

Sustainability and Biotechnology

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Abstract:

Granted, biofuels and biobased bulk chemicals are low hanging fruits (technically speaking), but the economic and ecological impact of biotechnology is estimated to be more effective with higher-value and more complex molecules. The “buzzword” biotechnology has led to different priorities, often without considering long-term socio-economic costs. Even so, biotechnology holds some very promising solutions to some of our problems with benign synthesis, smart products, and waste recycling. The commercial potential of biotechnology is huge, a colossal 1000 billion U.S. dollars, or about an order of magnitude more than today! In order not to disappoint investors and tax payers, however, we need to develop our tools further, especially for complex molecules for various applications.

Introduction

“Socialism collapsed because it did not allow prices to tell the economic truth. Capitalism may collapse because it does not allow prices to tell the ecological truth” [Øystein Dahle, ESSO Norway]. Economic theories do not explain why alpine glaciers in Europe are melting at an alarming rate, why fishing grounds suddenly collapse, or why the bee population is decreasing to such an extent that pollination becomes a problem for fruit growers. The conflict between economy and the earth’s natural systems is taking a growing economic toll.¹ Robert Costanza et al.² estimated that already over 10 years ago the earth’s ecosystems provided 33 trillion U.S. dollars worth of services per year. However, indicators show that the global economy has expanded far beyond what the natural ecosystem can provide. “Cleantech” and “bio-based economies” are solutions that have been proposed to balance economy and ecology and to stop this destructive overexploitation. The buzzword <<biotechnology>> has made it onto the agenda of top-ranking politicians expecting sustainable manufacturing, green house gas reduction, and new jobs based on these new “cleantech” and “biotech” technologies. Bang et al.³ from the World Wildlife Fund (WWF) claim that industrial biotechnology avoids ~33 million tons of CO₂ each year, without taking biofuels into consideration. The same authors have calculated the range of full climate change mitigation potential of industrial

biotechnology of up to 2.5 billion tons of CO₂ equivalent (tCO₂e) per year by 2030.⁴ This is more than Germany’s total reported emissions in 1990. Without doubt Biotechnology can provide attractive solutions. However, we should avoid a “green bubble” and unrealistic expectations. Let us, for example, consider the chemical market, one of the prime targets for biotechnology.

Sales of global chemical markets⁵ are expected to grow from 2292 billion euros (2950 billion U.S. dollars) in 2007, to 3235 billion euros (4160 billion U.S. dollars) in 2015 and to 4012 billion euros (5160 U.S. dollars) in 2020. Estimates vary, but only about 3–6% of all chemical sales have been generated with some help from biotechnology,⁶ but this figure is anticipated to grow faster than the average market figures. It is speculated that ~20% of global chemicals will be derived using biotechnology in 2020 that translates into 1000 billion U.S. dollars! That means about a 1 order of magnitude increase from today’s figures. The share of biotechnologically produced fine chemicals is also expected to grow from 8% to 60% between 2001 and 2010. The estimates of the global sales of industrial biotechnology products vary from 50 billion dollars to 140 billion U.S. dollars, depending on whether biofuels are included. Estimates and definitions may vary, but there is one common denominator and one clear message: the proportion of products manufactured using biotechnology is expected to increase overproportionally. However, if we want to make today’s dreams a reality tomorrow, we need to focus on harvesting the huge commercial potential of about 1000 billion U.S. dollars which biotechnology apparently represents for chemistry. Just for comparison the combined therapeutic protein and monoclonal market, or red biotechnology, was about 70–80 billion U.S. dollars in recent years.

There are no shortcuts in biotechnology, and in order to meet the anticipated 1000 billion U.S. dollars derived from biotechnology we need to develop appropriate tools.⁷ We should not forget that it took 200 years to develop the chemical toolbox. Biotechnology will not take as long, but it is not very probable that we will develop all the missing tools in one or even two decades. We need to move fast but the technological problems are too large for single companies. An African proverb says “If you want to go fast, go alone. If you want to go far, go

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- (3) Bang, J. K.; Follér, A.; Buttazzoni, M. Industrial Biotechnology. World Wildlife Fund: Denmark, Sep 2009 download: www.wwf.dk.

(4) CO₂ equivalent or mixture of green-house gases that would have the same global warming potential.

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together". In addition to focus, we need new forms of open collaboration within the industry itself and between industry and academia. Industrial biotechnology has made it onto the agenda of politicians, who are looking for a "green image", quick wins, and additional voters, but we need to make them aware that it will still take some time to make industrial biotechnology a widely used technology that creates many jobs. Today's reward and recognition schemes in industry and academia are not ideal for a rapid improvement of this situation.

Cleantech, Biobased Economy and Its Supply Chain. To solve the conflict between economy and ecology a holistic approach is needed. Cleantech encompasses many different innovative products, processes, and services aimed at optimizing the use of natural resources or reducing the negative environmental impact by their use. Companies and public organisations will adopt the cleantech principle because it can lead to lower costs, improved efficiency, and superior performance. Cleantech applies to all human activities from tourism to manufacturing, and biotechnology is only one amongst many technologies which can be applied for cleantech purposes. The big expectations are, however, in replacing carbon from oil with carbon from biomass and in providing the decisive contribution in CO₂ reduction by "decarbonisation" of the energy system". Two biology-based technologies are required to reach this goal, agrotechnology and biotechnology. Biotechnology can provide sustainable added value by fermentation (biosynthesis) and/or biotransformation for better products and services, whereas agrotechnology can contribute in other ways—either by fixing carbon dioxide directly in plant material and the targeted product or providing the biobased raw materials needed for biotransformation and biosynthesis, if global land resources and population-supporting capacities are in balance.⁸

Close to 30 billion metric tons of CO₂ were produced in 2006.⁹ On the other side of the equation is the fixation of CO₂ by photosynthesis and carbon assimilation by vegetation. Today this equation is obviously not balanced, as CO₂ is accumulating in the atmosphere and the stabilisation and reduction of greenhouse gases has become a generally accepted necessity. However, there is great divergence of opinions on how to achieve this goal. Sustainable growth means first of all that we need a different approach for the definition and the handling of waste. Waste, in fact should not exist. There should only be left-over materials that can be used for different purposes. "Industrial Biotechnology is expected to be one of the strongest driving forces behind the world's low-carbon revolution" states for example U.K. Secretary of State. Lord Mandelson.¹⁰ The World Wildlife Fund (WWF) estimate of 2.5 billion tCO₂e savings would be an important contribution which biotechnology can provide. However, there are several important unknown variables such as available arable land and water resources that are critical to the realisation of this goal. A Danish study assumes considerable cropland expansion, whilst other studies believe that we are facing a reduction of global arable land by

Table 1. Production and use of biomass on a global scale

	billion tons/year	proportion in %
annual production of biomass (photosynthesis)	170–180	100
used by humans	6	3.5
use as raw materials for chemistry	0.3	0.5

20% by 2030.¹¹ Table 1 on the other hand shows that the use of biomass as a raw material for chemicals was negligible up until now.^{12,13}

For the last 7000 years our economy has been biobased. From the beginning of agricultural society until the 19th century agriculture and nature provided for food, feed, shelter, fuels, and pharmaceuticals for all human beings. We need to return to a biobased economy at least partially and replace fossil fuel carbon by carbon from renewable resources. The reality is that most European countries, for example, are dependent on "ghost acreage" and have to import significant amounts of food to support their requirements. The question is, can we further increase the use of the biosphere without compromising sustainability and massively interfering with the food chain? A biobased economy also needs a reliable biomass supply chain without short-term price fluctuations. Although Table 1 suggests that there seems to be room for biobased bulk products, the following questions still arise. Will we need highly regulated and Soviet-type "collective farm" models to ensure the mass supply of agro-commodities, although Table 1 suggests that there seems to be room for biobased bulk products? Will we need more regulation instead of deregulation in an already overregulated agriculture? Will we need to increase government support payments and agricultural subsidies, which are already in the hundreds of billions of US dollars per year in OECD countries? What about the efforts that have been initiated to ensure biodiversity if monoculture or "green concrete" agriculture will have to prevail? Are we not trading an oil problem for a water problem?

About 95 million barrels of oil are used in one day worldwide. Between 5–7% are used for chemistry; the rest goes up in smoke. In fact there would be an oil glut for chemistry if we had the necessary installation for renewable energy generation and efficiency programmes (it is cheaper to save energy than to buy it after all) in place and realised! This gives an entirely different perspective on where to use biobased raw materials and where to continue to use petrochemicals. Thus, Table 2 has also considered this scenario, that the investments into existing renewable energy sources are realised.

Biofuels. There are 900 million vehicles running today, and there will be 1.5 billion vehicles running in 2030. With these perspectives and the problem of global warming, liquid biofuels have gained a lot of attention. Even otherwise ecologically indifferent administrations use biofuels to give themselves a

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Table 2. Biobased raw materials such as sugars, oils, and fats and proteins are generally “overfunctionalised” for biorefineries, if compared with oil-based feedstocks, and there seems to be simply not enough for food, fuels, plastics, and chemicals; here are the proposed priorities and applications of renewable and non-renewable resources

	Oil	biotechnology	renewable energy
energy	REPLACE	NICHE only	TOP PRIORITY: wind, solar thermal, PV, etc.
chemicals	REPLACE by biomass and biotechnology	PRIORITY	–
polymers and (short life) materials (long life)	REPLACE PRIORITY	OPPORTUNITY NICHE	–
various industrial applications	–	OPPORTUNITY	–
food and feed	–	TOP PRIORITY	–
dietary supplements	–	–	–
health care products	COMPLEMENT with biotechnology	PRIORITY to reduce waste	–

green touch without considering the socio-economic costs and consequences for agriculture and forestry. To make things worse, projections on cropland requirements, green house gas (GHG) savings, production costs, and water requirements for the different biomaterials vary considerably as different standards are used. The water demand for biofuels is especially alarming.¹⁴ However, the problems do not stop there as there are four obstacles to a biotechnological large-scale liquid biofuel production.

- (1) the limited arable land and water resources.
- (2) the low yield of photosynthesis (plants 1%; algae 4%).
- (3) the recalcitrance of lignocellulosic material to hydrolysis.
- (4) the low energy density in the biomass.
- (5) the uneven distribution of the biomass.

Although promising pretreatment methods like using ionic liquids such as 1-allyl-3-methylimidazolium chloride have been described,¹⁵ biological conversion of lignocellulosic material remains less attractive than nonbiological methods, such as the Fischer–Tropsch (FT) process which was developed in the 1920s and 1930s in Germany to produce liquid fuels from coal via the coal to liquid (CTL) process.^{16–18} Today this Fischer–Tropsch process can be applied for biomass to liquid (BTL). The rule of thumb states that it takes about 1 ton of biomass to produce one barrel of liquid fuel, but the problems of the low energy density in the biomass and its diluted presence remain. Transport alone is destroying the advantage of a large part of the CO₂ sequestered.

Algae. Algae grow an order of magnitude faster than terrestrial plants. When grown phototrophically they have the potential to sequester CO₂ from smokestacks of power plants and produce compounds such as unsaturated fatty acids and carotenoids or to be used as dried biomass. Sapphire Energy, San Diego, CA, U.S.A. apparently have already supplied algae-based jet fuel for the Continental Airlines and Japan Airlines for test flights.¹⁹ However, the large-scale mass cultivation of algae using sunlight is far from being solved, and the calculations are sobering. Algae using CO₂ as a carbon source are a

theoretically ideal solution but are a long way from being cost competitive²⁰ in practice. However, enterprises with excessively high CO₂ emissions, such as coal-powered power stations, may look at the economics in a different way because of CO₂ emission trading. The German power company RWE opened a pilot plant in November 2008 to test the use of CO₂ sequestration by growing algae on CO₂ from the power plant exhaust gases as the only carbon source.²¹

Methane. The situation is more favorable for biogas from various wastes (municipal, agriculture) in combination with a cogeneration plant (combined heat and power). The yield of the energy recovery can reach 90%. Since 1991, numerous methane plants with varying outputs have gone on stream. In 2006 Bioenergy Co., Ltd., commissioned a methane-generation plant with a planned power generation capacity of 24000 kW·h/day using waste from the food industry in the Tokyo metropolitan area.²² The technology has matured to such a degree that the necessary amount of raw waste material for the production of biogas is becoming scarce. “Naturemade Star” for example is a biogas electricity production programme in Switzerland struggling with supply problems and biomass waste limitations.

In conclusion, biofuels are not a solution for individual mass transportation and money spent on environmental education of motorists, and the broad public has a better return than investing in biotech fuels! There may be only one application for which liquid biofuel is requested and this is in jet fuels. The energy dilemma of the world will not be solved by first-, second-, nor third-generation liquid biofuels, which only drain limited financial resources for other more meaningful projects. For interested readers I recommend the book of David J. C. MacKay for further reading on the renewable energy options.²³

Chemicals. Manufacturing remains a driving force of the European economy, accounting for about 20% of all jobs. The €1.2 billion “Factories of the Future” EU programme supports the development of new technologies contributing to greener production.²⁴ The European chemical industry is a key economic

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Table 3. Roadmap requires an integral view which considers the future development of several aspects ranging from technological to political issues; Here is a selection

- How fast can combustion processes be replaced by geothermal, solar, wind, or other sources?
- acceptance of plant GMOs (e.g., Europe)
- policies (ICAP,⁶³ EU sustainable sourcing, eco score cards...)
- arable land, climate changes, demographic
- transportation, communication, health care⁶⁴
- supply chain and price volatility of agro commodities
- future need (clean H₂O, new antibiotics, CO₂ sinks...)
- development in synthetic biology, H₂ storage, fourth generation nuclear plants...

sector⁵ as its share of the global sales is more than 30%. An interesting detail is that Europe is clearly the leading global producer of enzymes with a 75% market share. Despite these facts, the chemical industry has to make some far-reaching and important decisions.

The world remains focussed on cheap oil. Although less than 7% of the oil is used for chemical purposes, practically all chemical feed stocks and basic chemicals are produced from oil. The rest is being burned! Thus, the sooner we are able to replace oil as energy carrier by alternatives (e.g., solar, wind, hydroelectric, geothermal) the more will be left for uses as feedstock for chemistry. Considering the availability of different forms of fossil materials (oil: ~40 years, natural gas: ~65 years, coal: >200 years, plus tar sand and other resources) one can conclude that the nonrenewable feedstock for chemistry alone are almost unlimited, but not as fuels. Moreover, as used products can be recycled, the feedstocks are recycled as well. Table 3 summarises aspects and burning issues of society which need to be considered when discussing a roadmap for the development and application of biotechnology.

The chemical industry has installed globally a very cost-efficient, complex, and integrated manufacturing system. It is obvious that a switch to renewable feedstock would ideally use the same integrated manufacturing system. Thus, the decision on whether to use oil-based and/or biobased feed-stocks and for which product needs a strategic and long-term analysis. Biotechnology has the technology to replace petroleum-based chemicals with for example succinic acid,²⁵ from which 2-pyrrolidone, dimethyl succinate, maleic anhydride and other chemicals can be derived. There are already over 25 bulk chemicals and products (>10'000 tons per year) where biotechnology is used for their manufacture.²⁶

The simplicity of some proposed chemical transformations of lignocellulosic biomass to bulk chemicals contrasts with the complexity of biological processes.²⁷ For example, the reaction of lignocellulosic biomass, as well as from purified cellulose, glucose, and fructose with *N,N*-dimethylacetamide (DMA) containing lithium chloride enables the direct synthesis of the renewable platform chemical 5-hydroxymethylfurfural (HMF) in one step. With time, synthetic biology and pathway engineering will also contribute more to the renewable chemical platform. For example the pathway engineering of *Escherichia coli* allows the production of structurally tailored fatty acids, fatty alcohols, and waxes directly from plant materials such as

hemicellulose,²⁸ which are used predominantly in soaps, detergents, cosmetic additives, and flavouring compounds.

The use of atmospheric CO₂ as a raw material and starting material for organic chemical synthesis has been basically neglected, although CO₂ is an attractive, renewable carbon building block and an environmentally friendly chemical reagent. Capturing the green house gas CO₂ and fixing it through chemical or biological means seems to be a perfect procedure, as it taps into an abundant resource which not only comes cheaply but is also privileged by carbon emission trade schemes. In 2009, the U.S. EPA ruled CO₂ and five other gases as hazardous, and companies drawing CO₂ out of the atmosphere can expect a tax premium. However, there is a major obstacle. Although CO₂ causes problems due to its increasing concentrations in the atmosphere (presently at 391 ppm), it is far too dilute (a rare gas in the air with a concentration of less than 0.04%) to allow for an economic CO₂ capture. But as D. J. C. Kay writes,²³ “*Capturing carbon from thin air may turn out to be our last line of defense.*” Although thermodynamically inert, there are chemical processes for carbon dioxide sequestration, such as the conversion of CO₂ into methanol with silanes over *N*-heterocyclic carbene catalysts,²⁹ sunlight-driven catalytic transformation processes to methanol,³⁰ or the electrocatalytic CO₂ conversion to oxalate with a copper complex.³¹ The catalytic reduction of CO₂ with hydrosilane would proceed exothermically and could facilitate utilization of CO₂. Nature has evolved using CO₂ as the carbon source *par excellence*. It seems obvious that we should have a deeper look into nature’s CO₂ toolbox. A biotechnological approach might be more promising since it has evolved to cope with the low-energy level and inertia of CO₂. S. M. Glueck et al. (2010) give an overview on the biological fixation of CO₂ and show that it is feasible that industrial enzymatic fixation of CO₂ can be used for the production of low-molecular weight organic compounds, which can serve as building blocks and starting materials.³²

Polymers and Materials. When talking about biopolymers, one typically thinks first about “bioplastics”, which are ideally derived from compostable polymer products based on “natural” monomers such as polylactic acid (PLA), polyhydroxyalkanoates (PHA), starch and the like, or from polyisoprene latex from the tree *Hevea brasiliensis* or from dandelion mutants. Although the very first artificial Thermoplast “celluloid” was invented in the 1860s, the global production of emerging biobased-plastics is still very low. Production reached 0.36 million tons at the end of 2007, which is only about 0.3% of the worldwide production of plastic but with a global growth rate of 38% (48% in Europe). About 40% of these polymers are for short-lived applications, where uncontrolled disposal of the oil-based plastic is a problem. In 1997, a huge plastic debris accumulation approximately the size of Texas, called the “pacific garbage patch”, was detected floating in the Pacific

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Table 4. Examples of biopolymers and their proposed main applications

spiders, insect and mussel proteins: medical devices, artificial tissues, high performance materials, etc.
PLA, PHA, starch, cellulose polymers: nondurable plastics, medical devices and wound dressing, consumer appliances.
collagen, gelatin: food, artificial tissues and bones, drugs, drug formulation.
hyaluronic acid: osteoarthritis, drug carrier coating, cosmetics.
xanthan: food, enhanced oil recovery
PLA = polylacticAcid, PHA = polyhydroxyalkanoates

ocean.³³ This shows that we need a responsible use of polymers. The total maximum technical substitution potential of biobased polymers for replacing their petrochemical counterparts is estimated at 270 million tons or 90% of the polymers consumed in 2007 worldwide. However, the global bioplastic capacity is expected to increase from only 360000 tons in 2007 to 2.3 million tons by 2013.³⁴ Major players in bulk biopolymers are Metabolix, Dow Chemicals, Novamont, Cereplast, Teijin, Natureworks, Hisun, Tianan, Plantic, Innovia, Procter & Gamble, Kaneka, and Arkema. The most important biobased-plastics or bioplastics are starch plastics (0.15 million tons) and PLA (0.15 million tons).³⁵ One can choose between four biotechnologically based methods to produce biobased plastics.

- (1) from natural polymers such polyester, polyisoprenoids, polysaccharides, proteins
- (2) from GMO crops
- (3) from monomers produced by fermentation which are polymerised chemically or enzymatically
- (4) biopolymers directly harvested after microbial fermentation

However, oil remains a good starting material for selected, durable, plastic products which store CO₂ over a long product lifetime in long-living goods, and can be recycled at the end of their product life cycle.

Many other novel biopolymers (Table 4 gives a selection of interesting biogenic biopolymers) some with highly unusual properties that can be found in spiders (*Arachnida*), insects (*Insecta*), molluscs (*Mollusca*) and other sources. These new products will need a cost-efficient heterologous expression in microbial hosts and downstream processing. Some examples of new products are the protein called byssal threads, that allow mussels to stay firmly attached on rocks even in pounding waves or spider proteins that we know from spider webs. In both cases the biopolymer's extraordinary properties lead to speculative discussions about their applications ranging from human skin replacement to applications in tires. Different biopolymers are also used in skin care products. Shiseido, the oldest cosmetics company in the world, was the first company to use the carbohydrate polymer hyaluronic acid in skin care products. Hyaluronic acid and collagen are examples of biopolymers, which can be sourced from animals (collagen from waste of slaughtered animals, hyaluronic acid from rooster combs). There are, however, safety concerns (such as BSE or bovine spongi-

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Table 5. Miscellaneous novel application of biotechnology products and enzymes for various applications

cross-linking of leather (transglutaminase)
rust prevention and removal (siderophores)
biofilm prevention (furanones)
products for skin care and protein stabilisation (ectoins and other extremophiles)
biosurfactants for medical and industrial (rhamnolipid, mannosetriol)
plant protection (iturin)
pesticide decontamination (phosphatases)

form encephalitis), product variance, or both that make a switch from animal-derived materials to biotechnology production by fermentation (microbial, yeast) or in whole plants necessary. In the case of collagen, there is a further option of sourcing collagen from marine invertebrates such as jellyfish (*Aurelia aurita*).³⁶

The importance of this aspect is also underlined by the fact that regenerative medicine using adherent primary cells or stem cells need functionalised (by biocatalysis?) carrier polymers such as collagen, which are safe and not animal derived to exclude infection of patients. Wherever we turn in the area of polymers, we see that this is an area where biotechnology can bring exceptional benefits and sustainable value propositions to society.

Various Industrial Applications. Biological products can be used in many different industrial applications, which are summarized in Table 5. Hydrophobins are proteins found on the outer surfaces of the fruiting bodies of fungi. They keep the fungi dry by ensuring that water droplets are able to runoff. The gene of *Aspergillus nidulans* was cloned, and hydrophobin is now produced on an industrial scale with *Escherichia coli*. Potential applications are manifold, but one patented invention relates to hydrophobins suitable for stabilising two-phase liquid systems.³⁷

Bacteria prefer to live in the biofilm state which leads to “fouling” effects in industrial installations or medical devices and implants. Microbial biofilm formation is an issue in many different domains such as marine surfaces (e.g. ship hulls), industrial equipment (e.g. heat exchanger), medical devices (e.g. tubes), and the food and water supply industry. Prevention or removal of the corroding and obstructing biofilms by nontoxic “green” antibiofilm and antifouling substances for biofilm control are needed.³⁸ The annual costs of “fouling” by biofilm formation in cardiovascular and orthopedic implants is more than 3 billion U.S. dollars in the United States alone.³⁹ Therefore, biofilm control is of increasing importance. Only a few compounds have been discovered, for example furanone from the marine algae *Delisea pulchra* or 5-hydroxyindole or 7-hydroxyindole which have these antifouling properties. Research in this area is focused on problems in health, personal,

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(38) Labbate, M.; Queck, S. Y.; Koh, K. S.; Scott, A.; Giskov, M.; Kjelleberg, S. M. *J. Bacteriol.* **2004**, *186* (3), 692.

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and dental care. Tooth decay by dental biofilms and oral cavity hygiene can be reduced using hydrolytic enzymes (mutanases)⁴⁰ or biological anti-adhesive compounds⁴¹. A remarkable property of biosurfactants (including amphiphilic biosurfactants) is the inhibitory activity against bacterial and fungal colonization of surfaces, including those of biomedical interest.⁴² Industrial applications will certainly be able to profit from R&D in the health care biofilm area. Biodegradability, reduced toxicity, availability from cheap raw materials, biocompatibility, efficacy at extreme temperatures, pH, and salinity make biological surfactants attractive for many applications.

Other products have been applied experimentally in microbially enhanced oil recovery to increase the yields of oil and gas fields, as over 50% of the energy carrier remains in the ground with traditional recovery processes. The highly viscous oligosaccharide xanthan, produced by fermentation of *Xanthomonas campestris*, can be applied to squeeze out the remaining oil from an “exhausted” oil field. Unfortunately, the product has proven to be too expensive for this application, but it has found widespread use in the food industry as a thickener. *Pseudomonas aeruginosa* is an opportunistic human pathogen producing rhamnolipid biosurfactants which were detected about 60 years ago. The small company, Jeneil Biosurfactant Co., Milwaukee (Wisconsin), produces the product called Zonix for bioremediation applications.⁴³ Due to its biodegradability and tensioactivity, the product is also a possible candidate for enhanced oil recovery.

Bacteria have developed methods for the uptake of iron using biological complexation compounds to retrieve Fe³⁺ from the environment. The siderophore desferrioxin E which is able to resorb iron(III) oxides from metal surfaces, can act as a biological rust removal agent.⁴⁴

Food and Dietary Supplements. The kitchen and the beverage and the food industries have used biotechnology since they began, and the role of biotechnology in these sectors keeps playing an increasing role in human nutrition. Biotechnology is already delivering different enzymes and services on an industrial scale to the food industry. Production of glucose from starch (hydrolytic enzymes), production of high fructose syrup (isomerase) and vitamin C (oxidoreductase), conversion of lactose to galactose and glucose (hydrolase), or cheese production (protease) are examples of large-scale applications.

We mentioned earlier the start of a convergence of pharma, food, and personal and skin care products and that the boundaries are becoming blurred. “Functional food”, “nutraceuticals”, and “cosmeceuticals” are examples of products appearing on the market with a real or claimed health benefit. One reason is that target and screening approaches, similar to those in the pharmaceutical industry, are now used for the

development of nutra- and cosmeceuticals using specific receptor technology for screening and development.⁴⁵

A dietary supplement, also known as a food or nutritional supplement, is a preparation intended to provide nutrients, such as vitamins, minerals, fiber, fatty acids, or amino acids, that are missing or are not consumed in sufficient quantity in a person’s diet. These products do not typically have any nutritional value and are sold, for example in the form of tablets or soft gel capsules. In contrast, a functional food or beverage looks similar to its food counterpart except that it provides additional health benefits beyond energy and essential nutrients. Nutraceutical ingredients are bioactive additives or chemical substances which are beneficial in maintaining health, preventing or treating diseases, or improving performance (e.g., omega-3 polyunsaturated fatty acids (PUFA), phytosterols, probiotics, certain carotenoids). Nutraceuticals differ from supplements in that they supply missing nutrients. Nutraceuticals are key components of functional foods, beverages, or dietary supplements. A significant number of these health ingredients added to food and beverages to make them “functional” can be derived by biotechnology. Lonza and other leading suppliers are increasingly moving to biotechnology for their production. Examples of fermentation-based health ingredients are PUFAs derived from algal or microbial fermentation, astaxanthin, carotenoids, antioxidants such as resveratrol, flavonoids, D-ribose, and probiotics for the prophylaxis of intestinal infections. Functional foods can also be fortified with nutraceuticals. The global nutraceutical market exceeds 140 billion U.S. dollars and is growing at 10% per year).

Flavours and fragrances are other biotechnology-relevant markets with a volume of 20 billion U.S. dollars. Over 10% of the supply is derived from bioprocesses, with more than 100 commercial aroma chemicals derived via biotechnology.⁴⁶ Switzerland holds a 25% share of this market and uses large amounts of precious ingredients from plants. However, especially with fragrances some of the exquisite, plant derived natural raw materials are becoming scarce. In order to relieve the pressure on the natural sources, companies are increasingly turning to novel biotechnological sources of raw material ingredients. The provision of raw material by biotransformation or *de novo* biosynthesis (fermentation, plant cell culture, GMO plants) as alternatives to plant extraction is an important opportunity for biotechnology. Consider also that Chinese folk medicines, Ajurvedic plant medicines, South American shaman phytomedicines are now being screened for novel bioactive (plant) compounds. The global botanical and plant derived drug market is expected to grow from 19.5 billion U.S. dollars (2008) to 32 billion U.S. dollars (2013) at a CAGR of 11%. But as in the case of the anticancer secondary metabolite taxol (paclitaxel, Bristol Myers Squibb) from the bark of the Pacific yew (*Taxus brevifolia*), alternative fermentative and biotransformation routes will be needed because of limited natural plant raw materials.

Healthcare Products. Pharmaceuticals. Healthcare products in general have a high negative environmental impact. The ecologic footprint of pharmaceuticals relative to sales generated is higher than in many other industries. This is particularly true

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Table 6. Fine chemicals markets by end use

pharmaceutical intermediates	61
agrochemical intermediates	9
flavour and fragrances	11
dyes	5
others	9

for the production of large-molecule biopharmaceuticals (typically injectable therapeutic proteins and monoclonal antibodies). The reasons for this heavy impact are the need for clean rooms, extensive heating, ventilation, and air conditioning (HVAC), huge amounts of purified water, water for injection or buffer, disposable plastic ware, energy, etc. This is also true for small-molecule pharmaceuticals and building blocks, dominated by chemical synthesis. Although the growth of the global pharma market for prescription drugs has slowed to 4.8% and reached 773 billion U.S. dollars in 2008,⁴⁷ it is expected to grow and reach 1100 billion U.S. dollars in 2010. Moreover, the pharmaceutical market is expected to experience a huge change from a long-term vertically integrated blockbuster model to a much more flexible and patient-adapted and individualised model.

Table 6 shows that the pharmaceutical market has been the largest market for fine chemicals for a long time with over 50% of all fine chemicals being used for small-molecule drugs and their intermediates.⁴⁸

The next-generation small-molecule pharmaceuticals will also be of much greater complexity requiring a variety of biotechnological manufacturing options for organic chemistry.⁴⁹ Jean-Baptiste Molière (1622–1673) wrote in his comedy “Le malade imaginaire”: “Doctors pour drugs of which they know little, to cure diseases of which they know less, into patients of whom they know nothing”. We will experience more personalised treatment. Consequently, there will be an urgent need for sustainable and ecologically responsible production of complex small molecules, peptides, nucleotides, and oligosaccharides. Unfortunately, the actual ecological footprint is particularly high in the production of exactly these products. The waste generated per kilogram of product in the chemical industry is several orders of magnitude higher than for today’s small-molecule pharmaceuticals and fine chemical building blocks.⁵⁰

Fortunately, scientific discoveries open the way for “greener” and biological manufacturing solutions. Until recently N-glycosylation for example was considered to be restricted to eukaryotes. Work by M. Aebi in Zürich on the discovery of a protein N-glycosylation machinery in *Campylobacter jejunii* showed that microbial glycosylation does indeed exist and is very versatile. The fact that the corresponding genes could be successfully transferred into *Escherichia coli* have raised exciting opportunities.⁵¹

On the other hand, the world also needs affordable drugs pertaining to health problems in the developing world. Here biotechnology is also able to provide promising solutions, as

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Table 7. Wish list in biotransformation; the main activity of the organisations and industries⁶⁴ publishing identified produce small-molecule pharmaceuticals, pharma intermediates, and fine chemicals for the Life Science industries

Oxidoreductases
robust P450 monooxygenases, Bayer–Villiger monooxygenases, dehydrogenases, enoate reductases, haloperoxidases, peroxidases, oxygenases
Lyases
asymmetric C–C bond lyases, C–N (aminolyases), and C–O (hydratases) bond formation
Transferases
mainly transaminases are needed; glucuronyl transferases and to some extent sulfotransferases

demonstrated by the example of the production of the anti-malaria drug precursor, artemisinic acid, in a pathway engineered yeast by the group of J. Keasling. This example shows what concerted action can achieve.⁵² The aerial parts of the tree *Artemisia annua* have been used by traditional Asiatic medicine to treat fever and malaria. The three partners, J. Keasling, Amyris Biotechnology, and the One World Health, successfully realised the switch to a more sustainable biotechnological fermentation process. The project, which can serve as an example for other similar problems, was financed by the Bill and Melissa Gates foundation with 42.5 million U.S. dollars, and the process is now used by pharma giant Sanofi-Aventis.

It is in the pharmaceutical area where biotechnology shows its greatest weakness. Chemical technology prevails with a well-filled toolbox, although biotechnology could provide more sustainable alternatives if they were developed. Besides the technological needs and quality constraints, it is the time frame given by drug development which makes the application of biotechnology for small-molecule pharmaceuticals and intermediates particularly demanding due to an inadequate toolbox.⁵³ Skimming through published data where priorities have been formulated by the industry for the use of biocatalysis, one can come-up with the following wish list^{54–58} shown in Table 7.

However, the actual focus shown in Table 8 is in stark contrast to the wish list.

Food and Feed, Dietary Supplements. The boundaries between pharmaceuticals and food products or personal and skin care products is becoming blurred. The production of bioactive products as additives for food or cosmetics is an attractive field for biotechnology, which goes well beyond the traditional

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Table 8. Overview of the enzyme classes presented as oral or poster presentations at the last four Biotrans symposia

enzyme class	2009 (%)	2007 (%) ^a	2005 (%)	2003 (%)
1 oxidoreductases	32	34	24	28
2 transferases	10	8	6	3
3 hydrolases	46	41	55	58
4 lyases	9	12	12	10
5 isomerases	3	2	2	1
6 ligases	0	1	0	0

^a An example of the % calculation: 34% of all presentations in 2007 dealt with oxidoreductases. The sum does not add up to 100% because some of the presented papers did not deal with biotransformations.

original purpose of food and cosmetic products. Terms like “nutraceuticals” or “cosmeceuticals” have been coined to indicate that they contain products that are claimed to have drug-like benefits. “Nutricosmetics” is another new word describing products taken orally to improve health and beauty. As we will see later, biotechnology plays a double role for these products and may allow the biotechnologically derived products to be labelled “natural”.

Personal Care Products. Biotechnology looks into a bright future in the beauty area with an annual market volume of well above 250 billion U.S. dollars and growth rates of 10% and more.⁵⁹ However, as in pharmaceuticals, personal care products are also becoming ever more sophisticated, and prestige, top-of-the-line products may include expensive recombinant proteins and other molecules with biological activity. No wonder that large cosmetic companies spend large amounts in R&D. For example L’Oréal spends 1 billion U.S. dollars per year in R&D (corresponding to 3.5% of sales in 2009) with more than 3300 R&D employees in 18 R&D centers., including some 1800 Ph.D. scientists. Average R&D spending of the cosmetic industry was 2.3% of sales. Some fermentation products such as Q10 or hyaluronic acid, produced mainly by the Japanese companies Kaneka and Shiseido, have become an established ingredient in creams. There are “cosmeceuticals” on the market already which actually even possess FDA approval, for example Renova from Johnson & Johnson or Avage developed by Allergan. There are numerous peptide candidates for dental care, dermatology, and skin care, and more than 25 different peptides are routinely found in skin care products in the United States alone by companies such as Atrium, Grant Industries, Lipotec, Pentapharm, Procyte, Sederma.⁶⁰

Table 9. In vivo manufacturing options offered by biotechnology and their applicability to the production of small and large molecules in different industrial sectors^a

	fuels	chemicals	polymers and materials	industrial applications	food and feed	health care
bacterial fermentation	+++	+++	+++	+++	+++	+++
yeast fermentation	+++	+++	++	+	+++	+++
fungal fermentation	+	++	+	+++	++	+++
algae fermentation	+++	+	+	+	+++	+
protozoa culture						+
plant cell culture		+	+	+	+	++
gm plants		+++	+++	++	++	++
insect cell culture						+
mammalian cell cul						+++
transgenic animals						+

^a +++ means great potential as a production method, + represents a very limited potential, and no mark means not of importance.

Conclusions

We have used the first half of about 1 trillion barrels of oil in the last 50 years. Most of it went up in smoke, and only very little was used for chemistry. To return to sustainable societies we need to carry out what Clark and Deswarte call “dematerialisation” and “transmaterialisation”.⁶¹ Biotechnology and renewable raw materials are not *per se* the better solutions, but they provide numerous manufacturing options (Table 9), which wait to be used or developed for sustainable manufacturing options. Although we need a new and balanced portfolio of carbon for the future (and we need it fast), biotechnology is far behind schedule for building a sustainable alternative to chemistry. The reasons are the following:

- (a) A commercial and reliable biobased supply chain is not in place.
- (b) Gigantic chemical capacities are now being built up in Asia, resulting in a technological lock-in.
- (c) The biotechnology toolbox is empty when compared with the 200-year-old chemical toolbox.

The synthetic efficiency of biological systems can theoretically provide reactions that are both selective (chemo-, regio-, diastereo-, and enantioselectivity) and economical in terms of atom count, resulting in an effective use of raw materials. However, we need a growth strategy with a focus for investments. We also have to be aware that pushing a growth strategy and maximizing profits at the same time do not work. We, as a community, have to define what benefit we are going to offer to which segment, and we have to set priorities. The author recommends a focus on developing biotechnological tools for higher-value products for the life sciences such as enantiomerically pure and complex molecules, biopolymers, pharmaceutical intermediates and drugs. These are not low-hanging fruits, but they are chosen for the following reasons. First, the life sciences in particular need sustainable synthetic and manufacturing methods replacing wasteful chemical synthesis, due to the ever-increasing complexity of products and molecules. Second, the life sciences are more likely to have the needed financial (non-government) backing. Third, the life sciences, and pharma in particular, remain a leading force in innovation. These results will benefit other non-life science areas as well. Fourth, much lower volumes are needed (even for bulk chemicals) because of the intrinsic and innate complexity of biobased molecules produced, as opposed to biofuels, where complex and mostly

chiral molecules from biomass are degraded to very simple molecules which are then burned. Thus, investments in projects to produce large amounts of high-density energy with biological systems are problematic. Production of liquid biofuels by biotechnological conversion and fermentation of biomass is highly questionable irrespective of the raw material used. Liquid biofuels may well be a waste of research money, as George Monbiot wrote in *The Guardian* “*Apart from used (potato) chip fat, there is no such thing as a sustainable biofuel*”.⁶²

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