS office coordinates the progress reports and the financial responsibilities of the programme for the subsidy provider, Agentschap NL (formerly SenterNovem) and procedures around the IP findings.
Around 30 patentable findings have resulted from the current B-Basic research. ACTS has already sold on two of these findings to industrial parties. Because ACTS is embedded in the NWO organisation, B-Basic has been able to further profit from the chemical research world's large network through the NWO Division of Chemical Sciences and from guaranteed testing of the scientific quality of the B-Basic projects via peer review.

Background

ACTS (Advanced Chemical Technologies for Sustainability) was established in 2002 by representatives of the business world, university research groups, the national research financier NWO and the government. Stemming from the IOP Catalysis and the Roadmap Catalysis (2001) and originally with the accent on catalysis, ACTS has broadened its field to include sustainable chemistry. With its public-private research programmes, ACTS supplies an important contribution to the "Catalysis and sustainable processes" line of innovation from the Chemical Steering Group's business plan. The B-Basic programme is related more to the 'Biotechnology for specialities' innovation line and B-Basic was shaped within that framework with the emphasis on biomass conversion along the biological route.

Future perspective

The Chemistry Steering Group (Regiegroep Chemie) has helped determine the policy for innovation and request-related research in the field of chemistry since 2006. The Chemistry Steering Group executed the 'Key area chemistry ensures growth' business plan by acting as ambassador for public-private collaborations such as DPI/PIP, CatchBio, DSTI and PI, financed by various subsidy arrangements. At the same time the position of ACTS within NWO safeguards the quality of the research programmes. The role of the Chemistry Steering Group and the ending of the present ACTS programmes have caused a review of ACTS' position and method of work to take place. With the accent on aspects of chemistry and catalysis, ACTS has developed the TASC (Technology Areas for Sustainable Chemistry) innovation programme in close collaboration with the most important stakeholders in the chemistry sector and the knowledge centres. The TASC programme plan is now with the Strategic Advisory Commission and NL Agency (formerly SenterNovem) for approval.

Research

Starring micro-organisms and enzymes as biocatalysts

Five research programmes form the basis for the realisation of the B-Basic programme's ambitions: new industrial processes to convert renewable raw materials into chemicals and products. Micro-organisms and enzymes play the main roles as biocatalysts in this green vision of the future.

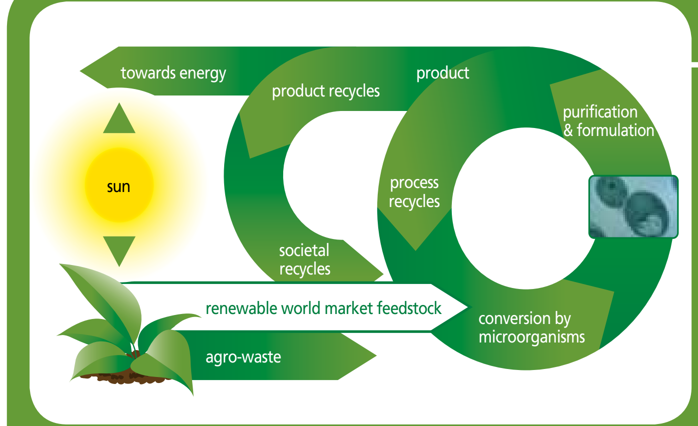
A world contending with environmental pollution, climate change and finite fossil materials needs sustainable production systems and a bio-based economy. The B-Basic consortium has therefore set itself the target of developing new biotechnological production concepts which make use of renewable raw materials. Herewith it offers the chemical industry and the energy sector a sustainable alternative for the future.

Industrial focus

The application areas in the chemical industry will be used as the starting point. Three major application areas can be distinguished: bulk chemicals, fine chemicals and biomaterials. In addition, renewable raw materials and recycling of organic production waste form an important basis for the bio-based economy. The B-Basic consortium has converted this into four research programmes which all aim for high yields and high selectivity in fermentation and biocatalysts and for low raw material and investment costs in all areas. Education is the theme of the fifth programme. This programme provides training for new scientists and develops educational material so that the developed knowledge is spread and embedded in the existing curricula.

Academic focus

The B-Basic research programme is aimed at the core of all bio-based production methods: the microbial cell. The performance of these microbial workhorses must be understood better and improved before the industrial processes can be developed, optimised and controlled properly. With molecular techniques and by familiarising micro-organisms with new nutrients and circumstances, the production of the required material can be very specifically improved. More robust micro-organisms and enzymes that are resistant to the extreme conditions in a bioreactor or during the purification of the product can be developed with these techniques. Therefore researchers are concentrating on the metabolic routes, the function of key enzymes and the stress-resistance of micro-organisms and enzymes.
Parallel to this runs the development of compact, clean and efficient integrated bioprocesses in the course of which novel test methods can map the optimal process conditions faster. For example with special chips which are able to screen the various process conditions simultaneously. This could reduce the total investment cost of the development and implementation of industrial bioprocesses further.
New concepts are also needed for the use of sustainable raw materials such as agricultural waste or recycled biomass from previous fermentations. The common problem with using cheap biomass is that these base materials are not pure, could contain toxins and are difficult to sterilise. Due to this it could be necessary to convert this biomass into a raw material of better quality. Biotechnology can help here too.



Five programme themes

Bulk Chemicals Programme

Dr. A.J.J. Straathof, TU Delft

The production of bulk chemicals, such as phenol, butanol and the ingredients for plastics, entails huge production volumes, relatively simple molecules and low prices per unit. The research in this programme concentrates on subjects such as the development of robust micro-organisms, in situ product removal and methods of developing fast biotechnological processes and screening them for feasibility.

Fine Chemicals Programme:

Prof. Dr. A.J.M. Driessen, University of Groningen

Fine chemical research relates to obtaining the highest degree of selectivity in the production of complex building blocks, which could for example be used in medicines. This programme researches how the production of mixtures and complex compounds can be improved by metabolic pathway engineering and biotransformation of the entire cell.

Performance Materials Programme

Prof. Dr. G. Eggink, Wageningen University, Food & Biobased Research (formerly AFSG)

Micro-organisms produce a large quantity of highly interesting biopolymers such as polysugars and polypeptides which are suitable for medical application, adhesives or coatings etc. Only a few have reached the commercial market. The research in this programme examines the production of these biopolymers and the relationship between the structure and the product quality.

Novel Feedstocks Programme

Dr. G. Muyzer, TU Delft

The Novel Feedstocks programme is developing a new approach to using cheap biomass as raw material for the production of bio-based chemicals. In addition the programme pays attention to the recycling of waste products from industrial fermentations and the use of microbial mixed cultures and complex raw materials such as waste water.

Educational Programme

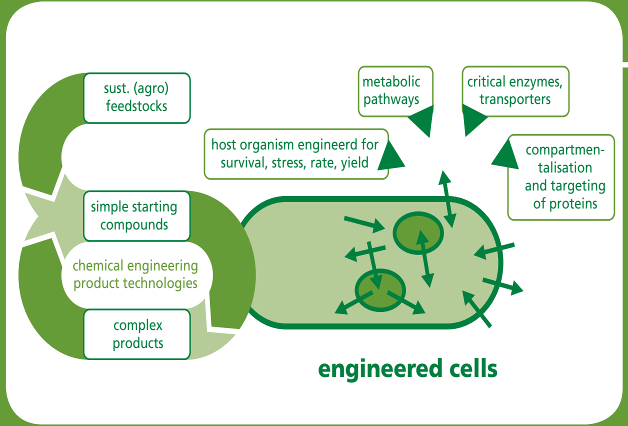
Prof. Dr. Ir. J. Tramper, Wageningen University

The B-Basic educational programme consists of various projects which are aimed at the development of biotechnological knowledge and skills, not only for facilitating and recording purposes, but also to firmly anchor them in learning programmes. Examples are the masterclasses for PhD students, a management course project for master students, various digital learning modules for bachelor students and learning material for secondary school pupils.

B-Basic cycle

Biomass as a green raw material for a sustainable chemical industry

Renewable feedstocks such as carbohydrates and vegetable oil are selectively converted by micro-organisms into products. The organic fraction of industrial, urban and agricultural waste can, in principle, be used as a substrate for these production processes as well. B-Basic investigates the potential routes for utilising these raw materials.



The microbial cell

Micro-organisms and enzymes are the biocatalysts for a sustainable chemical industry.

Bulk Chemicals

It won't be for a lack of technology

To produce bulk chemicals just as efficiently from biomass as the chemical industry does from oil the bioprocess technology needs above all enough time, thinks programme leader Adrie Straathof. "The greatest challenge lies in the complete synchronisation of production and recovery of the product."

"We will all be driving around in electric cars at some time but the plastic in the bodywork will have to be made from something. It cannot be replaced in the same way and you will always need raw materials for plastic," says Adrie Straathof, associate professor of biotechnology at the TU Delft. "Bulk chemicals are produced on a large scale, you are talking about more than 10,000 tons of product rolling out of the factory every year and we use about 5% of the petroleum for this."

The chemical industry uses only a small percentage of renewable raw materials although the production of bulk chemicals from this type of raw material is starting to get going. "This is mainly ethanol but substances that serve as the basis for all sorts of plastic products are now being added. Polylactic acid is already used in some cars by Toyota and Sony uses it in some mp3-Walkmans," according to Straathof. In his programme he focuses on succinic acid, fumaric acid, phenol and butanol. "Butanol is a good fuel but it is also a component for chemical products such as paint."

The combination counts

Two things are essential for making basic substances for the chemical industry on a large scale. Firstly bacteria, yeast or fungi that make the product in great quantities and secondly, a method for fishing the product out of the fermentation broth. "We started with the wild strains of which we knew they could make the compound, so that we could use our separation concepts as you can always improve the production again with metabolic engineering and this is mainly a question of time," guarantees Straathof.

In the last five years the B-Basic partners, DSM, Shell and AkzoNobel, and the knowledge institutions TNO and Food & Biobased Research of Wageningen UR have been working hard on new technologies and by synchronising production and product removal a large number of successes have been accomplished, according to Straathof. "Phenol is a toxic compound, for bacteria cells as well, but TNO still managed a production rate that was 40 times higher. The trick is to very selectively remove the phenol from the fermentation broth with an organic solvent as soon as it is made."

Elegant without waste

Straathof is the most pleased with the integrated process to produce fumaric acid. The process for harvesting the product is directly linked to the crystallisation process. "If we use a slightly lower pH for the production and allow the liquid to cool off a little after fermentation, the product crystallises out and is there for the taking. We expected this on the basis of theory and it worked in practice; very elegant and no waste, that is a really fine result."

The production of bio-based bulk chemicals will carry on worldwide, forecasts Straathof. The only driving force needed is the ever increasing price of oil; it won't be because of any lack of technology or bioprocesses. It's just going to work." According to him the bottleneck will be accessing the raw materials for sugar and glycerol.

Bio-building blocks for bulk chemicals

We already have efficient fermentations for the production of ethanol and lactic acid, also known as C2 and C3 building blocks. Microbiologist Rob Brooijmans has therefore modified the baker's yeast Saccharomyces cerevisiae so that it can make C4 building blocks; in theory, at least. "If it works, it will be party time here!"

"On account of the CO_2 problem and because oil will eventually run out, we want to be able to produce a basic set of molecular building blocks from renewable organic raw materials on a large scale. We will then be able to make all the compounds we need. It is known that yeast can make ethanol from sugar at a high rate and we want to use that capacity to make other high value-added compounds, namely dicarboxylic acids, such as succinic acid, fumaric acid and malic acid," explains Rob Brooijmans, post doc at the TU Delft. After his PhD research on lactic acid bacteria he threw himself into the metabolism of yeasts. Brooijmans is specifically interested in the production of fumaric acid which is a compound with a backbone of four carbon atoms with two acid groups at the ends. "Thereby enabling you to thread the molecules together to make long chains and use them to make plastics or resins. You are able to attach all sorts of functional groups to the carbon backbone which in turn increases the application possibilities."

Metabolic road system

The conversion of sugar to fumaric acid must occur as efficiently as possible, according to Brooijmans, otherwise you will loose the economic value. "Theoretically you could reach 200% efficiency and would then be able to get two fumaric acid molecules from one sugar molecule. But this conversion is not interesting for a yeast cell." Brooijmans therefore chose the route in which one sugar molecule supplies one product molecule. Sufficient energy is then released for the yeast cell to stay alive.
Brooijmans, "Normally you would start with a pen and paper model on which you would note all the metabolic routes and see how you would have to change them so that the yeast cell would produce fumaric acid but our brain has its limitations."
That's why Brooijmans reached for the genome scale metabolic model computer program. "You can put all the information into this model so that one large metabolic road map is created in which everything connects with each other. In this way it is possible to perform a wholly unprejudiced analysis, the computer calculates the most advantageous route to be taken to produce the required compound and shows which genes have to be turned on or off to achieve this."

Just evolve

The modified yeasts are ready. The mutants now just have to evolve so that the metabolism can adapt to the new situation. "When a gene has been turned off it always takes a while before the organism returns to its optimal growth rate and it has to grow optimally to secrete the product," according to Brooijmans. The ultimate test will follow soon. "And if it works, it will be party time!" For both Brooijmans, as top researcher, and for DSM, an industrial partner in the B-Basic project in which he is now working.
Then he has a year to collect more results, to tackle the patent issues and to publish before the bio-process technologies can start to scale the process up to industrial production.
Brooijmans already has the next organism to be researched on his wish list: algae. "Plants and algae make sugars from sunlight and yeast then converts them into other substances. Perhaps an alga could do that in one go. That would be even more efficient."

Biofuels 2.0

As a biofuel, biobutanol has several good qualities, but it can be difficult to produce in large quantities. "This is essential if it is to compete commercially with ethanol and later, fossil fuels," according to Minke Noordermeer from Shell.

"Once blended, biofuels can be used in today's vehicles. This is a big advantage," says Minke Noordermeer, researcher in the Shell Biofuel group. "The 2% that oil companies now have to mix perhaps seems very small but fuel is about huge volumes." Noordermeer has been involved in the B-Basic programme since the beginning of 2004. At that time biotechnology for the petrochemical company was virgin territory. "We wanted to build up a network for the future and be involved in the recent developments through B-Basic. We are continually working on cleaner and more efficient fuels, research into biofuels links up to this perfectly."

Difficult biobutanol

During the starting phase Noordermeer helped with the interpretation of the projects. "This was a very special time, we were listened to. Everything we found interesting was included in the project proposals." Shell has a broad interest in the efficient production of biofuels. The company is investing in advanced biofuels, using feedstocks such as crop wastes or inedible crops and new conversion processes that offer the potential for improved CO_2 reductions and improved fuel characteristics. "It is more environmentally and socially sustainable to use waste products than foodstuffs and moreover there is lots of it," says the researcher.

Biobutanol is interesting because it has several good properties and characteristics. But production is more difficult and much more expensive than the production of ethanol. Noordermeer: "Production is a tricky business. The bacteria concerned, *Clostridium acetobutylicum*, makes acetone as a by-product. This has been considerably reduced by modifications to the current production strain. The productivity must also be increased to become profitable. This is difficult partly because butanol is poisonous to the bacteria. It has not yet been possible to significantly improve the tolerance. This is disappointing. Another solution would be to remove the butanol from the fermentation liquid immediately after it is formed. A number of separation techniques have been investigated for this."

Sensitive projects

The collaboration with the universities in Delft and Wageningen was extremely helpful, according to Noordermeer. "I regularly meet with the researchers. They come to Shell twice a year and we present advances to one another. At the moment I mainly see publications which we scan for interesting results to patent. We have already applied for a couple of patents."

The collaboration was also good with the other partners, DSM, Paques, TNO and F&BR-WUR. "Very constructive. We have learnt much from each other. The times were also different then. Biofuels were in their infancy. They were not the most sensitive of projects. You knew beforehand that you had to share the results with the other partners. So you could be reasonably open."

Shell will continue researching biofuels but not in such a broad programme this time. "There are various options which we think are the most obtainable. These core projects are important and that means a greater degree of confidentiality. One on one research projects are more suitable for this, in which you are able to make good agreements about confidentiality."

Fine Chemicals

Micro-organisms as green medicine factories

Bacteria making medicines from inexpensive raw materials; that's the way forward, says Arnold Driessen, professor of Molecular Microbiology. "It is cheaper and less damaging to the environment."

Many raw materials for making fine chemicals, such as antibiotics and steroids, are obtained from natural sources such as fungi and plants. Extra chemical steps are necessary to eventually make medicines from these raw materials. "That is the classic method but we actually want to obtain full synthesis in micro-organisms," says professor Arnold Driessen, programme leader of the Fine Chemicals theme. "Chemical reactions and organic solvents are then no longer needed, there are fewer by-products and less CO_2 emission; all of which is better for the environment."

"It does mean that you have to let an organism carry out reactions which it normally would not carry out. This is why the necessary enzymes that can catalyse these reactions have to be inserted into the organism. We have also looked at the production of beta-amino acids, steroids, antibiotics, and others, in this research theme."

Enzymes

Researchers in the beta-amino acids project have looked for enzymes which specifically catalyse the synthesis of beta-amino acids. Beta-amino acids are important raw materials in the production of medicines against AIDS for instance. However it is alpha-amino acids which can mainly be found in nature. The search resulted in new enzymes which are now being tested for usefulness in the production of beta-amino acids.

In another project work is being done on new methods for producing antibiotics. The antibiotic penicillin has been produced for years on a large scale in fermentors by the *Penicillinium chrysogenum* fungus. Production is not easy because the fungus grows in filaments, yeasts are much easier to cultivate. Researchers have now successfully converted the production of penicillin to yeast in this project. Driessen is very proud of this result, "We can now concentrate on the modification of this yeast so that it can also make other penicillin."

In the steroids project enzymes from organisms that in nature can grow and thus can modify steroid-type compounds (sterols) were investigated. These sterols, which appear

frequently in plants, can be used as building blocks for compounds that are important for pharmaceutical purposes, for instance anti-inflammatory agents and hormones. "The combination of sterols and modified enzymes could lead to all sorts of new and interesting compounds," says Driessen.

Fine tuning

"The challenges of our programme are especially found in the complexity of the reactions," says Driessen. "Often a whole series of reactions is needed, one after the other and sometimes you get too much of an unwanted by-product. 'Fine tuning' the reactions so that they move towards the required product is not easy. When you have shown that the process works, the customary steps to an actual commercial product still have to be conquered."

Furthermore Driessen is very pleased with the collaboration between the industrial partners, DSM, MSD (formerly Schering-Plough) and Diosynth. "Sufficient informal discussions were also possible besides the formal meetings. The former is especially important because then you can have a quick discussion with the other without having to make an appointment. The project has produced much new knowledge," Driessen thinks. "And that will certainly be turned into a higher plan in the next project, BE-Basic."

Bacteria as producers of steroids

Researchers in Groningen have reconstructed bacteria that would naturally degrade steroids in nature in such a way that they can make new steroid molecules. Basic substances from plants serve as raw materials.

"Many complicated chemical conversions are needed to make compounds derived from steroids with high commercial value such as hormones," says Robert van der Geize, postdoc in the Microbiology research group at the University of Groningen. "You often get unwanted by-products which appear very similar to the required product and are therefore difficult to separate. The necessary chemical synthesises are also damaging to the environment but if you let a micro-organism do the job you won't have these disadvantages any longer."

Small biological factories

Van der Geize and his colleagues are focussing on the development of small biological factories for steroid conversion in the *Rhodococcus* bacterium. Much knowledge about this organism has already been obtained through research over the years and it was already known that these bacteria could make steroids from sterols, substances that are present in all sorts of plants, and break them down further. "We don't want the steroids to degrade because we want to make substances derived from steroids," says Van der Geize. "That's why we have removed the enzymes from the organism that degrades steroids. This newly made strain must form the basis for the production of all sorts of new steroids. We can make all sorts of steroids from inexpensive plant waste by the introduction of the necessary enzymes in this bacterial strain."

In the last years two PhD students, Jan Knol en Mirjam Petrusma have been studying three enzymes from the *Rhodococcus* bacterium to find out which interesting enzymes could be used for conversions. "We wanted to know which steroids they could convert the best," according to Van der Geize. "It is important to know which conversions are possible with these enzymes, and accordingly which steroids you can make. This is what the industry is especially interested in."

Crystal form

The enzymes were allowed to "try out" a whole series of different steroids, supplied by B-Basic partners Schering Plough (now MSD) and DSM among others and the enzymes proved clearly to have their own preferences. The researchers are looking into how and where the steroid connects spatially to the enzyme to further investigate the cause of these preferences. Together with Bauke Dijkstra's Biophysical chemistry group at the University of Groningen, they were successful in getting one of the enzymes in its crystal form. "This provided us with a lot of information about the spatial structure of the enzyme," says Van der Geize. "Research with mutants of the other enzymes should provide even more information about the actual mechanism of the enzyme."

Van der Geize is proud of the publications produced by the research up to now. "We are still in the fundamental stage of research but we have come quite a way partly thanks to the contributions by our B-Basic partners." He really enjoys working specifically towards an applicable product and would therefore also like to work for a company where this sort of work is done. "It would have to be work where scientific research is still involved."

Fine Chemicals Programme
Dr. Robert van der Geize,
Postdoc
Microbiology
University of Groningen

Programme partners:
University of Groningen, MSD (formerly Schering-Plough), DSM

Fine Chemicals Programme:
Prof. Dr. Roel Bovenberg
DSM Research Leader
Honorary Professor Synthetic
Biology and Cell Engineering
University of Groningen

Programme partners:
University of Groningen,
TU Delft, DSM

Yeast takes over penicillin production from fungus

The industry is still making penicillin with fungi but this can be done more efficiently and more environmentally-friendly with yeast. This is why researchers have unravelled the precise production route for penicillin and transferred it to yeast.

"As producer of penicillin we are naturally very interested in greener and more efficient production methods for this important antibiotic," says Prof. Roel Bovenberg, research leader at DSM. DSM Anti-Infectives has a leading position in the world market for penicillin and is determined to hold on to it.

Penicillin is part of the ß-lactam antibiotics. These are compounds that contain a ß-lactam group and which act on the cell walls of bacteria which then die. The production process for penicillin in the fungus *Penicillinium chrysogenum* in large fermentors is difficult because the fungus grows in filaments. This results in an increased viscosity of the growth medium during production. Furthermore the type of penicillin made by this organism is less suitable for the patient. Extra synthesis steps are always needed to modify the penicillin. "We want to get rid of these synthesis steps," says Bovenberg. "All modifications to the penicillin should occur in the fungus itself."

DNA sequence

DSM is starting an international research project to map out the complete DNA sequence of *P. chrysogenum* and the functions of the various genes to gain more insight into the mechanism of antibiotic production of this organism. "We made the DNA sequence available to the researchers in the penicillin programme before publication so that they could make a start," says Bovenberg. Several trainee assistants have worked on tracing and clarifying the enzymes and intracellular processes that are important in the production of penicillin. For instance they introduced enzymes from other organisms to make certain conversions possible. In this way they could also make a derivative of cephalosporin, also a ß-lactam antibiotic with *P. chrysogenum*, something that this organism cannot normally do.

Spherical organism

The idea of transferring penicillin production to yeast has been going around in the heads of Bovenberg and his colleagues in Groningen for quite a few years. For years the yeast *Hansenula polymorpha* has been known to be a production organism with the suitable intracellular infrastructure (organelles) that has proved to be essential for penicillin synthesis. "With a spherical organism like yeast you are immediately spared all the fungal filaments and the production will undoubtedly run more efficiently in our opinion." The researchers introduced essential genes for the production of penicillin into yeast, which then actually started to make penicillin! Bovenberg is very proud of this discovery. "That the principle works is the pinnacle of years of work however it is not yet good enough for production. Some necessary successes are still needed before this can happen."

"Collaboration between the research groups from the various universities and DSM runs perfectly," says Bovenberg. The partners in this programme had already worked together previously. The University of Groningen concentrated mainly on genetics, biochemistry and cell biology, the TU Delft on the physiology, modelling and fermentation on laboratory scale and DSM supplied the penicillin producing strains, enzymes and some analyses were carried out there. "The good thing was that everyone remained critical and that lively discussions could be carried out among themselves," thinks Bovenberg. "This has all contributed to the successful result."

Performance Materials

Making new compounds in a sustainable way

Gerrit Eggink wants to show that biotechnology can offer many opportunities for making interesting new materials in a safe and sustainable way. The polymers that are developed in his programme, and the biological production methods, prove him correct.

"The demand for new polymers for high-quality technological applications like drug delivery methods and therapeutic agents will only increase," thinks Gerrit Eggink. "You can produce very specific new compounds with biotechnology but the challenge is to develop a flexible process to enable these materials to be designed to size and this programme has contributed enormously in this."

Safe production

The Performance Materials programme supports materials, in this case polymers, with special properties, explains Eggink. These properties include gel formation, hydrophobicity and the temperature at which the material melts. These properties can be adapted as you please when you modify the enzyme or yeast with which they are produced. Moreover this production method is sustainable. "The polymers we study are mostly extracted from animal waste products, offal in other words. This brings with it various disadvantages in respect to the quality; examples are the large distribution of the length of the polymer chain and the risk of contamination by prions and viruses. Additionally, tons of waste are needed to produce a few hundred grams of usable material and now we want to reduce the production of meat because it is exceptionally damaging to the environment.

Enough reason to investigate new production methods for these special polymers. For the last five years Eggink has been the programme leader for about twelve researchers who have studied two important classes of compounds. Protein polymers such as collagen can be used as an autologous substance for drug delivery and they are also suitable as carriers for stem cells with which new tissue can be made. The second class, the so-called sugar polymers, glycosaminoglycans, are used for instance in the treatment of joint disorders and also help to remove wrinkles. Some of these polymers are even therapeutically active, against cancer for instance. "You would like to have a whole range of derivatives at your disposal for screening these potential medicines. With biotechnological production methods we can make this much easier and safer than by extraction from animal material," says Eggink.

Tools and applications

"We have developed the biotechnological tools and knowledge to make polymers with the required properties in this programme. We now know how the enzymes do their work and how we can genetically change the yeast to do what we want which offers perspective for sustainable production." The programme also involves the development of the knowledge that can eventually be applied and you must always take the application into account, says Eggink. The collaboration with Organon (now MSD) and DSM resulted in an industrial vision of these applications. "We set up a profitable collaboration with Organon especially, and we hope that this can be continued."
A pilot production demonstrated that collagen derivatives in particular could be made on a large scale. "But it is not yet finished," says Eggink. "The compounds that we make have unique properties and application possibilities. We will lead the way if we can produce these polymers by biotechnological methods on a commercial scale in the coming years."

Building blocks for a new gel

A cousin of baker's yeast can build a new type of collagen that will spontaneously form a gel. This collagen gel is extremely suitable for delivering medicines to the correct part of the body, the Portuguese researcher Helena Teles discovered. She received the B-Basic Innovation Trophy for her research.

"It's just like Lego," explains the Portuguese researcher Helena Teles. "Block by block you rebuild something you have seen. When it is finished it will look like the example but it will be just a little different." Teles made the protein polymer collagen from building blocks of amino acids with the help of the yeast *Pichia pastoris*. By changing the amino acids sequence at certain places, she was able to adapt the properties of the polymer, such as gel formation, hydrophobicity and the temperature at which the polymer melts. The objective was the development and production of a material that is suitable for drug delivery.

Packaging medicines

Collagen is the main constituent of connective tissue in the bodies of humans and animals. There are more than twenty different types of this protein polymer, one can be found in skin and ligaments for example, another is the main constituent of cartilage or hair. Teles was interested in a gel-forming type of collagen because that is suitable for packaging a medicine. The gel dissolves at body temperature and the medicine is released. Furthermore she preferred not to use animal collagen because of the risk of viruses, amongst others. Teles had then to find a method of producing it.

The researcher was successful in genetically altering *Pichia pastoris* so that it produced a high yield of collagen with the amino acid sequence of her choice. One part of the protein polymer must in fact consist of recurring pieces of protein containing one glycine amino acid and two proline amino acids. This sequence was chosen so that the collagen would be secreted by the cell after synthesis. After purification the compound automatically forms a gel. Special, because in nature an enzyme is needed to gelatize the collagen. Teles received the Innovation Trophy for this discovery.

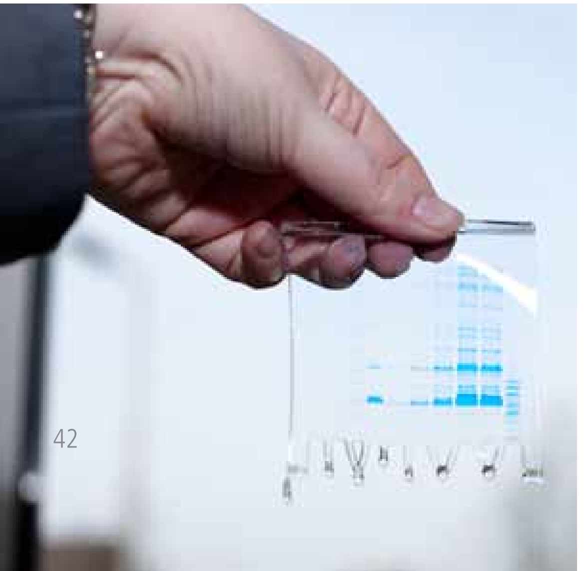
Commercial process

The new type of collagen proved to be perfectly suitable for drug delivery, Teles discovered. Moreover collagen is a substance found in the body so it does not cause an immune response. Teles has been able to investigate the scaling up of the process with the money from the Innovation Trophy she won. "The yield is just as high on a scale of hundred litres; three to six grams of polymer per litre of fermentation broth. The great advantage to industrial production is that the polymer is secreted. It is therefore not necessary to break down the yeast cells, which saves a lot of mess. Purification is now very simple: by adding salt several times to the collagen precipitates." Teles is convinced that the process could be commercially successful but she cannot take the step to the application herself. The defence of her dissertation is planned for September this year. Afterwards she wants to continue biotechnological research, preferably in the Netherlands "I am very pleased that I have completed this. Doctoral research is like running you own company, only you don't realise it until you are half-way through. It is your own business, you know the most about it and you have to make your own decisions."

Difficult small sugar polymers

With a little encouragement the well-known Escherichia coli bacterium makes enzymes which in turn produce tailor-made sugar polymers. The scientific experiment has been successful, now the path towards commercialisation.

"The best thing was that we managed to specifically make small sugar polymers, with precisely five sugar units for instance. I will always be a bit of a scientist, so I enjoyed delivering the scientific evidence for this." Aukje Zimmerman, group leader at the MSD pharmaceutical company in Oss (the former Organon), makes a sugar polymer related to heparin. Heparin uses include decreasing blood clotting in patients with, for example, thrombosis, lung embolism or during a heart operation.



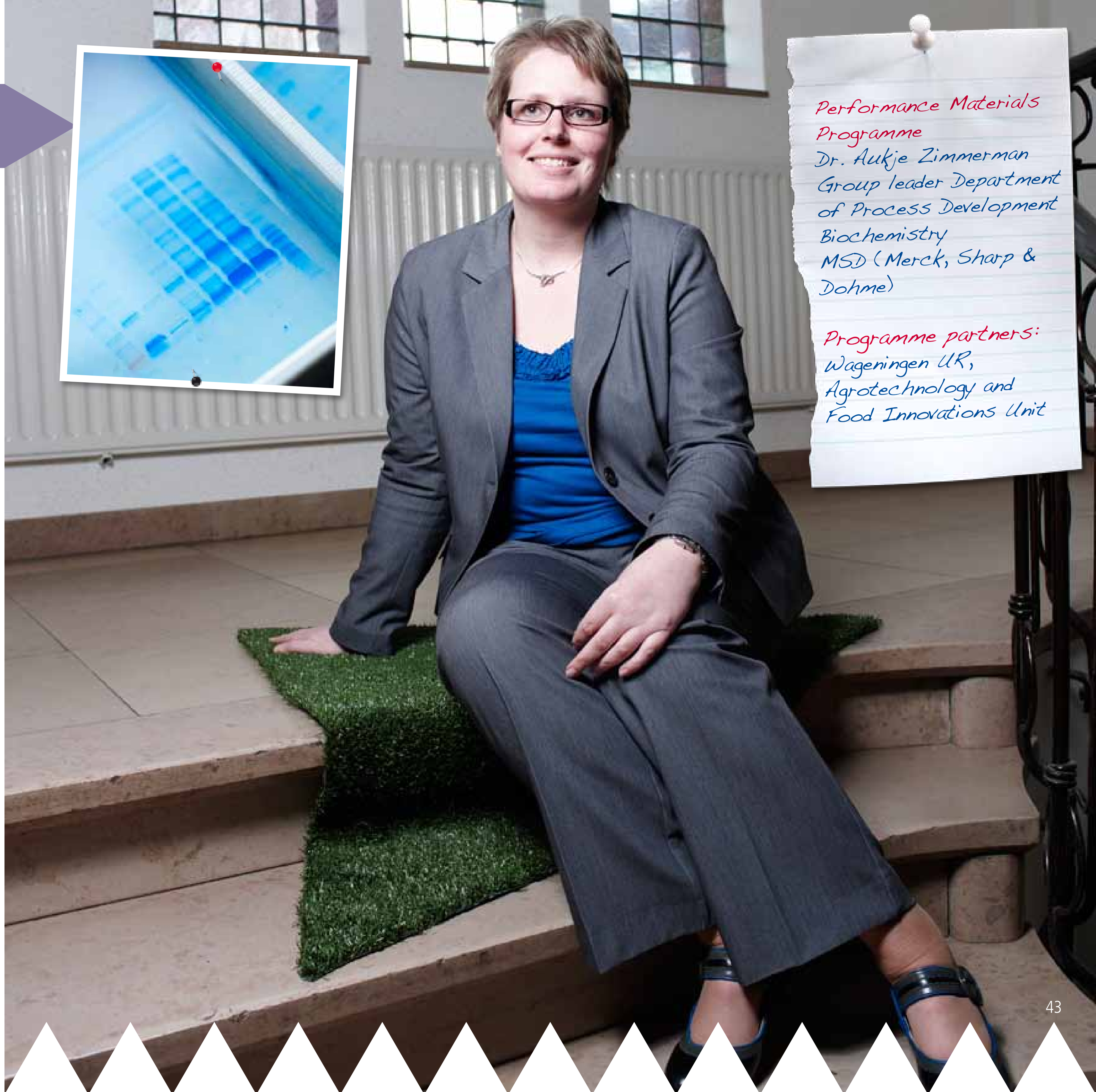
Shorter is better

Commercial unfractionated heparin, such as MSD produces, consists of a mixture of short and long heparin-polymers. "Smaller heparins are more specific in their anti-clotting actions and have fewer side effects. Additionally there are studies which show that short, heparin-like sugar molecules, for instance with only five sugar units, can inhibit the growth of cancer cells in a culture bottle. That's why we want to be able to specifically make these short sugar polymers. That was possible with an enzyme from a modified *Escherichia coli* bacterium," explains Zimmerman. Researchers at the Wageningen University made the recombinant bacterium and produced the enzymes needed by Zimmerman. The technology for this proved to be more widely applicable. "We use it now to make the enzymes that break down sugars instead of building them up. That is a good spin-off from our collaboration," says the researcher.

Recycling

The specific synthesis is not the only advantage. A biotechnological process presents more advantages compared to the current extraction from pig intestinal mucus. That contains relatively little heparin and needs a lot of raw material and more purification. Moreover the material contains potential pathogens such as viruses. "In five or six steps we can now produce on a small scale a sugar polymer with an enzyme. That is more sustainable than the present method." A disadvantage is that the sugar units still have to be linked to an additive that is necessary to catalyse the reaction. This additive is released after the polymerisation. "We must find another way to recycle this compound. You cannot leave it in the reaction mixture because in its free form it inhibits the enzyme reaction. Moreover ready-made sugar units containing the additive are very expensive to purchase," explains Zimmerman. Extending the life span of the enzyme is another challenge for commercialisation of the process. "After a while it loses its activity and becomes unusable. Enzymes are not cheap so all in all the process is still too expensive."

The heparin research is now only ticking over partly due to the reorganisation resulting from the recent incorporation by MSD. "The results are promising but not yet applicable on a large scale," says Zimmerman. "Sugar polymers are not yet being produced like this in large quantities anywhere in the world even though this has been a hot topic for all of ten years. That shows how difficult it is to make this process economically profitable. But we do have the know-how to jump aboard the commercial train immediately when an application is found for small heparins."



Novel Feedstocks

Novel Feedstocks Programme
Programme leader
Dr. Gerard Muyzer
Associate Professor
Environmental
Biotechnology TU Delft

Programme partners:
AkzoNobel, DSM, Paques,
TNO and Shell

Waste as feedstock for sustainable industrial production

Plant waste products form the basis for the sustainable industrial production of biofuels and biochemicals. New robust organisms are needed to utilise the complex composition of these raw materials, states programme leader Gerard Muyzer.

"The industrial production of bio-ethanol and biochemicals uses sugars from food as raw material. Think of corn, sugar cane or wheat. The competition with food production for people and animals is precarious," says Gerard Muyzer, associate professor of Environmental Biotechnology at the TU Delft. Inedible plants or agricultural waste products, such as straw, corn stalks and waste from sugar cane, do not have that disadvantage. The sugars in this type of plant waste product first have to be released with the help of steam, acid and enzymes. Muyzer, "What then remains is a raw extract that includes sugars such as arabinose and xylose along with glucose. They are ignored by the baker's yeast *Saccharomyces cerevisiae*, which is standardly used for the production of ethanol on an industrial scale."

Omnivorous microbes

An important part of his programme was therefore the metabolic adaptation of baker's yeast so that it is able to convert all sugars. "Eventually it emerged that pieces of genetic material from a lactic acid bacterium and from a fungus were needed for the baker's yeast. That is a great breakthrough," states Muyzer. "We now possess a strain which can ferment a mixture of sugars and which speeds up the bio-ethanol production twice as fast."
TNO researchers were then successful in modifying the model bacterium *Pseudomonas putida* so that it would grow on the sugar mixture and make hydroxybenzoate, a raw material for synthetic materials, at the same time. Muyzer, "This is a good example of sustainable production. This substance is chemically produced from phenol at a high temperature and under high pressure. *Pseudomonas* can do the same at normal atmospheric pressure and normal temperatures so that far less energy is needed".

Plastic from waste water

Along with agricultural waste, Muyzer is looking for more alternative raw materials. The microbial biomass is one of them. During the production of bio-ethanol or biobutanol much of this biomass is created that represents a valuable source of nutrients. "Normally this would be taken straight to the incinerators but we use it as a nutrient supplement for the next fermentation process. In this way you close the cycle once again."
Waste water can also be used as raw material but that is difficult because the reusable substances have been highly diluted. But still the researchers from the TU Delft were successful in making bioplastic from waste water by putting bacteria on a strict diet with periods of extreme hunger and periods of great abundance. The only bacteria to survive could quickly store the acetate in the waste water in the cell in the form of bioplastic. "The isolated bacterium produced at least 90% of their dry weight in bioplastic. That is extremely high."

Very fruitful collaborations with Shell, AkzoNobel, DSM, Paques and TNO can be found in this large research programme. Moreover all the effort has produced many publications and patents, according to a very satisfied Muyzer. "I think that we can all quite rightly be proud of this successful programme. The whole consortium has been rewarded, the researchers and industry. The greatest challenge now is to take the step towards industrial implementation."

Bacterium as production platform for biochemicals

Researcher Jean-Paul Meijnen has adapted the eating pattern of the Pseudomonas putida bacterium in such a way that it has less taste for sugars. This is an important step towards efficiently converting biological waste into biochemicals. "It works. That is important to industry but I also want to know how it does this."

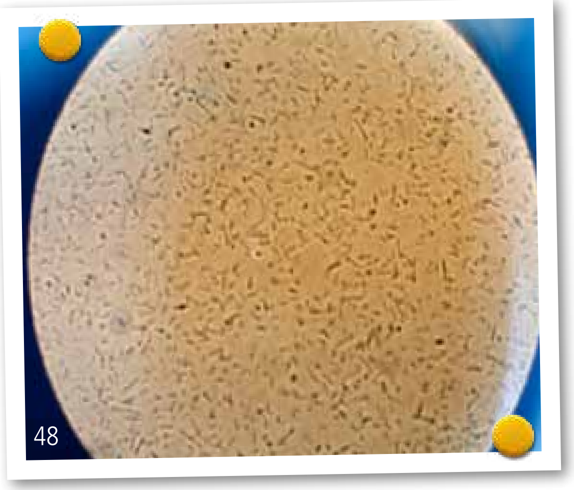
"Bacteria are just like people, they don't like everything. The sugars that we get from biological waste consist of 50% glucose, almost all organisms like them," explains Jean-Paul Meijnen, PhD student at the TU Delft. "But other sugars such as xylose and arabinose they often do not like. I am adapting and training my bacterium to eat these sugars. This is the only way to get an efficient process." Meijnen is working with the Bioconversion group at TNO for his research. DSM is following his progress from the sidelines as the industrial partner.

Surprise

Meijnen followed two strategies to get *Pseudomonas* to convert the sugar xylose into a substance on which it can grow. The first was the addition of genetic material for the conversion of xylose. This was a reasonably risk-free method because other groups had already investigated this. The other way was to make more use of the intrinsic properties of the bacterium. "*Pseudomonas* can convert xylose into an acid in nature but does nothing more with it. That's why I added genes, as a result of which the acid can be converted into a substance that it can use." The first try was successful, we got lucky. "You can figure it out rationally but the bacterium does have to cooperate." The surprise was then even greater when it emerged that his *Pseudomonas* could also use the less tasty sugar arabinose as a feedstock. "I then wanted to know straightaway how this is possible," states the researcher. Curiosity tore him apart during his training as a HLO laboratory assistant. Instead of carrying out all the assignments, he yearned for time for his own research. After his follow-up training in Biotechnology at the WUR, he quickly became fascinated by applied scientific research and landed up at B-Basic.

Detrained

The Bioconversion group at TNO succeeded in making the product *para*-hydroxybenzoate in an efficient manner with the knowledge he had gained from his trained, sugar eating *Pseudomonas*. *Para*-hydroxybenzoate is being used for the production of liquid crystal polymers, high-quality plastics you can find for instance in your cell phone. It is all ultimately about the total picture, as well as the production of the substance, you also have to get the efficient consumption of sugar right," explains Meijnen. "The organism is probably very suitable for producing C4 building blocks as well. The chemical industry can make many different products with these substances."
But the work is not finished yet. His *Pseudomonas* has a relatively low growth rate which makes the process very slow while the industry wants to produce as much as possible in a very short period. Meijnen, "Optimisation is quite fundamental work. Whilst tinkering with metabolism, you are looking for solutions for the production. This can be done by removing or introducing specific genes."
For the time being this fundamental aspect of the research makes you want more. When he has his degree Meijnen would most like to continue his career as a researcher in the academic world.



Surprised by high-tech biotech

While exploring the possibility to make basic bulk chemicals from bio-materials instead of fossil-based raw materials, Ulf Schröder of AkzoNobel was impressed by what can be achieved with biotechnology. "To me this really is high tech."

One of the chemicals AkzoNobel produces is the essential building block 'MEA', a soft sounding name for the big bulk chemical mono-ethanol amine with an annual production of more than 500 thousand metric tons. MEA is the starting point for a whole group of chemicals, which in turn are used in a wide range of products. "If you look at the list of ingredients on your bottle of shampoo next time you take a shower, you may read that it contains cocamide MEA; an ingredient made from MEA and a fatty acid from coconut oil. This is added to stabilize the foam," says Ulf Schröder of AkzoNobel in Sweden. He is responsible for R&D in the Ethylene Amines business, a part of the business unit Functional Chemicals. Beside cosmetics and personal care, detergents, paints, and adhesives, the compound MEA is also used in scrubber systems to clean natural gas.

Sustainable future

Today MEA is made by reaction of the fossil based ethylene oxide with excess ammonia. "MEA can also be made from renewable raw materials like glucose from sugar cane or corn. The technology to make bio-ethanol from glucose is well known, the same holds for the bio-based production of ethylene," says Schröder.. The possibility of making big volume products like MEA through fermentation of renewable raw materials would be a major step towards a bio-based economy, a key reason for AkzoNobel to join the B-Basic program. Sustainable development is very high on the AkzoNobel agenda and last year the company scored number 2 in the Dow Jones Sustainable Index. Schröder: "To continue to be a successful company in the long run we need to make sure our products and technologies are sustainable."

High tech

Schröder got really impressed by what can be done using biotechnology. "Introducing new genes to host cells and knocking out genes that would otherwise degrade MEA is to me really high tech. When we started the project I hoped to gain an understanding on the chances of a direct production of MEA from glucose using biotechnology. At the end we knew it is possible, although still difficult to do on an industrial scale."

The collaboration between AkzoNobel and the academics - B-Basic partners the Delft University of Technology and TNO - worked well according to Schröder. "There was a flow of ideas and knowledge at our project meetings. One of our researchers spent some of his time at the university. I think we should have had more of this exchange of people between the different groups," he says. AkzoNobel will continue to look at different possibilities for bio-based production of MEA, especially since a big new application has been added to the list: MEA can play a role in the mitigation of global warming by absorbing carbon dioxide from the flue-gas of coal fired power plants.

Education

A life time spent learning about biotechnology

Hans Tramper is professor of bioprocess technology 'with special attention to education'. That is certainly special because learning materials for secondary schools and courses for doctoral students and the business world were developed within a period of three years in the educational programme he thought up but Tramper is a long way from being finished.

"If you want to develop biotechnological knowledge a few courses for doctoral students are not enough," says Hans Tramper. "You must ensure a continuous supply of enthusiastic students from secondary education." The educational programme developed by the bioprocess technology professor in B-Basic therefore consists of more than just lessons for students. Tramper formulated a plan that provides schooling projects for pre-university students up to and including industry. Many of the projects use one of his hobby horses: adaptive digital learning material that modifies itself to the level of the user.

Food and fuel

Tramper is most proud of the 'Food or Fuel?' learning module made for pre-university students in which the topic of Natuur, Leven en Techniek (NLT) is introduced. This sort of multi-disciplinary topic is difficult for many teachers according to Tramper because they are too specialised in their own subject. Furthermore the subject is accessible to students from all types of different backgrounds; one has studied biology or physics, the other hasn't. Also fourth-formers and sixth-formers must both be able to follow the lessons. "I find NLT a beautiful and important subject in which more attention could be paid to biotechnology. A nice way to insure the intake of good students to the university," says Tramper. He developed this learning module, which consists of an adaptive digital module supported by manuals on paper, with teachers and lecturers, some from the TU Delft. The students learn the implications of the debate between food and fuel and they can make biofuel from waste. "We are very proud that the module has recently been certified and has now become official lesson material."

Good students

The development of a Life Long Learning project about the subject of bioreactors can be found at the other end. An old course was dusted off and supplemented with a digital module. "This project is also on the rails. Doctoral students may follow the course at a reduced price and people from the business world pay the market level price. In this way this project is valorised," says Tramper.

The product of education is good students. A sustainable product, thinks Tramper, because with education you can realise the move of a society based on oil to a biobased economy. "We want to put the emphasis more explicitly on biotechnology in the follow-up projects as the replacement for chemical technology."

Tramper is full of plans for follow-up projects at BE-Basic. He would like to expand the digital modules into large question pools so that when requested a made-to-measure lesson package could be compiled. "We want to start testing it on the Enzyme-kinetic module that we developed with the University of Groningen but a lot has to happen before anyone can find their own made-to-measure module easily." He also wants to develop the 'Distant Learning' concept further in which anyone anywhere in the world could follow learning modules via internet. "Digital learning material must be developed for more than one class and by working together you are able to profit from each other's expertise. We would like to do this with foreign institutes as well. A lot of beautiful things can be made together."

Digital learning modules for individual education

Little is known in beta didactics about the effectiveness of digital learning material that can adapt to the user. Researcher Janneke van Seters and her colleagues are developing the software and the learning modules and she is taking her doctorate with a study of whether the material does what it should.

Adaptive digital learning material is a learning module that adapts the next question to the answer given to the one before. Researchers from Wageningen developed the Proteus software packet in which digital learning modules can be made. PhD student Janneke van Seters is now researching how effective this lesson material is because not much is known about it.

Research proposal

After her study of Molecular Sciences, Van Seters wanted to continue with the research but not in the laboratory. "I had already worked with the adaptive digital learning material for the B-Basic educational programme but little is known about it in respect to science. I therefore wrote a research proposal myself for my PhD project, which includes all the things I consider important to be investigated."

The modules Van Seters develops consist of a database with questions and information, the correct answer to a question gains points. Feedback follows an incorrect answer, perhaps with more information or a web link. A student with little foreknowledge of the subject of the learning material will therefore take longer to learn the lesson module than a person with a lot of foreknowledge.

Van Seters looks at the effectiveness of the digital learning material with the help of questionnaires, among other things. To be sure that the lesson module she is researching is of good quality, Van Seters herself made one about PCR, a basic technique in genetic research. Van Seters wants the students to learn to design primers in the module and then use them to implement in a PCR. "An important basic principle when you are designing teaching material is to consider what you want the students to learn, how you want to teach them and finally how you test if they have actually learnt anything," she explains. "I test the student's knowledge by giving them a DNA sequence and asking them to design a primer. I then look at what they have to be capable of to manage this. For instance you must know what DNA is and how it is duplicated. I add this information and in this way I build up the structure of the learning module."

Culture differences

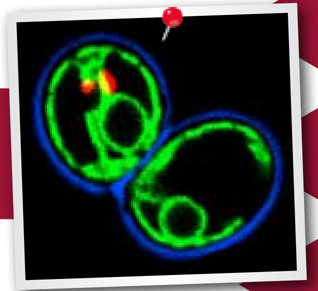
One thing Van Seter's research has shown up till now is that the preparatory training of a student does not determine how or how fast he learns. "The lesson material is therefore very specific to the individual student. Furthermore the students are very motivated by this sort of lesson material. Slow learners can also catch up by following our modules." In addition there are several methods of learning, one student is happy to learn from his mistakes while the other would rather be well prepared and not make any mistakes. "We also see cultural differences here," says Van Seters. "In the Asian culture it is for example very important to give the correct answer straightaway, in our culture you learn from your mistakes."

Van Seters plans to make the knowledge gained in her graduate research widely available. "I would like to make an accessible publication with guidelines and pitfalls for everyone who develops this type of learning material."

Educational Programme
Prof. Dr. Ida van der Klei
Professor of
Molecular Microbiology
University of Groningen

Programme partner:
Wageningen University

Learning from practice

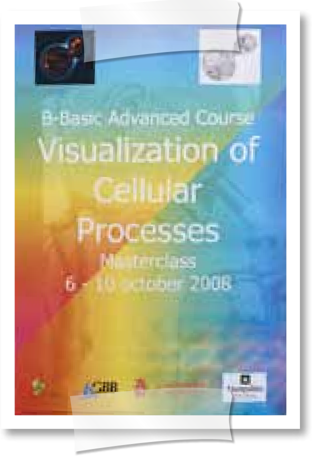


Doctoral students do not only research but also have to learn about the newest techniques and knowledge in their field. Masterclasses in which specialists give readings are a tried and tested formula for this. Ida van der Klei lifts the masterclass in B-Basic to a higher level with international speakers, a practical and a virtual preliminary study.

"Researchers must learn about the latest novelties in their field from the people who have developed and applied these techniques. You won't hear about them at congresses. You have to invite specialists and bring them into contact with the researchers. That is what we do in the B-Basic masterclasses," says Ida van der Klei, who coordinates these courses in the Groningen Biomolecular Sciences and Biotechnology Institute (GBB).

Foreign specialists

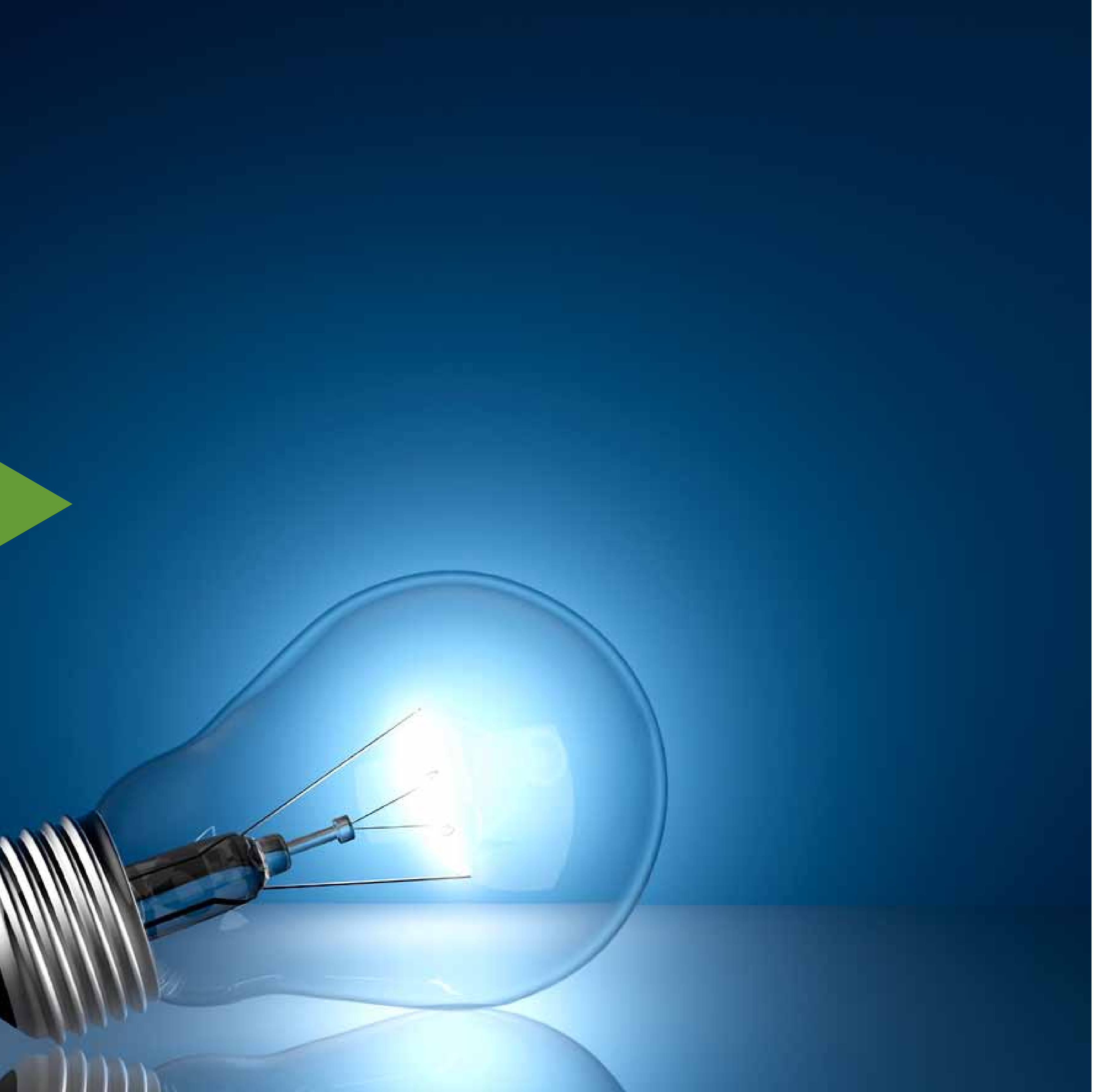
Two courses have been given since 2008. The Molecular Cell biology department, where Van der Klei is a professor, is specialised in advanced microscopy such as electron and fluorescence microscopy. She therefore organises a masterclass called 'visualisation of cellular processes'.



Dick Janssen from the Biotransformation and Biocatalysis group in the GBB gave a course called 'directed evolution and protein engineering', about all the facets of proteins and enzymes. There are a few pending for 2010 including one about transport processes in industrial micro-organisms and the existing masterclasses will also be repeated.
The masterclasses consist of readings from renowned speakers from The Netherlands and abroad, but there will also be time for discussion. The doctoral students will present their own research and get tips. "The researchers are very enthusiastic, there are many discussions and they ask a lot questions. They show that they have learned a lot," says Van der Klei. The masterclasses are accessible to all PhD students as long as their research relates to the subject of the masterclass.
"The practical lessons, in particular, are so popular that we have to make a selection," explains the professor.
The second part of the masterclass was a practical week. This is unique, according to the professor. It was a microscopy practical and companies were also invited with their fluorescent lifetime imaging equipment. "The students could use the equipment themselves which usually never happens. Practical lessons are usually only demonstrations. After a week of hands-on work they could operate the equipment themselves and some of them stayed in touch to make use of the equipment and the knowledge."

Virtual microscope

Van der Klei also makes new digital learning modules for the Proteus software package developed by the researchers at Wageningen University. "We have made a virtual microscopy practical where they can learn something that would otherwise take much time and money. They can make a micro-organism that produces fluorescent proteins by cloning and if they have done this correctly the bacteria will indeed make protein and they can study it under the virtual microscope. In addition we make a virtual lab where the students have to think up experiments to solve scientific issues."
"It is possible to educate far more people much quicker with these digital modules. Moreover the modules are fun to make and the PhD and master students enjoy working with them," according to Van der Klei. She would like to include the modules at the beginning of the masterclasses.
"The students all have very different backgrounds, it is a very heterogeneous group but you can level out the differences by allowing them to follow a module. We would like to use this in future."



Innovation & Valorisation

Innovation prize as stimulus for new ideas

The Leo Petrus Innovation Trophy is awarded annually to the person with the most innovative idea for making chemical substances or biofuels from biological material in a sustainable way or by a biological conversion. The creation of this prize has produced the necessary useful ideas and has improved the awareness of innovation. "But it could be even better," according to Peter Lednor.

"The initiative to develop the innovation prize came from representatives of the B-Basic industries and the B-Basic office," says Lednor. "The prize of 100,000 Euros will enable the winner to further develop his or her finding until it is ready for the market. In 2006 the prize was named after Leo Petrus, chief scientist at Shell who died unexpectedly." He was member of the Trophy committee.

Lednor, who succeeded Petrus as the Shell representative in B-Basic thought that the both the quality and the quantity of the entries for the Leo Petrus Innovation Trophy (LPIT) could be improved. In the first year there were only two finalists. Lednor had had the usual experience in the field of innovation management at Shell and therefore took the initiative by organising an innovation workshop together with B-Basic for PhD students and Shell employees. The purpose was to stimulate the generation of ideas and contacts between academics and people from the industry. A more extensive and improved workshop took place a year later at DSM. "The researchers learned to view their ideas critically in relation to what was required by the market," according to Lednor. "We also created our own logo and website to give the Trophy an identity and to make it more widely known."

Business plans

Lednor noticed that many scientists do not know exactly what innovation in business involves. "As well as the actual finding, you also have to consider who will implement the innovation. How will the property rights be regulated, what are the developmental costs, what will it bring in, who is the competition, etc."
Lednor therefore sought collaboration with the Rotterdam School of Management to set up special workshops for LPIT entrants. These workshops in which LPIT entrants learn more about innovation and improving business plans from their colleagues in Rotterdam started in 2008. Eventually the entrants with the best business plans may present them to the LPIT jury, which includes representatives from the B-Basic companies and a PhD student.

More entries

"The quality of the business plans from the Trophy finalists in 2007-2009 was clearly much improved," says Lednor. "More entries arrived, from outside B-Basic as well." In 2008 Deltares, with the TU Delft, won with their finding for making bio-cement from waste products and soil bacteria. In 2009 an outsider won: the University of Twente won with an idea for the improved gasifying of biomass."
"Innovation does not just happen; you have to work hard at it," according to Lednor. "Unfortunately there has been only a very small minority up to now who are enthusiastic enough to think up new ideas. Enthusiasm for innovation has been stirred up by making the participation in the competition educational and challenging. The Leo Petrus Innovation Trophy will be improved and elaborated even further in the subsequent programme, BE-Basic."

Leo Petrus Innovation Trophy '09

Innovation & Valorisation
Chairman of the LPIT commission
Dr. Peter Lednor
Freelance consultant (now)
Manager of biofuels innovation and external relations (until retirement in 2009) at the Shell Technology Center

Bio-cement reinforces dikes and dunes

Innovation & Valorisation
Leo Petrus Innovation Trophy 2008
Dr. Ir. Wouter van der Star
Smartsoils researcher
Deltares

Researchers from Deltares and the TU Delft have come up with a method of making calcium carbonate sustainably with the help of bacteria and waste materials. They won the Leo Petrus Innovation Trophy in 2008 with their findings. Reinforcement of dunes, dikes and underground channels is a potential application.

"The great thing about this method is that no large pressures are needed to make calcium carbonate, it is just a matter of injecting it into the ground," explains Wouter van der Star from knowledge institute Deltares. The finding is based on earlier research into the hardening of sand. Calcium chloride, urea and dedicated bacteria were injected into the ground for this purpose. The bacteria split the urea resulting in the release of carbonate (CO_3^{2-}-) which precipitates with the calcium to become calcium carbonate, also known as calcite. The calcite sticks the grains of sand to each other and they become calcium carbonate.
"The principle works and has already been demonstrated on a large scale. Calcifying a container full of sand works perfectly," says Van der Star. However the biggest disadvantage of this process is that the ammonia released when the urea is split has to be removed. Van der Star and his fellow researcher Leon van Paassen therefore went in search of a more sustainable alternative. They found it in denitrifiers, bacteria which are found naturally in large numbers in the soil. If you feed these bacteria nitrate with sufficient fatty acids, such as acetate, they will also produce carbonate. With the calcium this will in turn form calcite. Harmless nitrogen gas, N_2, is the principal side product.

Waste materials

"We were looking for a way to make calcium carbonate from waste materials so that the process would be even more sustainable and economical," explains Van der Star. Waste materials from the food industry or from sewer treatment installations, for example.
In the meantime, the conversion of waste materials into nutrients that the bacteria can use has been successful. "But the finding is not yet ready for the market because we are still working on having the whole process - from waste materials to the formation of calcium silicate - take place in sequence. After that, scale up can take place. We are using much knowledge and experience gained from the process based on urea. This process already works on a large scale and we will be doing a pilot soon with a scaled up urea process for a customer."

Workshop

Van der Star has had been greatly helped in putting the finding on the market by the workshop to which the participants for the Innovation Trophy were invited. "The workshop was very useful because I had no experience in writing business plans or giving a venture pitch. Besides we got tips on how to make our business plan stronger and we had to calculate how much saving our finding could bring the market parties."
He also found the coaching by students from the Rotterdam Business School very informative. "They get you to focus on business affairs that you wouldn't think of yourself. We would not have come so far without the Trophy and the workshop," states Van der Star. "Because of this we can clearly see what the problems are for our market parties and we are able to concentrate our finding on them."

Converting ideas into commercial applications

New ideas to make building blocks and materials sustainably from biomass don't just fall into your lap and besides they must also be practically applicable. "Innovation workshops can help generate new ideas," according to Dr. Ir. Peter Nossin, committee member of the B-Basic programme, "but then you must create the right conditions."

"In B-Basic we work towards the commercial application of findings as much as possible. We must however leave room for new ideas and not 'cast it in stone'," thinks Peter Nossin, who works at the Dutch Polymer Institute. "Researchers, PhD students and postdocs especially often have good ideas which are interesting to companies."
That's why Nossin organised Innovation

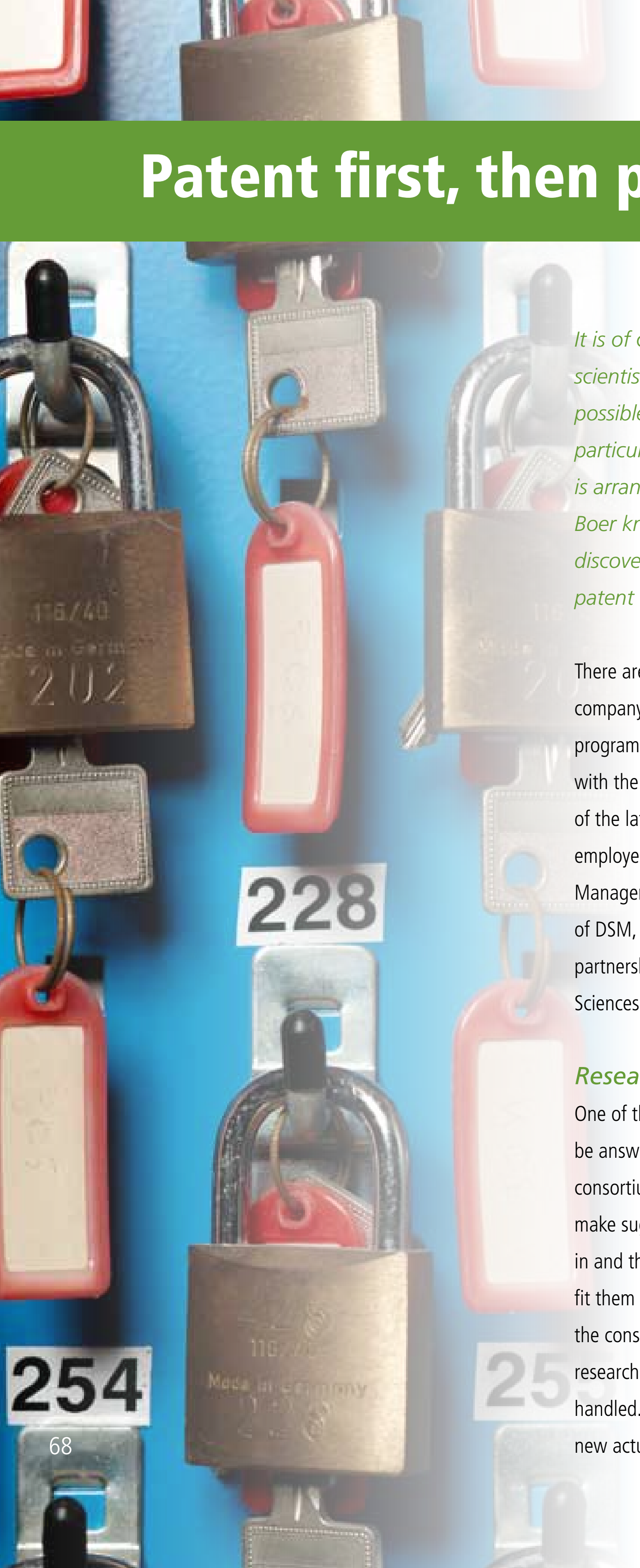
Workshops in B-Basic to stimulate the generation of ideas and to expand the interaction between industry and academia. During the first workshops at Shell led by Peter Lednor in 2006, PhD students, their university supervisors and a number of people from Shell generated ideas in brainstorming sessions and they presented these ideas later in so-called elevator pitches. Nossin, "The idea behind this is that when you meet some one from senior management in the elevator you try to convince him in a couple of minutes of a proposal. You have to explain in a few words why your idea is so important to the company. Everyone was very enthusiastic about this."

Inspirational

Participants also had to hold pitch sessions during the second workshop organised by Peter Nossin at DSM in 2007. "We asked three DSM business units to sketch out a problem in the development of a future or existing application that could be solved by biotechnology.
Various workgroups took their turn in finding solutions which were presented later. Bringing researchers and business units from companies together proved to be very inspirational and the researchers learned from people in the business world what is industrially relevant in turning a finding into a successful innovation. Nossin is exceedingly pleased with the success of the workshop at DSM. "Much preparation and conviction was required to get people so far that they actually joined in with presenting the cases. And then the flood gates were open."

Brush up

Nossin, who as a member of the jury was involved in the organisation of the Leo Petrus Innovation Trophy, ascertained that applications for the first Trophy were not concrete enough and could have been worked out better.In the end industry showed little interest in the winning idea at the time because they were not convinced of its commercial interest.
Nossin, "We realised that many of the people from universities knew little about how to turn a finding into a product that would be of interest to the market. That's why we involved students of Innovation Management from the Rotterdam School of Management (Erasmus University) to brush up the applicant's knowledge in workshops."
It was not only the participants who learnt a lot in the workshops, Nossin also gained experience in the organisation of a good innovative workshop and he uses this knowledge in his current work at the Dutch Polymer Institute to organise workshops about biopolymers.



Patent first, then publish

It is of course a very exciting moment: scientists want to publish as quickly as possible and the industrial partner who particularly wants to wait until the patent is arranged and patent expert Wim de Boer knows all about this. "Once a discovery has been published, requesting a patent is pointless."

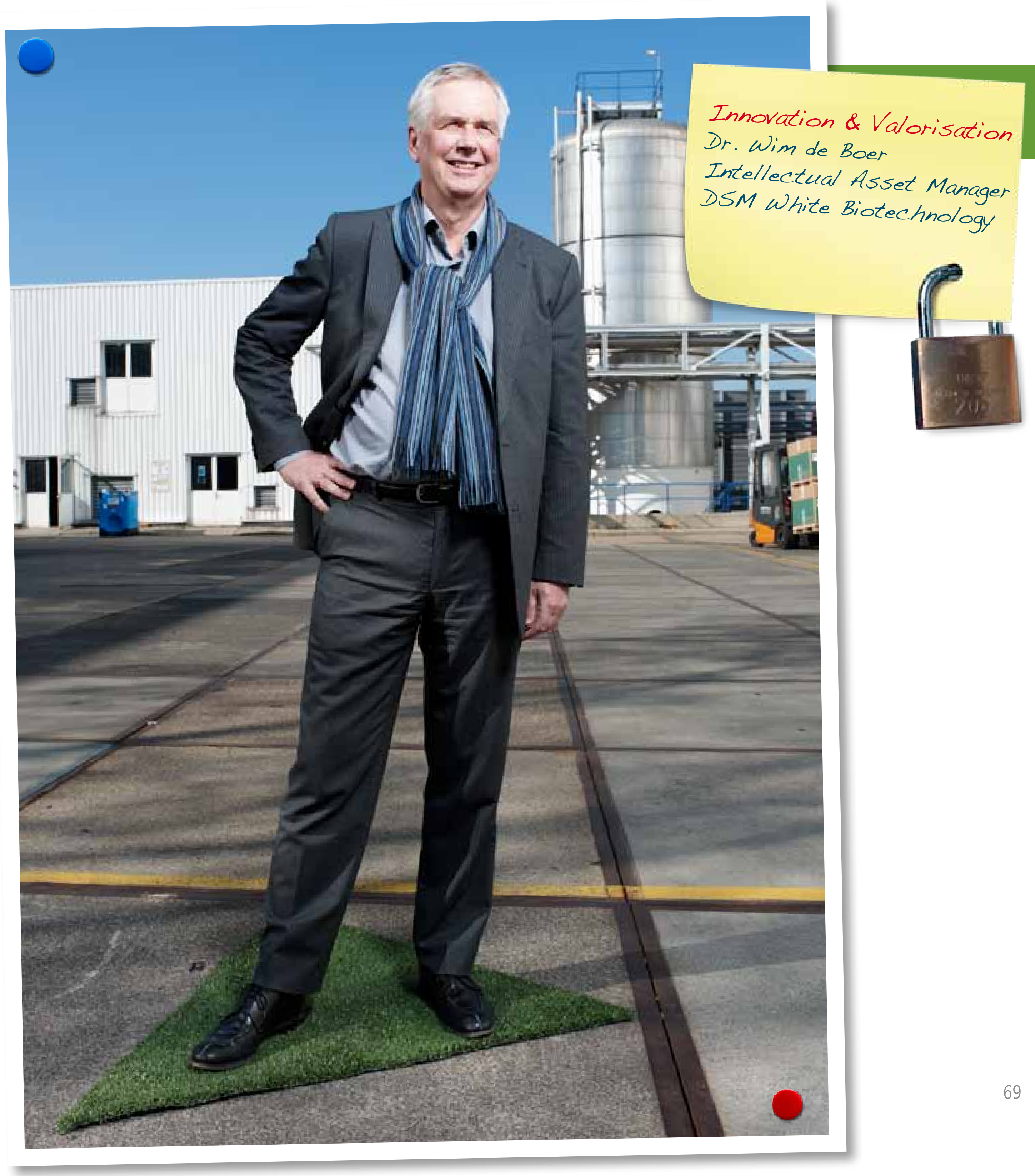
There are a number of good reasons for a company like DSM to join a public-private research programme. "You want to maintain good contact with the university, you want to be kept informed of the latest developments and it is source of new employees," says Wim de Boer, Intellectual Asset Manager at DSM White Biotechnology. On behalf of DSM, he is involved in all the public-private partnerships that are drawn up in the field of Life Sciences.

Research question

One of the first big questions that has to be answered during the start is: what is the consortium going to research? De Boer, "We make suggestions in the field we are interested in and the professors see if and how they can fit them in." Everything is then recorded in the consortium agreement which includes the research programme and how the results are handled. Before there can be a patent something new actually has to be found. "Something that could be used by the company and could lead to a new process or a sellable product," explains De Boer. This could be for example a new method of purifying a product or a micro-organism that has learned a new trick, like the yeast that, after modification, is capable of converting difficult sugars like arabinose into alcohol. "We have a patent for this based on research carried out within B-Basic which includes what this new strain can do, how it is made and its use. In this way you try to build up a series of claims around the discovery so that it is protected as broadly as possible."

Patent value

In the past, several chances were lost. Every research group wants to show that they are doing pioneering research and publish the most striking results quickly but in the meantime everyone knows the tricks of the trade. "Frequently we get a call about an important congress that will be held shortly where they want to be the first to report the results, we have to move very fast if we wish to submit a patent application. We then have another year to develop the original discovery further, but the researcher may tell his story at the congress."
In B-Basic, NWO-ACTS becomes the formal owner of the patent because ultimately it is research that has been subsidised by the government. The patent may be sold to a participating company



for a market level price. But what is the value of a research result that is beginning to be developed? The parties could discuss this issue for a long time. "If it relates to penicillin research it could be very interesting to us if it improves the profits but companies like AkzoNobel or Shell would not spend a penny on it. So what is such a result worth? A percentage of the expected profit improvement? It would be difficult to judge because it still remains to be seen whether or not it gets that far," according to De Boer.

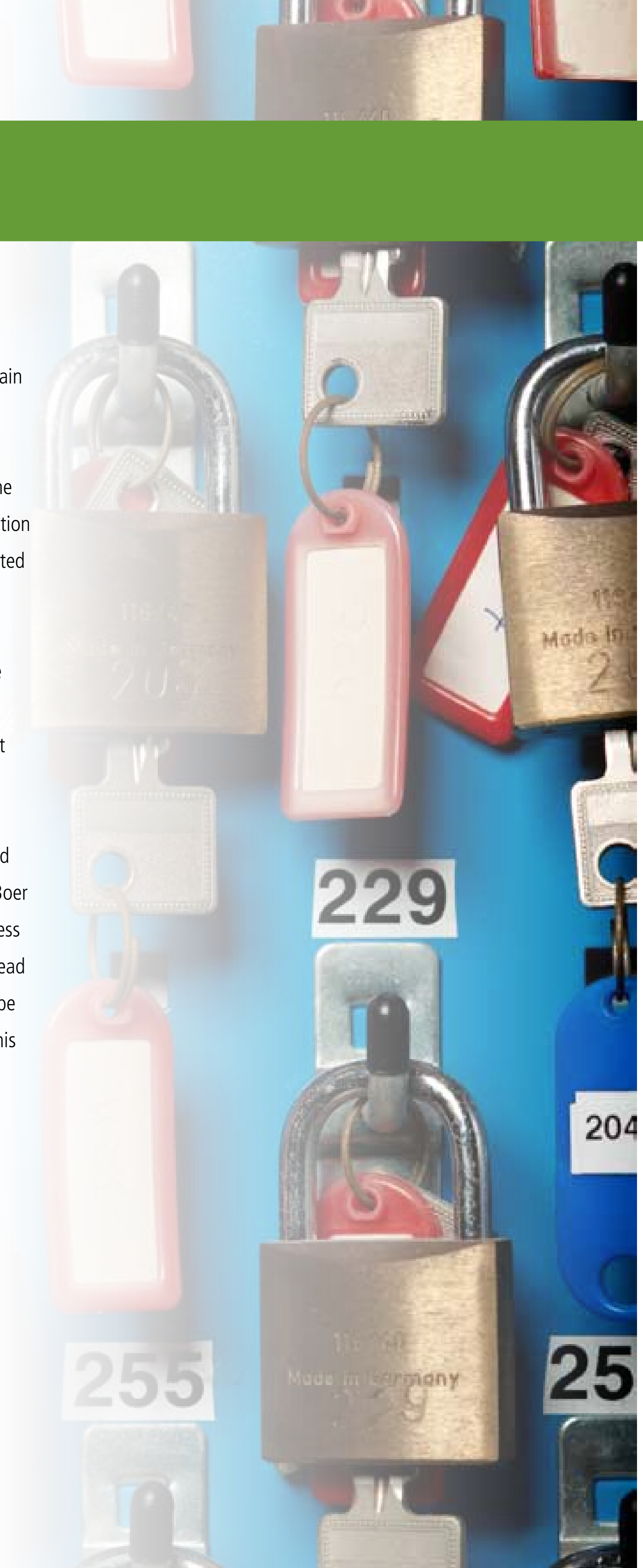
The logical unit

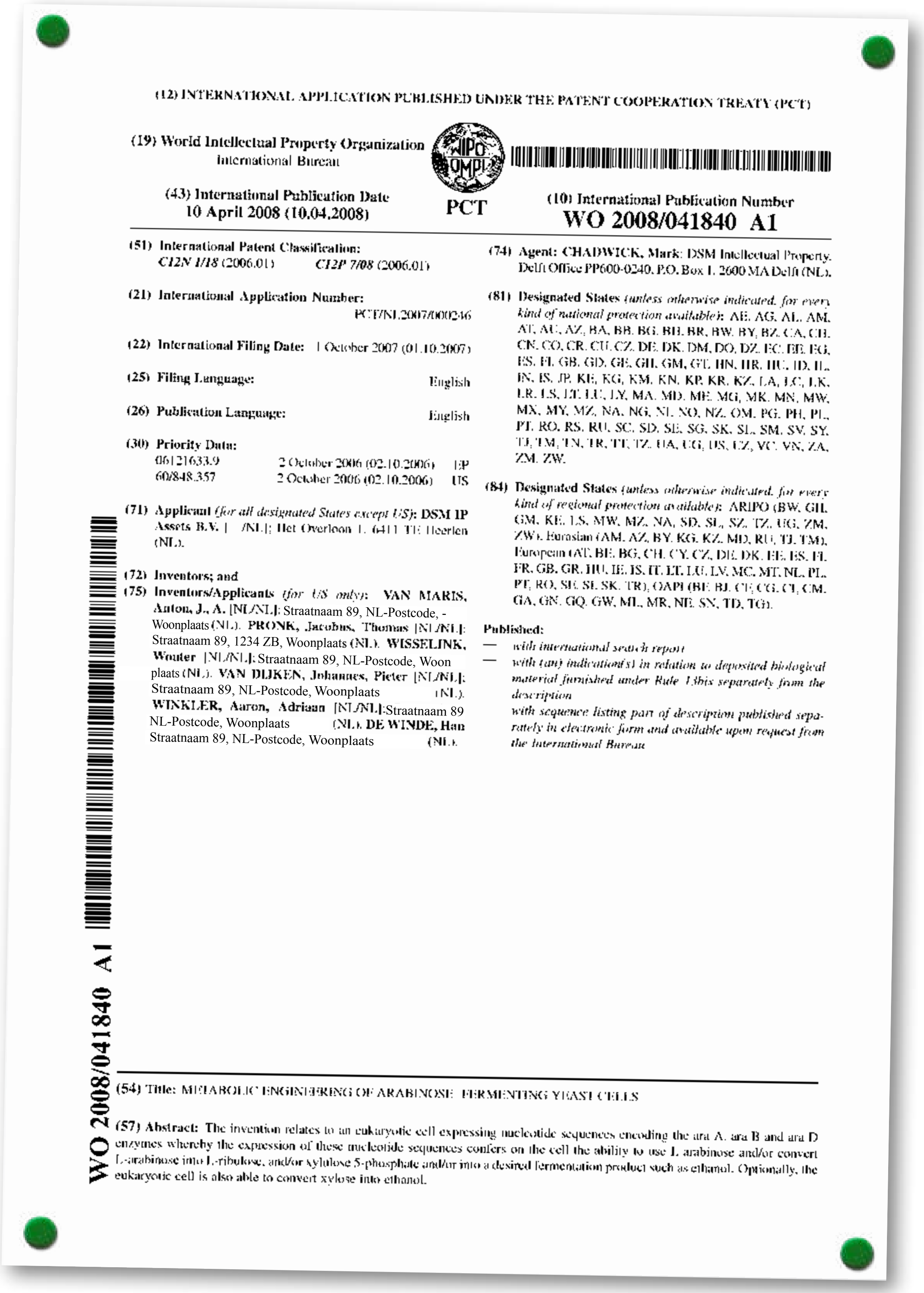
An answer to the question has been found during the B-Basic programme. "In talks with NWO-ACTS we have developed the concept of the logical unit," explains De Boer. "It enables you to calculate the expenses that have been made in arriving at the result, i.e. the time spent by the researcher, the cost of the work space at the university and the supervision hours added together."

The professor involved makes the calculations and the B-Basic programme committee then approves the calculated logical unit that will then apply as the market value for the research result or the patent. When several companies are interested the costs are divided up. One of the companies is the patent holder, the other has the licences. Taking over these results has advantages: there is a 100% chance of a result.

Negotiation element

Much has been learned that could be used again in future public-private partnerships. "We are going to do it just a little bit differently in BE-Basic. Payment of the market value will stay the same but there will be more space for negotiation between the research institute and the interested company, about the payment instalments for instance. It would be very disappointing if the result after further calculations does not prove to be interesting if you have just paid the full price," states De Boer. The amounts can mount up. Suppose that a researcher has worked for a year, this would mean a sum of more than 100,000 Euros. Companies are more interested in spreading the risk a little. According to De Boer this would be possible by buying a sort of access right, where a part is paid for and the rest spread over a number of years if the results prove to be of interest. "Disappointments are prevented this way," says De Boer.





(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

WIPO OMPI

PCT

(43) International Publication Date
10 April 2008 (10.04.2008)

(10) International Publication Number
WO 2008/041840 A1

(51) International Patent Classification:
C12N 1/18 (2006.01) *C12P 7/08* (2006.01)

(21) International Application Number: PCT/NL2007/000246

(22) International Filing Date: 1 October 2007 (01.10.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
06121633.9 2 October 2006 (02.10.2006) EP
60/848,357 2 October 2006 (02.10.2006) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description*
with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

WO 2008/041840 A1

(54) Title: METABOLIC ENGINEERING OF ARABINOSE- FERMENTING YEAST CELLS

(57) Abstract: The invention relates to an eukaryotic cell expressing nucleotide sequences encoding the ara A, ara B and ara D enzymes whereby the expression of these nucleotide sequences confers on the cell the ability to use L arabinose and/or convert L-arabinose into L-ribulose, and/or xylulose 5-phosphate and/or into a desired fermentation product such as ethanol. Optionally, the eukaryotic cell is also able to convert xylose into ethanol.

Society

Hard work to combat climate change

If we do nothing the consequences will be huge, thinks André Faaij, we must start to live much more sustainably, and do this quickly. The use of biomass for energy and materials plays an important role in this. "It doesn't matter to me if you believe in climate change or not it will save money!"

André Faaij wants to be optimistic but the transition to the biobased economy is not going fast enough for him. "I find it inconceivable that we can sit like rabbits staring into the headlights and do nothing. We get increasingly harder feedback from the climate in the form of flooding, storms and melting ice. All the stops must be pulled out to decrease the consequences of climate change but I am still optimistic because there is no choice!"

Faaij works at the Copernicus Institute in Utrecht. This institute develops future scenarios and looks at the ecological and social-economic impact they have. They also optimise and assess the sustainability of, for example, land use or production chains and help B-Basic in the social discussions relating to biotechnology, among other things.

Saving money

Biomass plays a unique role in the theme of sustainability, says Faaij. Biomass is not only sustainable but also has high economic value as a replacement for oil and gas without CO_2 emissions. "The International Energy Agency IEA has calculated that converting to biomass is cheaper in the long run than to remain using oil because the cost of biomass will decrease due to volume enlargement and the cost of fossil fuel will as well because there will be less demand. Biomass saves money!"

But the transition to a biobased economy does not only entail converting to another type of fuel. "In addition to climate and energy there are many other sustainability themes needing attention, such as food supply, rural development, combating poverty, better soil management, water and biodiversity," explains Faaij. A 'food versus fuel' dilemma is not necessary according to the researcher. There is enough capacity to produce food as well as sustainable biomass with strict demands on water use and biodiversity.

"A sustainable food supply is a question of investment and combating poverty. With good policies and land and resource management, you are able to create a synergy between these aspects with the help of biomass."

Our own resources

Energy from biomass is already quite important in our own country. "If we work hard it is possible for the Netherlands to satisfy thirty percent of its energy demand with biomass, with a third of this coming from our own resources," thinks Faaij. Those are for instance waste wood from forests, better management of grasslands, fertilizers and the waste products from industries and we will have to import the rest from abroad. It is about two things in our country: international trade and technology development.

"Our knowledge infrastructure is still one of

the best but research similar to B-Basic's must be directly linked to industry and especially to policy." Stable policy is of crucial importance, says Faaij. "The policy keeps itself very aloof. In the last years we have lost much time and money with subsidies and market support without there being an actual target such as economic profitability. The market requires clarity from the government, climate legislation for example, and a policy for the long term that offers security for investment by companies."

Speeding up the biobased economy

We cannot go back anymore, thinks Roel Bol. However you look at it everyone will have something to do with the biobased economy. The government's role is to stimulate the development and exchange of knowledge. "I see chances in the biobased economy. Luckily more and more people see them as well."

The biobased economy is a challenge, thinks Roel Bol. As programme leader Biobased Economy at the Ministry of Agriculture, Nature and Food Quality (LNV), he is responsible for government policy in the transition to a new economy based on biomass. "The biobased economy is a development in which biomass instead of oil and gas will be applied sustainably and renewably in the economy in all sorts of places," specifies Bol. "This development is irreversible, no one believes that we would want to return to complete domination by fossil fuels anymore."

Being clever with biomass

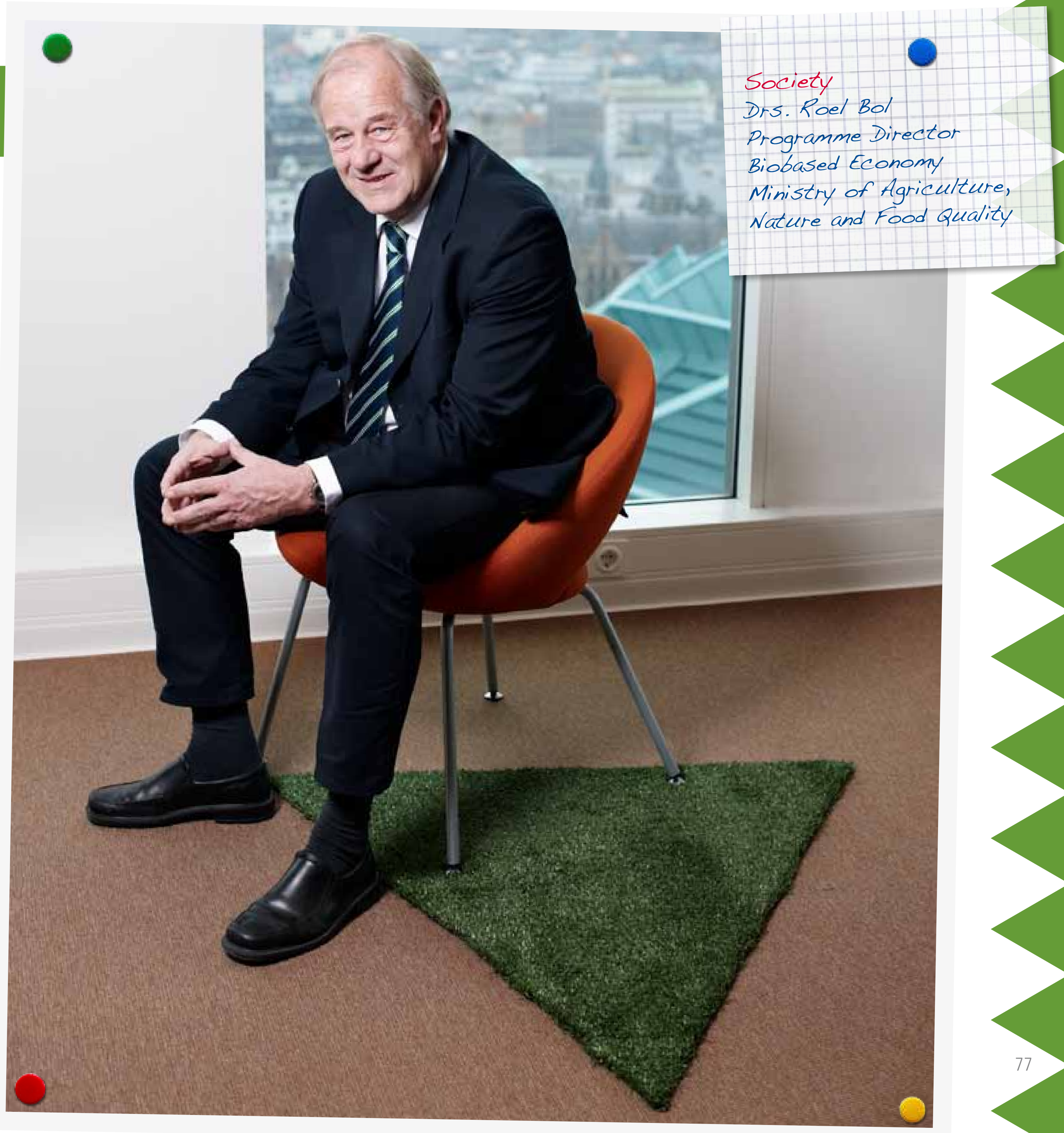
In 2007 an interdepartmental commission, with Roel Bol as a member, presented the government's vision of energy transition. The long and the short being that we could handle biomass much more cleverly than we do now, explains Bol. "That would be better for the economy, for innovation and for sustainability. You have to consider the whole value chain of biomass. We must think much more in systems, in co-productions with other sectors and that demands a turnaround. As government we must stimulate that."

You cannot find out how to handle biomass from behind your desk. It is partly market-controlled, thinks Bol. Knowledge in that field has to be developed better and opened up properly and a programme such as B-Basic is wat we need for this. The government points the way on for the developments. "In the coming years we will research which way the biobased economy is going," explains Bol. "You can then determine what is needed in the field of knowledge development, infrastructure, stimulation policy and legislation and with this we can create a consistent set of policy instruments."

Dynamic

The SBIR programme is one example of government stimulation. In this programme small companies with a tender get the chance to develop new, innovative products, often together with scientists. Special products such as biological chemicals for leather-working, algae for bioplastics and solvent-free steel coatings from biobased raw materials receive money for a feasibility study because large companies such as Shell and DSM are not the only ones actively involved in the biobased economy, says Bol. "I have a weak spot for SMEs. I think it is fantastic that more and more clever ideas are coming from the medium and small-scale businesses, perhaps these will be the multinationals of the future. That is the splendid dynamic of the industrial landscape."

We are quite far along the way to the biobased economy, according to Bol. Good contacts between science and the business world have been made so that the practical requirements have been made clear. "You no longer need to explain the concept but companies have to make the decision to invest in biobased products themselves. Personally I would hurry things along not because I am afraid the oil will run out but because there is so much positive energy in the companies and institutes that the technology can be quickly proved. You have to make use of that strength right now."



International

On a mission in Brazil

Can sugar cane form the basis of a sustainable chemical industry? A group of Dutch researchers and companies visited Brazil, the largest sugar producer in the world, to investigate that option. Collaboration must be timely because the competition is lying in wait.

Energy production in Brazil is based on renewable sources for the largest part, including sugar cane. For more than thirty years a large part of the sugar cane has been processed into ethanol for fuel and chemical products and the rest of the plant is used to generate steam and electricity.

Brazil ranks worldwide as an outstanding model in the field of renewable resources linked to an impressive infrastructure for processing and transport. Countries on the way to a more sustainable basis for their energy needs could learn a lot there because the demand for sustainable resources and alternatives to crude oil are increasing. The largest sugar producer in the world has been visited in the framework of the B-Basic programme.

Talking together

In the last few years three missions to Brazil were undertaken by representatives of the B-Basic consortium. The first visit to the South American country was aimed mainly at gaining more insight into the way biotechnological and chemical education and research is organised, and how the knowledge centres and Brazilian biotechnological industry work together. The principal destination was the university of Campinas, a town about 100 kilometres northwest of São Paulo, with whom the TU Delft runs an exchange programme. An important result of the first trip in 2004 was a cooperation agreement between NWO and its Brazilian counterpart FAPESP from São Paulo state. The second visit was part of the Dutch trade delegation from Economic Affairs, in which the emphasis lay on chances for cooperation between Dutch and Brazilian biobased industrial chemistry.

The third mission was a joint venture by B-Basic and the Biobased Raw Materials Platform and was organised in collaboration with Brazilian partners. The mission with the theme of 'Biobased Economy for Sustainable Energy and Chemicals', the BEST mission in short, visited the various companies, institutes and universities who play a role in the production of biochemicals and bio-energy.

Working Together

The summit for the Dutch delegation was the 'Innovation in Biofuels' workshop, organised by the Brazilian Foundation for Innovation, UNIEMP. About fifty Brazilians working at universities, government institutions and in industry took part. As well as the necessary networking, the role of governments, legislation, finance and the transport of biomass and biofuels were extensively discussed and, of course, cooperation in the future. The most important conclusion of the BEST mission was that there are big chances for cooperation the field of industrial biotechnology, but that urgency is called for as the competition will not wait. About ten sugar factories have already been purchased by the Japanese and Koreans and the rest of the international business world has also found the path to Brazil.

Accompanying the Mission
TU Delft, TNO, WUR, DSM, Shell, SenterNovem (now Agentschap NL) and ECN.

Biobased Raw Materials Platform

The Biobased Raw Materials Platform aims at replacing 30% of the fossil resources in the Netherlands with biobased raw materials by 2030 which would result in less CO_2 emissions and less dependence on crude oil, coal and natural gas. The platform has formulated five transitional paths for this aim which are routes to a biobased economy that will be actively stimulated by the platform. The first two relate to having enough biomass available, the last three relate to the processing.

Network in action

Together to a sustainable bio-based society

"International collaboration is crucial to implement sustainable bio-based production into society," says Professor Richard Templer, director of the British Porter Alliance. The Alliance collaborates with B-Basic among other centres of excellence to search for new routes to a plant based chemical and fuel industry.

The Porter Alliance was set up in 2005 bringing together many different experts like plant scientists, molecular biologists, mathematicians, instrumentation developers, and economic experts from seven UK institutions. Also companies and knowledge institutions are involved.

When comparing Porter Alliance with B-Basic, Richard Templer remarks that in the focus of their technological research the two are complementary. "B-Basic concentrates on high value pharmaceuticals whereas we focus on biofuels and commodity chemicals."

Biorefinering

However both share the same vision. "We are aware that our future depends on integrated biorefinering. By using the components of a plant efficiently one can produce multiple things, like biofuels and high value chemicals. Some plant derived products like a plastic say, extract CO_2 from the atmosphere and store in a useful product for a long time. Together this can all contribute to a low carbon future."

Templer also stresses that companies should be able to make money with bio-based production and it should be socially sustainable; people's lifes should not be damaged by the bio-based production.

"The Dutch government has facilitated and stimulated innovative research in bio-based production of chemicals to an impressive degree, whilst the UK government's record of support has been more modest," says Templer. "Since the Netherlands hardly has any undeveloped land and bio-based production must rely on imports, this has driven the Dutch government's focus on research in sustainable and bio-based production of chemicals."

Climate change

The Porter Alliance and B-Basic were major contributors to a big project for which they won a grant from the European Institute of Innovation and Technology (EIT). The project will focus on innovations to mitigate and adapt to effects of climate change. "One of the issues we wish to resolve is the sustainable use of land for all forms of plant-based production," says Templer. "Changing agricultural land-use to grow crops for plastics or medicines say, does not necessarily jeopardize food production and, if designed well, can decrease overall green house gas emissions. For example growing perennial crops to produce biorenewables can be done without tilling and with greatly reduced fertilisation, which makes a large reduction in carbon dioxide emissions from the soil. If we avoid transporting this feedstock large distances to a biorefinery, by placing refinery and crop nearby we greatly reduce the energy and greenhouse gas emissions in producing the biorenewable products. Combining such simple steps with a range of new technologies will, I believe, set us on a path to a sustainable future."

"To reverse climate change, a huge transformation of the global economy is required," says Templer. Bio-based production is a young technology, but can contribute significantly to the changes that are required. Plants produce many different molecules and with care these can be extracted and used to make products that are kinder to our planet. "By working together I believe we will reach the right answers a lot quicker."

Reliable information about renewable resources

"We want to become the organisation that one can approach for advice on renewable resources," says Kim Meulenbroeks from the Global Biorenewables Research Society. "Our reports will be a reliable source of information for international negotiations about the climate, biodiversity and the development of policy for the sustainable production of biorenewables."

"The Society has been established to provide science-based knowledge for a balanced debate on the bio-economy" says Kim Meulenbroeks, executive secretary of the Global Biorenewables Research Society (GBR Society). "All sorts of information about renewable raw materials, also known as biorenewables, and the economy based on them is available, but not everything is equally reliable. Therefore it is difficult for policy-makers to estimate the value of information. We want to make a contribution by assessing the information and translating it into comprehensible language. The assessment will be done by scientists internationally renowned in the field of biorenewables and related areas such as agriculture, the economy and the environment."

Land use

A number of workshops which were held at the initiative of the European-American 'Task Force on Biotechnology Research' were the reason for B-Basic and leading international partners such as the Energy Biosciences Institute (US) and the Porter Alliance (UK) for setting up the GBR Society in 2009. It appeared that a good and impartial examination of the issues facing the use of biological feedstocks for fuels and materials applications had not yet been made. "An adequate policy cannot be carried out for as long as such an assessment has not been made," according to Meulenbroeks.

The GBR Society aims at making such assessments. The independent network of scientists will evaluate studies by clear rules. Standardising methodologies and creating solid databases are essential criteria for a balanced recommendation. 'Land use changes' is one of the first topics that the GBR Society will take a closer look at. Meulenbroeks, "There is much discussion about this at the moment. The idea is that food production would be threatened by the increasing cultivation of crops for the production of biofuels. But is this really the case? We hope to create more clarity by comparing all the research in this area."

Assessment

The GBR Society's approach is international and interdisciplinary. Experts from various continents work together on one large report which, after peer review by colleague scientists and other experts, will then go to the policy-makers involved in the negotiations of international and regional treaties in the field of agriculture, the environment and the economy.

"Our reports must eventually reach the negotiators of the climate and biodiversity conferences of the United Nations," according to Meulenbroeks. "Unfortunately the Convention on Climate Change in Copenhagen in 2009 was too soon for us but we were able to see what was needed most, which parties were involved, etc. We are going to contribute with information on land use changes at the coming UN Conference on Biological Diversity in Japan where themes such as agriculture and biodiversity will be handled. That fits well."

The international collaboration in the GBR Society appeals greatly to Meulenbroeks: "By involving as many countries as possible in the initiatives for the development of sustainable production processes you can get a better idea of what is needed and when. Not only Europe and the US benefit from this, there are also many chances for developing countries. As Executive Secretary I hope to lead the whole initiative in the right direction."

International
Ir. Kim Meulenbroeks
Executive Secretary
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TU Delft

Future

BE-Basic takes the step towards a larger scale

The new BE-Basic consortium is larger, more innovative and more international and goes further in the development of biobased industrial chemistry. Extra emphasis is given to increasing the scale, open innovation and creating business opportunities. The programme continues to build on the breakthroughs from the B-Basic and Ecogenomics research programmes with this. "The focus lies on speeding up the whole course of innovation," according to general director, Luuk van der Wielen.

By laying the first bio-brick in February, the Minister of Economic Affairs Maria van der Hoeven, fired the starting signal for the new BE-Basic consortium. The public-private partnership comprises eleven universities, three research institutes and ten companies, of which six belong to the SME. Under the inspired leadership of the leadership team consisting of Luuk van der Wielen, Gerda Lourens and Bram Brouwer, they are proceeding full steam ahead with the development of materials, chemicals and fuels from renewable raw materials. BE-Basic is the abbreviation for Biobased Ecologically Balanced Sustainable Industrial Chemistry.

Innovations

"In the past five years important results have been achieved in the metabolic engineering of micro-organisms and in understanding their energy management." But this has had limited impact in respect to direct application," says Luuk van der Wielen, Director of B-Basic and Professor of Biotechnology at the TU Delft. "Therefore the basis at BE-Basic lies firmly in the whole course of innovation. The pilot facility with which companies are able to carry out tests on a large scale plays a central role here. In addition we are going to start strategic alliances with the capital world for setting up new activities. After all setting out a pretty business plan for a new discovery is not the only thing."

Populations

Important developments are also to be found intrinsically. B-Basic had strong roots in the conventional biotechnology where a single modified organism takes care of the production but the work field in BE-Basic has been enlarged by whole populations. Van der Wielen, "Metagenomics form an important knowledge base here with which we can develop new and better processes and products as well as more robust organisms on the one hand. We are moving towards synthetic biology with this. On the other hand it forms the basis for a service sector, as metagenomics enable you to measure the impact of human actions on the environment: whether the effects are from the humans themselves or from the industrial world or, in the case of a biobased economy, from the increasing agricultural activity. Furthermore environmental biotechnology will receive more emphasis in the programme."

Agreement

Gerda Lourens will take care of the financial part of the organisation. She is an expert in setting up and running complex public private partnerships and did the same work for B-Basic. "We have shown that we can cooperate well with industry; literally next to each other in a lab instead of in steering committees. An even larger partnership and even larger amounts of money are involved this time. The whole programme now has a budget of 120 million."

This year she has negotiated the required consortium agreement with Yvette van Scheppingen, Support Office manager, which was to be signed by at least 24 parties. "This is very complex and entails justifying the programme, mobilising the parties, discussions and consultations and eventually drawing up the contracts with the lawyers," explains Lourens.

Snowball effect

The Bioprocess Pilot Facility is her other big job. "This facility is a crucial factor in the development of the bio-based economy, but cannot be financed with FES (Economic Structure Enhancing Fund) money. We have good hope that it will be subsidised by other means." A part will be brought in via European Regional Development Fund, another part via the programme Clean and Efficient from the Ministry of Agriculture (LNV) and the Biobased Raw Materials Platform. This ads up to a budget of about 80 million with the industrial co-financiers.

The pilot facility will be open to all users in accordance with the open innovation concept so that large and small companies with good ideas but no means to test them on a large scale can come here. "It is unique in the world," according to Lourens. "We have noticed this by the growing interest shown by potential users. The user sessions, intended to define the equipment and pre-conditions, have caused a snowball effect; companies that do not belong to the consortium are already indicating that they wish to be part of it." For that matter this is not limited to only Dutch parties according to Lourens. "Enthusiastic reactions are coming from abroad, from Switzerland, Japan and Malaysia for example. This will attract new industry."

Ecology

Bram Brouwer, Professor of Environmental Toxicology at the VU in Amsterdam and coordinator of the Ecogenomics consortium, takes care of the E-factor in the new BE-Basic: nature as the source of new products and processes. Ecogenomics researchers will develop measuring systems to see if the new findings are actually more sustainable and environmentally friendly. "Words alone won't get you there, we are going to make the plan concrete," says Brouwer.

Furthermore he will be the driving force behind BE-BIC, the business innovation centre specifically for the SME. As well as being a scientist he is in fact also a creditable entrepreneur. His company BioDetection Systems has been in existence for nine years and MicroLife Solutions is now being established, both companies make use of the newest molecular techniques and whatever nature has on offer, for the new antibiotic strategies for instance. Brouwer, "A continual battle for food and space rages in the soil. Micro-organisms use all kinds of tricks to quite literally kill each other off and we can extract these properties and apply them in industrial fermentations."

Building on breakthroughs

Brouwer will apply himself in BE-BIC to the commercialisation and valorisation of findings resulting from the B-Basic and Ecogenomics programmes and later from BE-Basic. "We are going to scout around for new findings and for parties who want to bring these to the next level. Furthermore a finding can be made to be sold in a wide area by selling licences but it could also lead to a new company being set up. Large companies often find the investment too risky, whilst the SME only exists by the grace of the pioneers who further develop new findings." Six SME companies are now associated with BE-Basic and Brouwer expects this number to double within five years. He bases this ambition on his experience with earlier programmes and the quality of the ideas already available. "We can generate and valorise the knowledge and turn it into real activity with the knowledge infrastructure we now have. All this with the objective of helping The Netherlands Ltd. get ahead"