



**SusChem**

**INDUSTRIAL BIOTECHNOLOGY**  
**IAP Update 2010**

## **INDUSTRIAL BIOTECHNOLOGY UPDATE 2010**

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## Industrial Biotechnology IAP Update

### 1. Introduction

The core group for the Industrial Biotech pillar of SusChem was established in 2005 for the development of the SRA and IAP. The core group is relying on two existing groups: the scientific committee of ESAB (EFB section on Applied Biocatalysis) and the IB Council of EuropaBio, therefore gathering some of the key scientists and industries in the Industrial Biotechnology field. Since the publication of the IAP, the core group has provided advice on a regular basis to the European Commission and the ERA-IB (European Research Area Network on Industrial Biotechnology, coordinated by Dr. Louis Vertegaal, NWO, The Netherlands).

### Implementation in FP7

Within FP7, research on Industrial Biotechnology is essentially supported in the theme KBBE, activity 2.3 'Life sciences, biotechnology and biochemistry for sustainable non-food products and processes'. The two other key activities in the KBBE theme are focusing on the sustainable production and management of biological resources (agriculture, forestry, and fishery) and on food quality and safety. Within the non-food area, Industrial Biotechnology related calls can be found in the priorities on:

- Industrial biotechnology: novel high added-value bio-products and bioprocesses
- Biorefinery
- Environmental biotechnology
- Emerging trends in biotechnology (synthetic biology, nanobiotech)

Funding for IB in the KBBE area represents roughly 1/6<sup>th</sup> of the KBBE budget (about 320 million euro in FP7 on a 2 billion euro budget).

So far projects funding in FP7 with a focus on SusChem priorities for industrial biotechnology is estimated at 176 million euro (79Mi€ in KBBE, 40Mi€ in energy, and 57Mi€ in Biorefinery joint call). The figures below represent the number of project topics published in the call for proposal and their indicative funding in million euro considering the size of the projects (e.g. 6 topics/ 20 Mi€). Only the numbers indicated as 'funded' correspond to actual project funding, other numbers are estimates.

THEME	1st call - 2007	2nd call - 2008	3rd call - 2009	Total Mi€
Industrial Biotech	Funded 6 / 20 Mi€	6 / 23 Mi€	4 / 12 Mi€	55
Biorefinery (KBBE)	-	3 / 13 Mi€	2 / 2 Mi€	15
Biofuels (KBBE)	Funded 1 / 3 Mi€	1 / 6 Mi€	-	9
Biofuels (Energy)	4 / 20 Mi€	1 / 5 Mi€	3 / 15 Mi€	40
Biorefinery (joint call)	-	-	5 / 57Mi€	57
<b>TOTAL</b>	<b>43 Mi€</b>	<b>47 Mi€</b>	<b>86 Mi€</b>	<b>176</b>

The priorities proposed on Industrial Biotechnology by SusChem IAP are covering rather broad issues/ challenges for technology development, which cannot be solved with the funding of one FP7 project but

rather a multiplicity of efforts and research funding going in this direction (e.g. the call topic on lipid enzymes addresses only one class of enzymes, similar work is necessary for other classes of enzymes).

Therefore it is essential for SusChem in cooperation with ERA-IB and the KBBE-net (Knowledge based bioeconomy network – MS representative network for the coordination of KBBE research activities in Europe) to continue their effort for coherence and alignment of European and national research programmes.

Participation from industry in the seventh framework programme has increased neatly compared with FP6 with at least one company taking part in each of the projects funded under the KBBE 1<sup>st</sup> and 2<sup>nd</sup> call. However industrial participation remains insufficient and scattered. Flexibility, rapidity and reactivity of funding are key aspects to facilitate industry participation, especially for SMEs.

### **Evolution of the broader framework around IB research**

The priorities as defined in the Strategic Research Agenda (2006) and the Implementation Action Plan (2007) are still valid and essential in the current context for the development of industrial biotechnology and the biobased economy.

Some specific issues and topics (industry needs) may have risen since the publication of the SRA but they are in line with the priorities formulated in 2006. Other priorities have moved forward and are closer to being resolved. For instance the development of enzymes for the break-down of lignocellulosic biomass is now closer to market. Further efforts are needed in this respect in the scale-up and cost reduction of the technology, the development of enzyme cocktails optimized for specific biomass but also in the development of the next step namely the development robust fermentation organisms metabolising both C5 and C6 sugars.

The broader framework around industrial biotech has been evolving in the past year with new priorities such as the implementation of REACH regulation or GHS impact on innovation in the chemical sector. European research and innovation policy also has to be looked at in a broader context, namely what is being developed at national level in the EU27 and in other competing regions of the world. A number of initiatives of been developed at MS level from support to basic and applied research to development of public private partnership such as B-Basic (The Netherlands), CLIB2021 (Germany) or public funding of pilot projects such as Bio-Hub (France).

## **2. Recommendations for IAP update and future FP7 calls**

### **2.1. Topic 1: Development of biocatalytic glycosylation technologies for small molecules**

Glycosylation is an important source of structural diversity of many small molecules such as alkaloids, steroids, flavonoids, antibiotics, etc. It is well documented that these glycosides can have very different effects compared to the non-glycosylated aglycon, as glycosylation can strongly influence their biological activity, stability or physical characteristics. The glycosylation of molecules can significantly modify drug activity and pharmacokinetics, induce drug targeting, improve stability, solubility and bio-availability of vitamins, modulate toxicity of antibiotics towards micro-organisms, influence taste and aroma, etc.

Whereas conventional chemical technologies can glycosylate small molecules, these are generally inefficient and generate a lot of chemical waste and other molecules can simply not be glycosylated with conventional technologies. There is a clear need for inexpensive and efficient technologies to glycosylate small molecules such as vitamins, drugs, flavours, cosmetics, alkaloids, steroids, etc..

This can be performed through the use of glycosyltransferases that do not require expensive nucleotide-activated donor sugars. As the exploitation of these enzymes is hampered by their limited activity spectrum, more research is needed to broaden the scope of the enzymatic glycosylation reactions that can be performed.

### **2.1.1. R&D objectives**

The engineering of such glycosyltransferases by means of directed evolution and/or rational design should allow the creation of a range of efficient biocatalysts. A particularly promising approach consists in mixing in silico identification of key amino acid residues in the catalytic site of a glycosyltransferase for the synthesis of a given glycoconjugate, with the massive mutagenesis of these sites followed by a screening of the catalytic efficiency of the corresponding variants. This will open up the way towards the efficient production of a many novel glycosylated compounds with a wide range of applications

### **2.1.2. Relation to SusChem IAP**

This topic relates to the IAP topic 'optimisation of biocatalysts through screening, directed evolution and rational design' and 'Integration of biocatalysts into industrial processes' under biobased economy.

### **2.1.3. FP7 Uptake of this topic**

There has been some coverage in FP7 on new and improved biocatalysts but so far focusing on other classes of enzymes such as lipases or cellulases. Glycosyltransferases are an interesting area of application as it can impact diverse industrial sectors.

### **2.1.4. Recommendation**

This topic should be addressed through a small to medium-scale collaborative project.

## **2.2. Topic 2: Sustainable Synthesis of Stereo-isomers**

Efficient synthesis of stereo-isomers is of great relevance for the Chemistry sector. Target molecules in important application areas such as pharmaceuticals and agrochemicals are becoming more selective and complex, resulting in higher selectivities and lower dosages. As a result of more selective active ingredients, side effects but also the environmental burden of such compounds is reduced.

Frequently, selective active ingredients are single stereo-isomers. The synthesis of these stereo-isomers is complex relative to 'flat' organic chemistry and enzymes frequently provide a solution. However, thus far, stereo-specific syntheses using enzymes are typically enzymatic resolutions, resulting in the desired stereoisomer and an (at least) equal amount of waste. These so-called 50% yield processes are inefficient from an economical and ecological point of view.

### **2.2.1. R&D objectives**

Stereo-specific enzymes that enable the controlled synthesis of only one of the possible stereo-isomers (100% yield) are not as abundantly available as hydrolytic enzymes that are used for 50% routes. Particularly oxido-reductases and lyases are enzymes that could be used in 100% routes, and appropriate enzymes that can be used should be developed. This programme is aimed at the discovery, improvement and application in industrial conversion at kg scale of enzymes in 100% yield routes towards stereo-isomers.

### **2.2.2. Relation to SusChem IAP**

This topic relates to the IAP topics 'novel biocatalysts for specific applications' and 'developing methods and technologies for biocatalysts improvement' under biobased economy.

### **2.2.3. FP7 Uptake of this topic**

There has been some coverage in FP7 on new and improved biocatalysts but so far focusing on other classes of enzymes or functions.

#### **2.2.4. Recommendation**

This topic should be addressed through a large to medium-scale collaborative project.

### **2.3. Topic 3: Downstream processing**

The interest in the implementation of biotechnological processes for the manufacturing of bulk-chemicals requires innovative strategies in product purification. This call addresses research into generic purification strategies for the continuous or discontinuous biotechnological production of bulk chemicals, manufactured either by biotransformation or fermentation, with a specific focus on the integration and development of selective membrane-, extraction-, adsorption, and crystallization technologies. Other technologies might also be addressed as long as their suitability for bulk-processes is either subject of the project or can be convincingly demonstrated.

#### **2.3.1. R&D objectives**

Research topics can include (but are not limited to): The integration of separation technologies into (semi-)continuous biotechnological production processes, the development of novel materials for selective product removal, and strategies to deal with surfactants in the production of hydrophobic compounds.

#### **2.3.2. Relation to SusChem IAP**

This topic relates to the IAP priority 'Innovative downstream processing' under biobased economy.

#### **2.3.3. FP7 Uptake of this topic**

There has been no coverage of this topic as a specific call. However it may have been considered in individual project in the 'sustainable biorefinery' joint call, as these projects integrate a part on industrial demonstration and may have to develop specific downstream processing for this purpose.

#### **2.3.4. Recommendation**

Type of project: medium-scale collaborative project

### **2.4. Topic 4: Metabolite Production**

The combination of genomics techniques with biochemical and evolutionary engineering (selection of mutants equipped with new, better and more enzymes) must be exploited. Gaps in the knowledge of the regulatory systems in cells must be filled. This also holds for product export from cells and metabolic compartmentalisation in eukaryotic cell factories. Crucial in this respect is that the information about cellular function should be obtained for conditions typical of industrial processes which involve stress, slow growth, fluctuations in nutrient concentrations, mixed substrate utilisation, product formation under "zero growth conditions", kinetics of membrane transport at the extreme conditions in industrial bioreactors and product inhibition in relation to product recovery.

#### **2.4.1. R&D objectives**

Advanced metabolic engineering research for the efficient production of metabolites, biomaterials, bulk and speciality chemicals including enantiopure molecules is also required. Research on the design and invention of new pathways and/or networks with a focus on "new to nature" products, and on the extension of the range of industrial microbial production hosts will also be important.

Modelling of microbial metabolism has to be developed, directed towards both steady state and dynamic models, including the development of methodological tools, particularly for flux analysis and measurement of intracellular metabolites. Special emphasis has to be given to relevant operating conditions with the aim to create new and robust production systems for industrially important metabolites. The empha

sis on a reaction sequence or pathway toward metabolite production should build upon multi-step biocatalysis knowledge as a bottom-up approach complementing the top-down approach of systems biology.

#### **2.4.2. Relation to SusChem IAP**

This relates to the IAP topic 'novel and improved pathways and products through genetic and metabolic engineering'.

#### **2.4.3. FP7 Uptake of this topic**

This topic has been partly covered under the calls KBBE-2007-3-3-01 on synthetic biology and KBBE-2007-3-2-05- on Improved microbes through metabolic engineering and modelling. This topic however focuses on the integration of both methodologies and on the development of industrially important metabolites.

#### **2.4.4. Recommendation**

This topic should be addressed through a small collaborative project.

### **2.5. Topic 6: Metabolic engineering for the production of tailor-made biosurfactants for industrial applications**

Surfactants are performance molecules that intervene in nearly every product and every aspect of human life and are produced on a very large scale. The large majority of these surfactants are currently produced by chemical means from petroleum. The use of these compounds may lead to significant environmental problems due to their ecotoxicity, bio-accumulation and poor biodegradability. Yet, microorganisms can produce biosurfactants that offer the benefits of good performance, fast biodegradation, low ecotoxicity and the production from renewable resources by fermentation. Unfortunately, nature offers us only a limited range of biosurfactants that can be industrially produced and their application is currently limited to small specialty markets.

#### **2.5.1. R&D objectives**

Broadening the spectrum of biosurfactants can be performed by metabolic engineering of the biosurfactant production strains. This will lead to an expansion of the range of useful biosurfactants beyond the natural variety and will create new and tailor-made biosurfactants with new and better properties. The targets for tailor made modifications of glycolipid biosurfactants are the lipid tail and the carbohydrate head, in this way altering the hydrophilic-lipophilic balance. Thus, a vast range of new-to-nature and tailor-made biosurfactants can be obtained, extending the biosynthetic capabilities of the production strains beyond their natural synthesis power. An additional target will be to increase the specific production rate, in view to reach a significant decrease of the production cost of such biosurfactants. This will permit the penetration of biosurfactants into the mainstream surfactant market.

#### **2.5.2. Relation to SusChem IAP**

This relates to the IAP topic 'novel and improved pathways and products through genetic and metabolic engineering'.

#### **2.5.3. FP7 Uptake of this topic**

Biosurfactants are a large industrial market in Europe, representing a large array of molecules, and for which biocatalysis as a strong potential to be used for replacing chemical synthesis. This sector could be used as example to test a number of techniques (metabolic engineering, enzymatic coupling or biocatalytic process design) which could then be applied to other sectors.

#### **2.5.4. Recommendation**

This topic should be addressed through a small collaborative project.

### **3. Going beyond IB technological development**

#### **3.1. Evaluating the potential and feasibility to replace hazardous chemicals by biotech processes or products**

As REACH is moving forward in the registration of hazardous substances, the question of potential substitutes will be posed. The aim of this project would be to identify classes of substances for which biotech alternatives could be developed in the short to medium term and therefore pave the way for strategic research funding in this area.

This topic could be supported through a Coordination and support action.

#### **3.2. Study to support the development of policies encouraging reconversion towards biobased economy**

The objective to analyse and propose policies facilitating and stimulating the reconversion towards a biobased economy:

- assessment of infrastructure/equipment and expertise (skills, disciplines, etc.) needed in a future EU biobased economy
- how to accelerate research into primary and co-products applications and markets
- how to stimulate the development of joint supplier-customer application development platforms/projects with the aim share risks and cost
- assessment of policies and regulations that are bottlenecks or stimulate a transition towards a biobased economy
- research into consumer (public) acceptance of IB products and processes (including GMO and/or GMM content acceptance)

This topic could be supported through a Coordination and support action.

#### **3.3. Demonstration projects via public-private partnerships**

Industry sees a lot of unlocked potential in the combination of life sciences and other technologies. However, the inherent risks with these projects (new technologies, new products, and new kind of partnerships) are such that private parties on their own cannot today push this agenda forward.

- Europe needs a programme to accelerate the transformation of knowledge into commercial products (such as small scale demonstrators) and to integrate different production processes (such as small scale integrated biorefineries).
- Different stakeholders could be involved in such projects: Regional Development, Structural funds, Member States, the European Investment Bank, and of course individual companies. A consistent vision and a long term program would really add to the success of this initiative.

This needs to be addressed through a coordinated action beyond FP7 at European level involving European institutions and Member States.