



## Biotechnology as an Enabler in Bioeconomy IBC Finland

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# *Biotechnology for the production of chemicals, intermediates & pharmaceutical ingredients*

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# How do Finland and Switzerland compare?

## Switzerland

Population: 8 million

GDP growth ~2%

Unemployment ~4%

Sectors I 1 %; II 28 % III 71 %

Km<sup>2</sup>: 41'200

Natural resources: ~0

Arable land: 15'320 km<sup>2</sup>



## Finland

Population: 5,5 million

GDP growth 0.8%

Unemployment ~8%

Sectors I 4 %; II 23 % III 73 %

Km<sup>2</sup>: 338'000

Natural resources: minerals, timber, fish....

Arable land: 22'180 km<sup>2</sup>

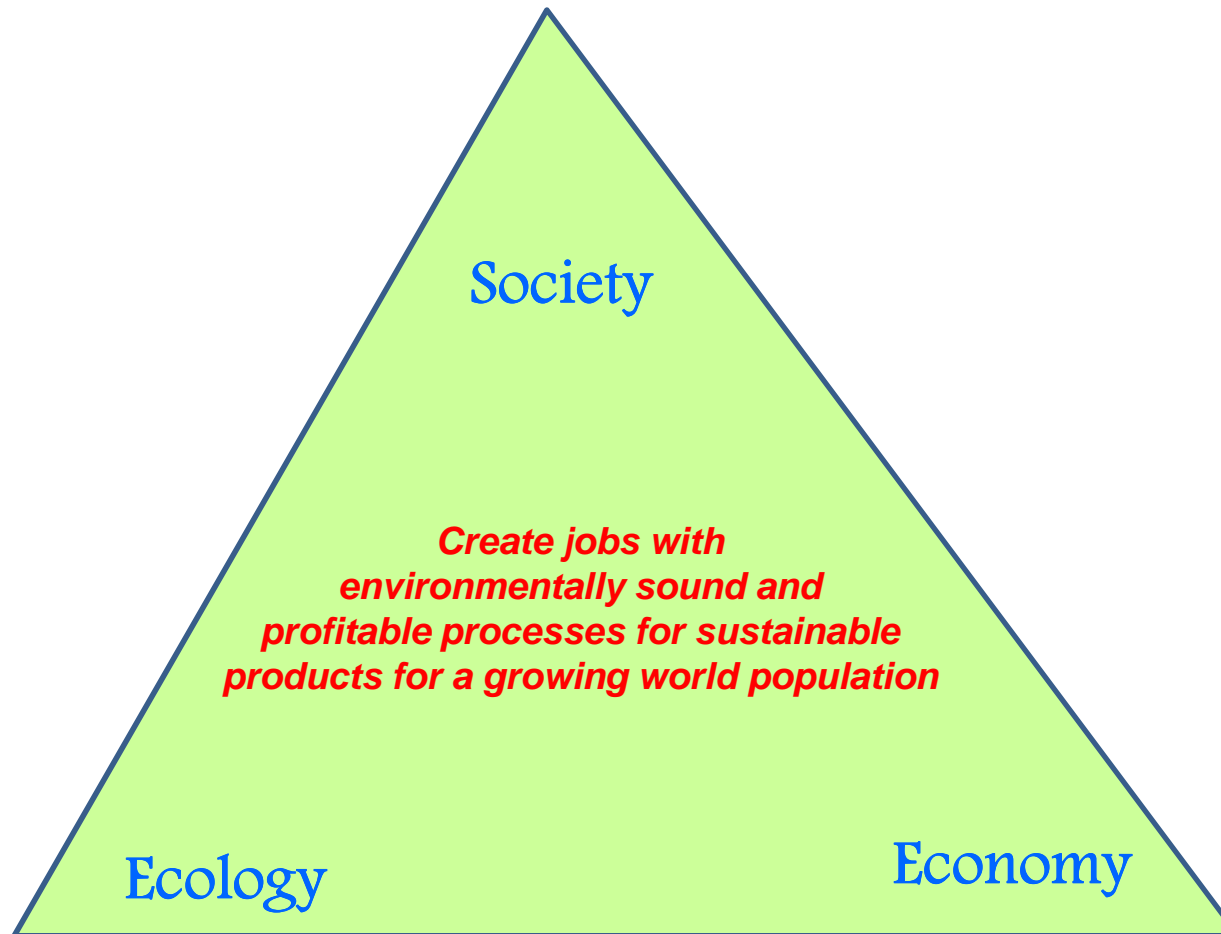


***“Only a country whose entire economy is based on science can reach and maintain first place in the economic battle between nations.”***

# To make sure we talk about the same thing...

Market	Color Code	Type of Products	Market Size	Companies
Pharma Biotechnology	<b>Red Biotechnology</b>	Monoclonal antibodies, other therapeutic proteins, vaccines, insulins, pDNA	> 170 Billion US\$ CAGR 12%	> 6'000
Industrial Biotechnology	<b>White Biotechnology</b>	Small molecule pharma & fine chemicals, flavour & fragrance, bulk chemicals a.o.	> 50 Billion US\$ CAGR	> 4'000
Agro Biotechnology	<b>Green Biotechnology</b>	Transgenic or genetically modified (GM) seeds and plants	15 Billion US\$ CAGR 11%	100
Environmental Biotechnology	<b>Grey Biotechnology</b>	Environmental biotechnology, services & solution for bioremediation and waste treatment	< 1 Billion US\$ CAGR 5-10%	< 50
Marine Biotechnology	<b>Blue Biotechnology</b>	Products and lead substances from the marine environment	2 Billion US\$ CAGR	< 50
<b>Total Biotechnology Market</b>	<b>n.a.</b>	All compounds produced by means of biotechnologies	> 260 Billion US\$ CAGR 11%	10'600

To make sure we talk about the same thing...



# The Swiss biotech history in a nutshell...

- **The beginning**

Organic chemistry for the dyes used by the textile industry

- **Strong R&D**

1930s separate pharma R&D

- **Early focus on high value products**

1950s First pharma, agro, food by fermentation & biotransformations

- **Early outsourcing of production (fermentation)**

1950s Manufacturing in Germany, Austria, Italy...often in fermentation plants financed by the Marshall plan with US production know-how from antibiotics

- **In-house manufacturing facilities**

1960s Some fermentation manufacturing in CH

- **Red biotech cannibalizes white biotech**

1990s white biotech is a marginal GDP provider. Red biotechnology is the star.

- **Actual threats**

Strong Swiss Franc, high labour costs...

# Examples of Swiss companies

## Active in pharmaceuticals, fine & specialty chemicals, flavor & fragrance, agchem...

- AVA BIOCHEM [www.ava-biochem.com](http://www.ava-biochem.com) 5-Hydroxymethylfurfural (HMF, CAS 67-47-0) from renewable biomass ←
- BACHEM [www.bache.com](http://www.bache.com) Peptide synthesis pioneer
- CLARIANT [www.clariant.com](http://www.clariant.com) Specialty chemical company largest € biofuel plant (through acquisition) ←
- CURADEN [www.curaden.ch](http://www.curaden.ch) "Enzycal" lactoseperoxidase based toothpaste
- DEBIOPHARM Group [www.debiopharm.com](http://www.debiopharm.com) Prescription drugs targeting unmet medical needs
- DOTTIKON ES [www.dottikon.com](http://www.dottikon.com) Fine chemical sand hazardous reactions specialist
- EMS Group [www.ems-group.com](http://www.ems-group.com) High performance polymers and specialty chemicals
- EVOLVA [www.evolva.com](http://www.evolva.com) Biosynthetic technologies for food, beverage and consumer health sectors ←
- FIRMENICH [www.firmenich.com](http://www.firmenich.com) Perfume & flavor business ←
- GEISTLICH [www.geistlich.com](http://www.geistlich.com) Biomaterials, dietary supplements, adhesives ←
- GIVAUDAN [www.givaudan.com](http://www.givaudan.com) Flavour & fragrances ←
- HELSINN ADVANCED SYTHESIS [www.helsinn.com](http://www.helsinn.com) Pharmaceutical products
- INOFEA [www.inofea.com](http://www.inofea.com) immobilization for the functionalization of molecules and oligomers ←
- LONZA [www.lonza.com](http://www.lonza.com) CMO & life science products from stem cells to wood preservation ←
- MIBELLE [www.mibellebiochemistry.com](http://www.mibellebiochemistry.com) Actives for the cosmetic industry ←
- NOVARTIS [www.novartis.com](http://www.novartis.com) Second\* largest global pharmaceutical company ←
- ROCHE [www.roche.com](http://www.roche.com) Third\* largest global pharmaceutical company ←
- ROHNERCHEM [www.rohnerchem.ch](http://www.rohnerchem.ch) Fine chemicals and APIs (cooperation with EVOCATAL) ←
- SIEGFRIED [www.siegfried.com](http://www.siegfried.com) Drug product and chemical manufacturing
- SOCIÉTÉ SUISSE DES EXPLOSIFS [www.explosif.ch](http://www.explosif.ch) Explosifs and fine chemicals (VALSYNTHESE)
- SWISSAUSTRAL enzymes and products from extremophiles ←
- SYNGENTA [www.syngenta.com](http://www.syngenta.com) Crop protection, seeds, seed care ←
- ...

\* Largest global pharma company 2014 was JOHNSON & JOHNSON (71.4 bio us\$)

CMO Contract Manufacturing Organisation

CDO Contract Development Organisation

## Global sales of the top ten Swiss chemical-pharmaceutical companies in billion Swiss Francs (2012)

Pharmaceuticals.....	71
Fine chemicals & Specialities.....	46.4
Agrochemicals.....	11.7
Diagnostics.....	11.5
Vitamins, Flavor & Fragrance.....	8.5
Total.....	145

Source: scienceindustries

- **Growth engine!**
- **Chemical-pharma-biotech sector >40% of all exports from Switzerland (81 B in 2013)**
- **Chemical-pharmaceutical exports grow regularly at a much higher rate than other exports**
- **Pharma remains the driving force in the Swiss economy with high growth rates**
- **The pharmaceutical market is the most important driver for innovation in biotechnology**
- **Red biotechnology (not white biotechnology) is the main driver**

**Strength:** High-tech platform (bio)technologies available. High quality standard.

**Weakness:** Biotech solutions for small molecule APIs, fine chemicals, flavor & fragrance are neglected

**Opportunity:** Use track record outside of red biotechnology.

**Threat:** Confusing messages and lobbying to investors and stakeholders

# The production of pharmaceuticals & fine chemicals is a dirty business...

## Waste generated per kg of product produced in the chemical industry...

Bulk chemicals.....	> 0,1 kg
Fine Chemicals.....	5 to 50 kg
Pharmaceuticals.....	25 to 100 kg
Oligonucleotides.....	>1000 kg
Peptides.....	>1000 kg
Oligosaccharides.....	>1000 kg

## Example for a peptide...

Raw material	Bill of material needed for producing 20 kg peptides
Amino acids	0.4 tons
TCTU	0.3 tons
Piperidine	6.5 tons
NMP	100 tons
DCM	80 tons
Acetonitrile	35 tons
USP water	300 tons

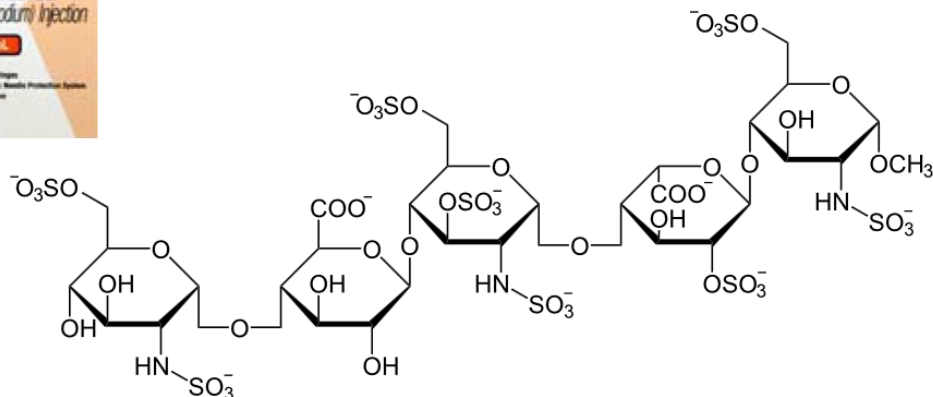
H.-P. Meyer, O. Werbitzky Oleg. *How Green Can the Industry Become with Biotechnology?* In: "Biocatalysis for Green Chemistry and Chemical Processes", 1st Edition edited by A. Tao and R. Kazlauskas, (2011) John Wiley & Sons Ltd. ISBN 978-1-118-02830-8 p. 23-43.

H.-P. Meyer *Sustainability and Biotechnology Organic Process Research & Development* (2011) **15**:180-188.

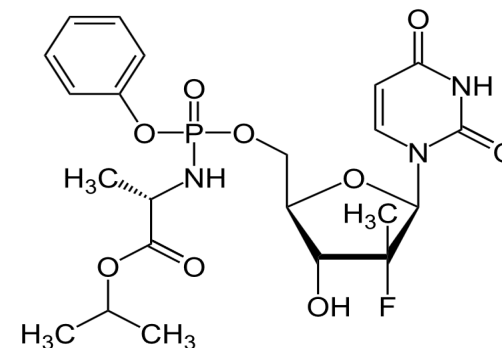
J.M. Woodley, *New opportunities for biocatalysis: making pharmaceutical processes greener*. TIBTEC, (2008), **26**: 321-327].



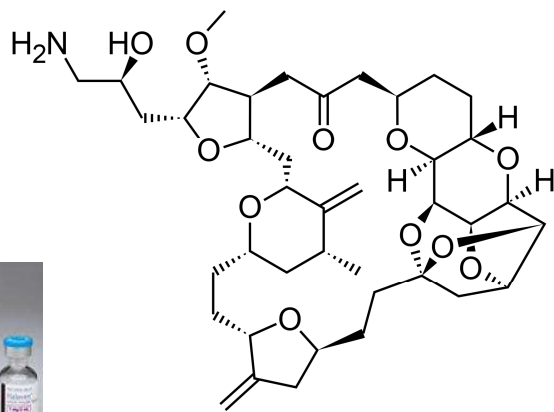
# Why are these (pharma) products produced chemically?



Fondaparinux (Arixtra™)



Sofosbuvir (Sovaldi™)



Eribulin (Halaven™)

**We have basically three options for the “contained” biotechnology production**

- Chemical synthesis: using chemo- & biocatalysis
- Recombinant production in a pro- or eukaryote of the end product or intermediates
- Suspension culture with the natural producer (e.g. plant cells)

T.A. Aicher et al. *Total synthesis of halichondrin B and norhalichondrin B*. J Am Chem Soc (1992) **114**(8):3162-3164

Y. Hirata, D. Uemura *Halichondrins - antitumor polyether macrolides from a marine sponge* Pure and Applied Chemistry (1986) **58**(5):701-710

H.-P. Meyer, O. Werbitzky, G. A. Signorell *Bridging the Gap Between Chemistry and Biotechnology – Large Molecules with Potential, How Could Biotechnology Complement Chemistry*. Current Organic Chemistry (2014) **18**:944-959

# Other bio-based products of interest

## Biotechnology for “green chemistry”. There is plenty of work: 80% are small molecule APIs

- High selectivity increasingly required in all domains
- More sustainable production
- Keep or make drugs orally available
- Modifications: Thioester cyclisation, PEGylation, glycosylation or polysialylation, peptide/protein tag, lipidization...
- Molecular diversity corresponding to patient diversity
- Need of novel anti-infectives
- ...

# Other bio-based products of interest

## Examples of biopolymers of potential interest mainly for the medtech and pharma market in Switzerland...

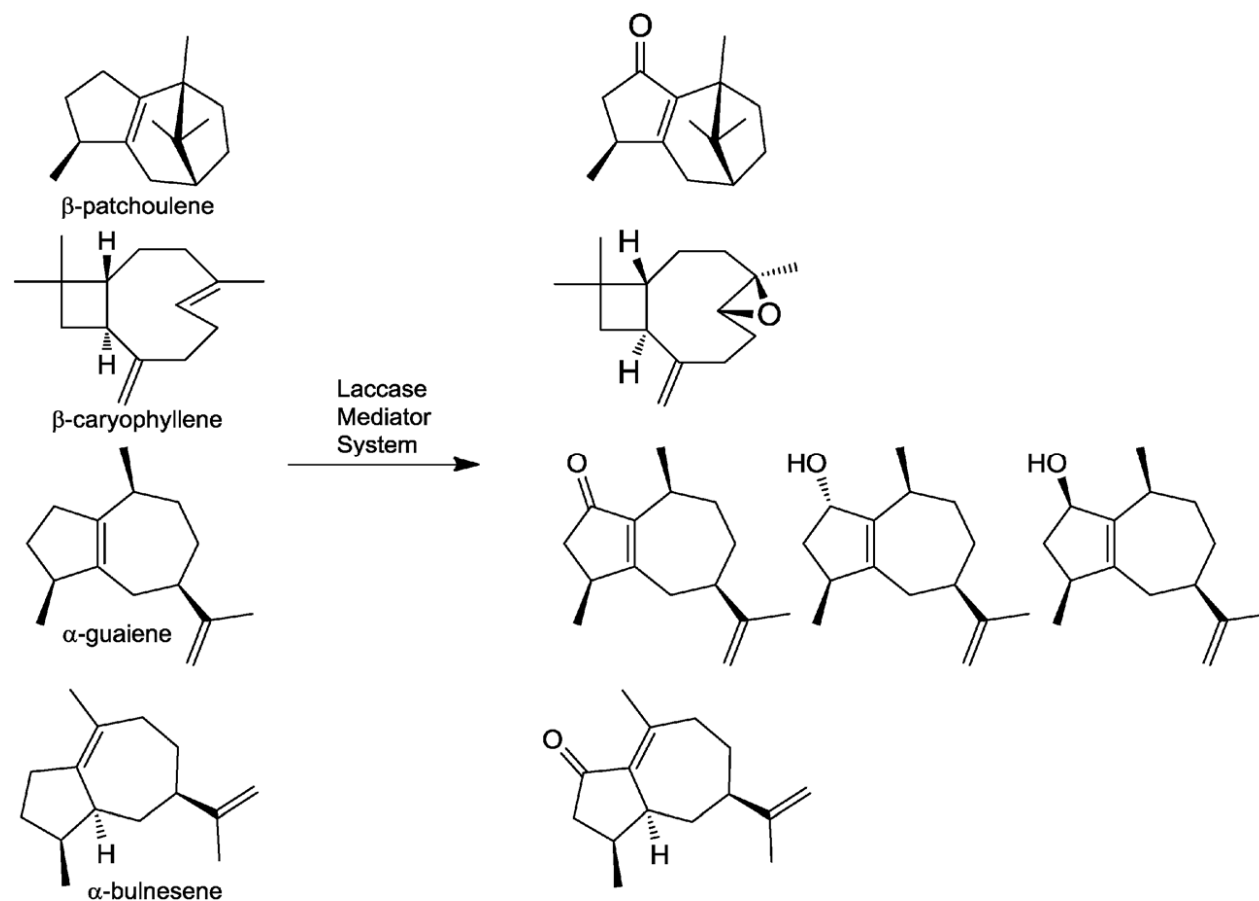
- Insect silk
- Spider silk
- Collagen
- Gelatin
- Fibrin
- Mussel proteins
- PHA
- PLA
- Hyaluronic acid
- ...

«non animal  
derived»

# New bio-based products of interest

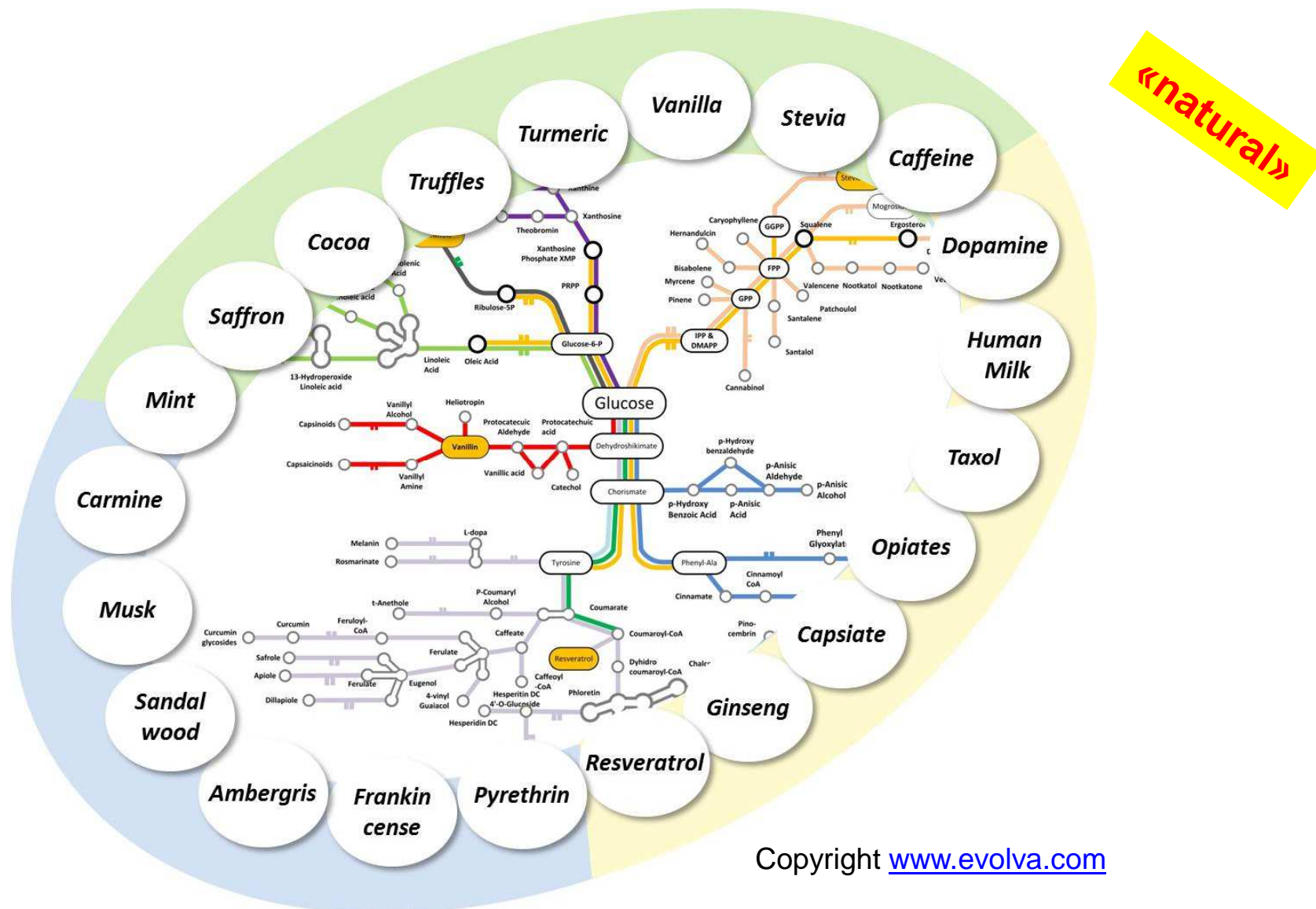
## Laccase-mediator system for octahydroazulene derivatives with pleasant floral and woody odor.

GIVAUDAN, Switzerland



# New bio-based products of interest

Supply issues. The use of yeast as production platform for functional food ingredients.  
**EVOLVA, Switzerland.**



Copyright [www.evolva.com](http://www.evolva.com)

# New bio-based products of interest

**Supply issues. Academic and industrial partners in Switzerland are working on pathway grafting to produce e.g. terpenes. FIRMENICH, Switzerland**

## Historically:

F&F industry was historically based on extraction of Plant and Animal secondary metabolites.



Z- $\alpha$ -santalol  
(santalwood)



Nootkatone  
(grapefruit)



Patchoulol  
(patchouli)



L-menthol  
(peppermint)



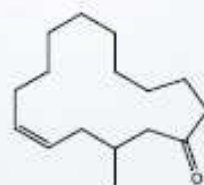
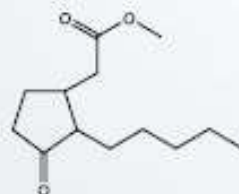
Ambrox  
(synthesis from  
sclareol - clary sage)

«natural»

## More recently:

Organic synthesis was developed for the production of F&F ingredients.

- Hedione<sup>®</sup>
- Cetalox<sup>®</sup>
- Muscenone<sup>®</sup>



## Today:

Concerns about the environmental impact, green technologies, sustainability.

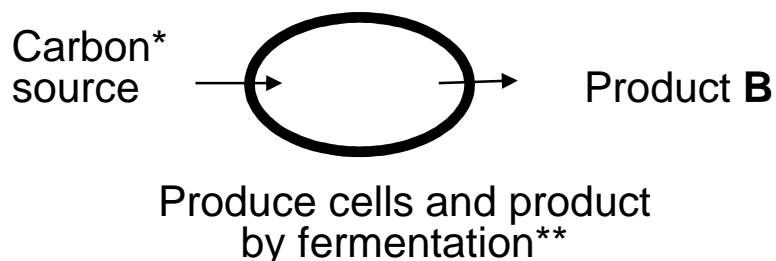
Pressure on resources.

Increasing demands for affordable F&F materials.

Copyright [www.firmenich.com](http://www.firmenich.com)

## Two preferred basic processes with variations such as cell free, immobilized...

### Biosynthesis *de novo* synthesis of product B



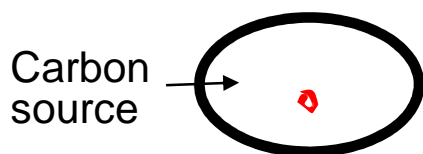
### Products of advanced genetic engineering

- Opiates
- (S)-Reticuline alkaloid
- Artemisinin
- Echinomycin
- Hydrocortisone
- Polyketides
- Shikimic acid, aminoshikimic acid
- Thymidine

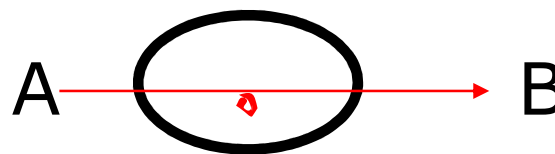
*De novo* biosynthesis will change the way we produce chemicals

Biocatalysis complementary (niche) technology in chemical synthesis”for molecules incompatible with life

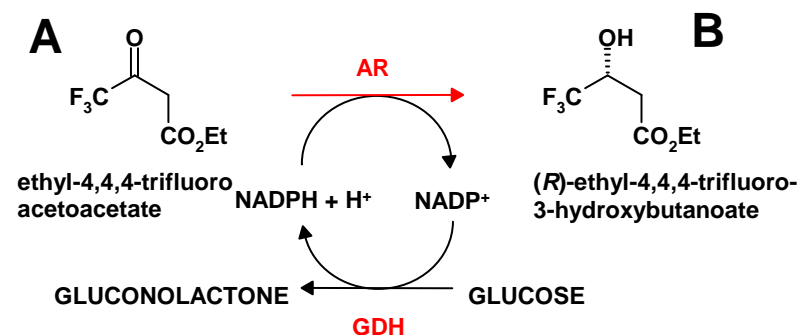
### Biotransformation & Biocatalysis



Produce biocatalytically active cells by fermentation



Carry out biotransformation



\* Not discussed Light & CO<sub>2</sub>

\*\* Not discusse plant based production

# Do not forget consumer education

## Education of consumers to reduce excess packaging or drive cars with much higher mileage.

Use of plastic in Europe

Packaging.....	40%
Construction & Building.....	19%
Vehicle construction.....	8%
Elektronik & Electric.....	5%
Agriculture.....	4%
Other.....	22%

Science, Plastics Europe



# Do not forget consumer education

*“...although governments are keenly promoting biofuels, most private investment in industrial biotech is going into other, less prominent areas”.*

(The Economist, 2010)

- **25 – 100 l/100 km**, \*547 g – 2'200 kg CO<sub>2</sub>/km, 736 kW, acc 2,5 s, V<sub>max</sub>= 407 km/h\*
- 2012: **6,21 l/100 km**; 151 CO<sub>2</sub>/km\*\* 175 g CO<sub>2</sub>/km, 105 kW, acc ~10 s, V<sub>max</sub>~190 km/h\*, 1'500 kg
- **<3,5 l/100 km**; <80 g/CO<sub>2</sub> km, 35 kW, Vmax~135 km/h\*\*\*

\* Bugatti Veyron

\*\* Average car sold in 2008 and 2012 in CH

\*\*\* Immediately feasible with existing technology



## Economy & Market

- Biotechnology is vital for the economic future of Switzerland
- Focus on complex manufacturing problems & high hanging fruits
- High value products not commodities & biofuels. Relentless cost-management
- Growing emphasis on customized products, eco-labels...

## Raw materials & value chain

- No «Soviet» style agriculture for bio-based economy in Switzerland
- Non-Swiss partners active upstream of the value chain
- Focus on contained production not “pharming”
- Access to raw material. Cost/price pressure.

## Technology & Innovation

- Be innovative outside the lab (novel business models & cooperations... e.g. SIBC)
- Improve turning know-how into products

## Communication

- Cultural difficulties biology & organic chemistry
- Industry's short-term objectives vs academia's long-term perspective
- Include all stakeholders and «customers» in the innovation process
- KBBE – lobbying and confusing investors

# SIBC Swiss Industrial Biocatalysis Consortium

Cooperations are vital!

## Creating a shared consortium strain database

incl. physical exchange of proprietary strains

→ legal framework for SIBC strain databank incl. sample MTA

- **Knowhow exchange**
- **Win-win situations** among members
- **Networking**
- **Support** to academia authorities
- **Offer knowhow and network** to associations and
- **Opinion leaders** in industrial biotechnology

**Do not worry about  
technology...  
but worry about the rest....**



Kiitos!  
Danke!  
Merci!  
Grazie  
Thank you!

**Back-up slides**

# Biocatalysis will remain a niche technology

Table 3.1.-1 Overview of the enzyme classes presented as oral or poster presentations at the last six “Biotrans Symposia”. In order to identify the research focus in biocatalysis, all abstracts submitted to the “International Symposium on Biocatalysis and Biotransformations” for the years 2003 to 2013 have been analysed and the relative numbers indicated in %.

Enzyme class	2013	2011	2009	2007	2005	2003
Oxidoreductas	43	39	32	34	24	28
Transferases	13	13	10	8	6	3
Hydrolases	25	35	46	41	55	58
Lyases	9	13	9	12	12	10
Isomerases	10	3	3	2	2	1
Ligases	1	1	0	1	1	0

**Biocatalysis will become an important niche technology complementing chemical synthesis. But the long term preferred production option will be *de novo* biosynthesis by fermentation!**

A. Wells and H.-P. Meyer *Biocatalysis as a Strategic Green Technology for the Chemical Industry*. ChemCatChem (2014) **6**:918-920

H.-P. Meyer, E. Eichhorn, S. Hanlon, S. Lütz, M. Schürmann, R. Wohlgemuth, R. Coppolecchia *The use of enzymes in organic synthesis and the life sciences: perspectives from the Swiss Industrial Biocatalysis Consortium* Catalysis, Science & Technology (2012) DOI : 10.1039/c2cy20350b