European Commission

Maximising the impact of KET Biotechnology

Report of the EC Workshop

22 September 2015

Rapporteur:
Beatriz Gómez Sala

EN

Research and Innovation

EUROPEAN COMMISSION

Directorate-General for Research and Innovation
Directorate D — Key Enabling Technologies
Unit D.2 — Advanced Manufacturing Systems and Biotechnologies

Contact: José-Lorenzo Vallés

E-mail: *Jose-Lorenzo.Valles @ec.europa.eu*
RTD-PUBLICATIONS@ec.europa.eu

European Commission
B-1049 Brussels

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1. INTRODUCTION AND OBJECTIVES

The Workshop on "Maximising the impact of Key Enabling Technologies (KET) Biotechnology" was held in Brussels on 22 September 2015.

DG Research and Innovation (RTD) of the European Commission hosted the workshop, which brought together around 50 participants, most of them involved in ongoing projects, funded by the EU Framework Programmes for Research and Innovation, FP7 and H2020. The workshop also involved representatives of key stakeholders such as EuropaBio, SusChem and the European Federation of Biotechnology (EFB), of academia and industry and several European Commission services.

The main objective of the workshop was to contribute to maximise the impact of the European KET Biotechnology projects through fostering the creation of an Industrial Biotechnology community and exploring in particular the potential of clustering.

The specific objectives of the workshop were: (1) to convey the expectations of KET Biotechnology in Horizon 2020, which has evolved into being much more application-oriented speeding-up the time-to-market of new biotechnology applications and bio-based products, (2) to recognize the current needs of society in regards of the Industrial Biotechnology sector so that they can be fully taken into account in future work programmes, (3) to get a better understanding of the prospects for KET Biotechnology from the point of view and experience of industry and academia, and (4) to debate on the possible existence of barriers and how they could be removed to facilitate the further development of KET Biotechnology.

A total of 12 projects (five from FP7 "KBBE" programme and seven from Horizon 2020 "KET Biotechnology" programme) were presented during the workshop. Each project summarised its technological goals, industrial potential and level of overall progress made to date. The workshop allowed the exploration of opportunities for synergies and cooperation by giving participants a chance to network, to discover common interests and to share the challenges encountered throughout the development of their projects. All participants, including the stakeholder representatives, shared their views and concerns in order to maximise the impact of KET Biotechnology and to drive long-term sustainability leading to growth across a variety of economic sectors.

This report highlights the main success factors and benefits of projects working in the area of KET Biotechnology as well as the barriers that need to be overcome to meet the necessary technological, industrial and societal goals.

2. BACKGROUND

Biotechnology has been identified as one of the six Key Enabling Technologies (KET) that have the potential of strengthening the EU's industrial and innovation capacity while addressing societal challenges such as competitiveness, environmental sustainability and enhancement of quality of life.

The High Level Group on KETs (HLG-KETs) defines **Industrial Biotechnology** as "*the application of biotechnology for the industrial processing and production of chemicals, materials and fuels. It includes the practice of using microorganisms or components of microorganisms like enzymes to*

generate industrially useful products, substances and chemical building blocks with specific capabilities that conventional petrochemical processes cannot provide"[1].

In a recent document[2], the HLG-KETs provides advice for boosting the potential of the six KETs in Europe, including biotechnology. The experts recommend that European companies should be more ambitious and work on projects of a European dimension in strategic areas. They also recommend stimulating market demand for innovative products and services based on KETs as well as helping to tackle some of the societal challenges. Consequently, the HLG stresses the necessity of modernisation of EU policies and initiatives to respond to the needs of industry in order to capture the benefit of KETs for the whole European economy. Finally, the HLG proposes a set of concrete action to ensure that the growth potential of KETs is not hindered by the lack of a skilled workforce (see Box 1).

BOX 1: HLG-KET eight recommendations for full implementation of the European strategy for KETs

1. Boost European technology infrastructures to support industry
2. Strengthen KETs pilot lines and demonstration activities
3. Unleash significant investment into manufacturing through new EU tools
4. Escalate regional Smart Specialisation Strategies to a European level
5. Establish bonding between KETs and societal challenges for a sustainable and competitive Europe
6. Ensure European interests are met in trade and investments agreements
7. Fully exploit the dual-use potential of KETs
8. Investment in KETs-related skills to ensure Europe's innovation potential

In FP7 Framework Programme for Research and Technological Development (2007-2013), most biotechnology projects were embedded in the "Food, Agriculture and Fisheries, and Biotechnology" (KBBE) thematic area. In the current Framework Programme for Research and Innovation, Horizon 2020, KET Biotechnology is part of the Leadership in Enabling and Industrial Technologies (LEIT) pillar and it develops around three areas: (1) Cutting-edge biotechnologies as future innovation drivers; (2) Biotechnological-based industrial processes driving competitiveness and sustainability, and (3) Innovative and competitive platform technologies (more information is provided in section 5). Furthermore, KET Biotechnology projects are expected to develop generic technologies for building blocks, enabling true stepping stones towards solutions for a number of societal challenges (SC) such as better health (SC1), low-carbon energy generation (SC3) and resource- and energy-efficiency and industrial pollution reduction (SC5). Besides, under Horizon 2020 a new institutionalised Public-Private Partnership on Bio-based Industries (BBI) has been established[3] with the aim to overcome the "valley of death" on the way from research to the market.

[1] Working Group Report. *KET-Industrial Biotechnology*. June 2011. http://ec.europa.eu/DocsRoom/documents/11283

[2] High-Level Expert Group on Key Enabling Technologies. *KETs: Time to Act-Final Report.* June 2015. http://ec.europa.eu/growth/industry/key-enabling-technologies/european-strategy/high-level-group/index_en.htm

[3] http://www.bbi-europe.eu

3. WORKSHOP OVERVIEW

The workshop on "Maximising the impact of KET Biotechnology" was held in Brussels at the Albert Borschette Conference Centre of the European Commission. It was divided into six main sessions following a short introduction to kick off the workshop.

Firstly, Mrs Clara de la Torre (Director for Key Enabling Technologies) delivered a welcome address emphasising that the aim of the current framework programme, Horizon 2020, is to close the gap from lab to market. In this line, she mentioned the explicit interest of the Commissioner for Research, Science and Innovation, Mr Carlos Moedas, that funds spent on research have an impact on industry. She asked participants to share with the European Commission officials any legal framework problem encountered that could somehow hinder progress and in turn the expected impact. Following this, Mr José-Lorenzo Vallés (Head of Unit, Advanced Manufacturing Systems and Biotechnologies) presented a short overview of the sessions planned for the day and the objectives.

FP7 KBBE Biotechnology projects (session 1): Five biotechnology projects (IB2Market, Indox, Metacode, Synpol and TRANSBIO) funded by the FP7 KBBE made short presentations. These projects started between 2011 and 2013, thus they were, at least, halfway through their planned duration.

KET Biotechnology in Horizon 2020 (session 2): A presentation by José-Lorenzo Vallés summarised in particular the results of the 2014 and 2015 KET Biotechnology calls and introduced the relevant topics in the new Work Programme for 2016 and 2017.

Horizon 2020 projects in KET Biotechnology (session 3): Short presentations were made by the ongoing KET Biotechnology projects (MycoSynVac, EmPowerPutida, P4SB, ROBOX, CarbaZymes, DiViNe and NextBioPharmaDSP) funded under Horizon 2020. As these projects have just begun in April-May 2015 they mainly presented an outline, the first steps in the life of the project and the plans for a successful achievement of the objectives and exploitation of the industrially-relevant results.

KET Biotechnology in Europe - industrial and societal needs (session 4): The representatives of the key stakeholders EuropaBio, SusChem and EFB made presentations focused on the industrial and societal needs related to KET Biotechnology.

A vision of KET Biotechnology in 2030 (session 5): Two experts from industry and academia, respectively, summarised their vision of KET Biotechnology from now to 2030.

Panel debate - Maximising the impact of KET Biotechnology (session 6): The workshop closed with a panel discussion chaired by Mr Andrea Gentili (Deputy Head of Unit, Advanced Manufacturing Systems and Biotechnologies) about maximising the impact of KET Biotechnology. The panel was composed of representatives from the industry, the Bio-based Industries public-private partnership and a representative from the European Commission, DG GROW.

The last session was followed by a short presentation of Mr Waldemar Kütt (Head of Unit, Biobased products and processes) on the future opportunities within the Bio-based Industries (BBI) institutionalised Public-Private Partnership, introducing the Bio-based Industries Consortium (BIC) and the importance of clustering.

4. FP7 FOOD, AGRICULTURE AND FISHERIES, AND BIOTECHNOLOGY (KBBE) BIOTECHNOLOGY PROJECTS

Bringing innovative industrial biotechnology research to the market - IB2Market

The **IB2Market** project aims to enable the market introduction of new industrial biotechnology processes that have been recently developed to produce new to market molecules such as biosurfactants and speciality carbohydrates. To that end, the production processes are developed to meet end-user specifications and scaled-up. Concomitantly, valorisation plans are developed for each product based on techno-economic analysis, Life-Cycle Assessment (LCA) and market potential.

Since the start of the project, three different fucosylated oligosaccharides, sophorose, bola-sophorolipids and acidic sophorolipids, have been developed, their production processes evaluated and their potential assessed in several markets. Each step of process development is integrated in the innovation chain and feedback about the lessons learned is provided throughout the process. The production processes are adjusted accordingly.

Project starting year: 2013
Project reference: 613937
Coordinator: Bio Base Europe Pilot Plant VZW (Belgium)
Website: www.ib2market.eu

Optimized oxidoreductases for medium and large scale industrial biotransformations - Indox

The **Indox** project aims to provide relevant industrial case stories to demonstrate the efficacy of optimized biocatalysts on targeted reactions and to establish their scalability, sustainability and cost-efficiency versus that of chemical conversion processes.

The project deals with oxidative enzymes (oxidoreductases) with a strong potential for the chemical sector. The industrially relevant target reactions foreseen in this project are medium and large scale biotransformations, including i) intermediates for agrochemicals/APIs, ii) polymer precursors and functionalized polymers and iii) intermediates for dye-stuffs. The project flow comprises the recovery of selective oxidoreductase biocatalysts from fungal genomes and other sources, the improvement of their oxidative activity and stability by protein engineering and the optimization of reaction conditions and reactor configurations, followed by the evaluation of cost efficiency compared to chemical processing. A highly specialized consortium of SMEs, large companies and research/academic institutions supports this approach.

The expected impact from the **Indox** project relies mainly on the European chemical industry for manufacturing bulk chemicals and large volume specialty chemicals as illustrated by the above-mentioned target biotransformations selected in the work plan. Moreover, the joint development of new oxidoreductase biocatalysts will impact the European biotechnology sector and the developed biocatalytic processes themselves offer extensive advantages over traditional chemistry in terms of environmental impact.

Project starting year: 2013
Project reference: 613549
Coordinator: Agencia Estatal Consejo Superior de Investigaciones Científicas (Spain)
Website: www.indoxproject.eu

Code-engineered new-to-nature microbial cell factories for novel and safety enhanced bio-production - Metacode

The **Metacode** project is driven by both biotechnological applications and a deep scientific interest in understanding the workings of natural systems. In particular, if one understands the mechanisms of adaptation for novel chemical functionalities during the experimental evolution of *Escherichia coli* at the system level – it will be able to develop new biotechnologies from complex biological systems.

In this context, **Metacode** is a synthetic biology project aimed to bring new chemical functionalities by designing artificial and safe industrial microbial strains (i.e. synthetic microbial cell factories) for mass production of desired protein/peptide based products. Synthetic cells, which function as small programmable production units for almost any imaginable product, are not only a fundamental scientific challenge but also an alternative chemistry resource for the development of new technologies with beneficial societal impact. In addition, these types of platforms with engineered genetic code are necessary for transferring chemical reactions/functionalities and processes from the chemical synthetic laboratory into the biochemistry of living cells.

Metacode demonstrated these possibilities by recruiting organic synthetic reactions –metathesis– for the core biochemistry of the living cell to expand its genetic code. In this way, first and important steps have been taken towards the creation of living cells (i.e. mainly microbes) with artificial biodiversity, which certainly represent promising technologies for the future.

Project starting year: 2011
Project reference: 289572
Coordinator: Technische Universitaet Berlin (Germany)
Website: www.meta-code.eu/project-main

Biopolymers from syngas fermentation - Synpol

Synpol aims to produce biopolymers from syngas fermentation. It is a platform to convert complex wastes into bioplastics by transforming highly complex waste into simple molecules (CO, H_2 and CO_2). These simple molecules are converted into value-added products by using biological transformation processes, such as bacterial fermentations, instead of the conventional chemical catalytic processes.

At social level, **Synpol** will contribute both to facilitate the management of contaminant waste and to reduce the greenhouse effects of oil-based plastics. At technological level, the platform integrates all steps of the process from waste to polymers. The project starts with the production of syngas using microwave ovens at large scale. Metabolic engineering tools together with systems biology models are used to design bacterial chassis capable to efficiently transform syngas to polyhydroxyalkanoates and polymer building blocks. The development of new bioreactor devices has been fundamental to control the syngas fermentation process. New biobased polymers and polymer composites of commercial utility have been produced by chemical and biocatalytic approaches. An exhaustive life cycle assessment has been conducted in order to guarantee the recyclability of the polymers and the economic feasibility of the process. A pilot plant design will be available to scale up the process at industrial level.

Project starting year: 2012
Project reference: 311815
Coordinator: Agencia Estatal Consejo Superior de Investigaciones Científicas (Spain)
Website: www.synpol.org

BioTRANSformation of by-products from fruit and vegetable processing industry into valuable BIOproducts - TRANSBIO

The main goal of **TRANSBIO** is the implementation of an innovative cascading concept for the valorisation of sub-products from the fruit and vegetable processing industry, using environmentally friendly biotechnological and sustainable solutions.

The first results of the project involve the production of PHB by fermentation. Currently, the SME partner responsible for the results analyses the opportunities to patent the PHB producing strain. The production of succinic acid is another product resulting from this project and is achieved by yeast fermentation. The economic evaluation of the enzymes obtained in the project is being carried out by one of the SME partners. Finally, the biogas production has been tested for the remaining biomass after hydrolysis with good results and it will be used by other industrial partners to implement biogas plants across Europe.

Project starting year: 2011
Project reference: 289603
Coordinator: Fundación Tecnalia Research & Innovation (Spain)
Website: www.transbio.eu

5. KET BIOTECHN0LOGY IN HORIZON 2020

Biotechnology has been identified as one of the six Key Enabling Technologies under the pillar of Leadership in Enabling and Industrial Technologies (LEIT), which considers the **European industry** as one of the world leaders.

The themes (1) Industrial biotechnology, (2) Environmental biotechnology and (3) Emerging trends in biotechnology, which in FP7 were part of the Knowledge Bio-Based Economy (KBBE) area moved in Horizon 2020 under the LEIT pillar (Fig. 1). The themes (4) Novel sources of biomass and bioproducts, (5) Marine and fresh-water biotechnology and (6) Biorefinery also part of FP7 KBBE were included in the Societal Challenge 2 of Horizon 2020 (Fig. 1).

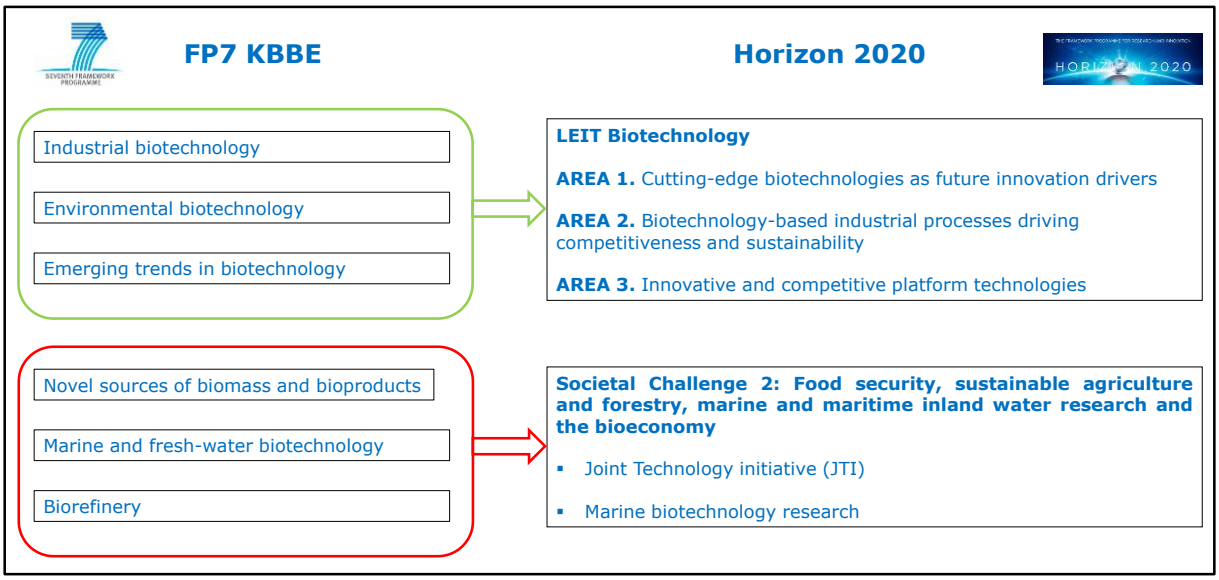

Fig. 1. Biotechnology in FP7 KBBE and Horizon 2020

In the LEIT pillar, KET Biotechnology addresses three main areas (Fig. 1), two of them are a natural continuation of those in FP7 and one is newly introduced in Horizon 2020.

Cutting-edge biotechnologies as future innovation drivers: Ensuring a leadership position in the long term, requires the development of new science, thus this area is driven by the vision that cutting-edge biotechnologies are paramount to assure that the European industry is to stay at the front line of innovation, also in the medium and long term.

Biotechnology-based industrial processes driving competitiveness and sustainability: This area addresses technology driven R&D targeting industrial bottlenecks and it could include new approaches to valorising new feedstock resources and increasing bioprocess efficiencies. The overall aim is to maintain the European leadership in industrial biotechnology.

Innovative and competitive platform technologies: This new area deals with the development of new technological platforms related to biocatalysis and biodesign for a wide range of sectors for industrial applications.

The 2014 Horizon 2020 Biotechnology call for proposals included three topics (BIOTEC 1, BIOTEC 3 and BIOTEC 4) (see Box 2). Out of all the proposals received, seven proposals were funded with a total budget of EUR 51 864 711 and a project duration from four to five years. As a whole, funded projects include a total of 34 industrial and 39 academic and research centre beneficiaries. Also,

three out of the seven projects are coordinated by industry, and one of the consortia is composed only of industrial partners.

BOX 2. Horizon 2020 Work Programme 2014-2015

Biotechnology

BIOTEC 1: Synthetic biology – construction of organisms for new products and processes (RIA)

BIOTEC 2: New bioinformatics approaches in service of biotechnology (RIA)

BIOTEC 3: Widening industrial applications of enzymatic processes (IA)

BIOTEC 4: Downstream processes unlocking biotechnological transformations (IA)

BIOTEC 5: SME-boosting biotechnological-based industrial processes driving competitiveness and sustainability (SME instrument)

BIOTEC 6: Metagenomics as innovation driver (RIA)

RIA: Research and Innovation Actions; IA: Innovation Actions

Furthermore, **two new biotechnology topics** were announced in the 2015 call for proposals: (1) New bioinformatics approaches in service of biotechnology (BIOTEC 2), and (2) Metagenomics as innovation driver (BIOTEC 6) (see Box 2). The second phase of the evaluation of proposals received is about to start.

Biotechnology activities are also funded through the **SME instrument**. For example, in 2014 50 proposals were funded to conduct feasibility studies (Phase I) and two proposals for development and demonstration activities (Phase II) (see Box 3).

BOX 3. SME instrument

PHASE I (proof-of-concept): aims to cover the **assessment of technical feasibility** and market potential of new ideas.

PHASE II (Development and demonstration): aims to cover R&I activities with a particular focus on **demonstration activities** and **market replication** encouraging the involvement of end users or potential clients.

PHASE III (go-to-market): concerns support measures aimed at helping SMEs move towards **commercialising** their innovative products and services through measures like networking, training, coaching and mentoring, facilitating access to private capital or better interaction with key.

KET Biotechnology also contributes to the **Bio-Based Industries (BBI) Joint Undertaking**[4]. This is a EUR 3.7 billion Joint Technology Initiative between the European Commission and the Bio-based Industries Consortium (BIC), which is an industrial partner with 70 industrial members and over 100 associate members.

The next Work Programme that will cover 2016 and 2017 is in its final stages prior to publication in mid-October. The 2016 call will include two topics for a Research and Innovation Action[5] (RIA), a topic for an ERA-NET Cofund[6] and a topic for a Coordination and Support Action[7] (CSA) (see Box

[4] www.bbi-europe.eu

[5] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-d-ria_en.pdf

[6] https://ec.europa.eu/research/era/pdf/cofund-2014-infoday/3_era-net_cofund.pdf

4). In the Work Programme for 2016 the ERA-NET Cofund on Biotechnologies will aim to merge the previous ERA-NETs in Industrial Biotechnology, Synthetic Biology and Systems Biology. The KET Biotechnology call for 2017 in addition to two RIA and a CSA, includes a topic for an Innovation Action[8] (IA).

BOX 4. Horizon 2020 Work programme 2016-2017

Biotechnology

BIOTEC-01-2016: ERA-NET Cofund on Biotechnologies

BIOTEC-02-2016: Bioconversion of non-agricultural waste into biomolecules for industrial applications (RIA)

BIOTEC 03-2016: Microbial chassis platform with optimized metabolic pathways for industrial innovations through systems biology (RIA)

BIOTEC 04-2016: KET Biotechnology foresight identifying gaps and high-value opportunities for the EU industry (CSA)

BIOTEC 05-2017: Microbial platforms for CO2-reuse processes in the low-carbon economy

BIOTEC-06-2017: Optimization of biocatalysis and downstream processing for the sustainable production of high value-added platform chemicals (IA)

BIOTEC 07-2017: New Plant Breeding Techniques (NPTB) in molecular farming: Multipurpose crops for industrial bioproducts.

BIOTEC 08-2017: Support for enhancing and demonstrating the impact of KET Biotechnology projects (CSA)

RIA: Research and Innovation Actions; IA: Innovation Actions; CSA: Coordination and Support Actions

[7] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-d-csa_en.pdf

[8] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-d-ia_en.pdf

6. HORIZON 2020 PROJECTS IN KET BIOTECHNOLOGY

Horizon 2020 projects were funded through three different topics: (1) Synthetic Biology – construction of organisms for new products and processes, (2) Widening industrial applications of enzymatic processes, and (3) Downstream processes unlocking biotechnological transformations, and as such are presented below.

BIOTEC 1. Synthetic biology – construction of organisms for new products and processes

Engineering of *Mycoplasma pneumoniae* as a broad-spectrum animal vaccine - MycoSynVac

Yearly, infections caused by *Mycoplasma* species in poultry, cows, and pigs result in multimillion Euro losses in the USA and Europe. There is no effective vaccination against many Mycoplasmas that infect pets, humans and farm animals (e.g. *Mycoplasma bovis* cow infection). Furthermore, most Mycoplasmas are difficult to grow in axenic culture, requiring a complex media that includes animal serum. Consequently, even in those cases for which effective vaccines are available (namely *M. hyopneumoniae* in pigs, *M. gallisepticum* and *M. synoviae* in poultry), the production process of the vaccines is very irreproducible and prone to contamination by animal viruses.

The aim of **MycoSynVac** is to design a universal Mycoplasma chassis optimized for fast growth in a serum-free medium that can be deployed as a single- or a multi-vaccine in a range of animal hosts. Using this chassis, heterologous antigens from one or more pathogens (i.e. Mycoplasma and virus) and biological adjuvants will be expressed to create a targeted vector vaccine. Foreseeable risks will be avoided and all ethical issues will be handled in a transparent manner.

The expected impacts of **MycoSynVac** include: (1) decreasing the infection levels by Mycoplasma more efficiently; (2) improved safety profile of animals; (3) economically produced vaccines; (4) protection against novel and emerging pathogens and (5) one shot protection.

Project starting year: 2015
Project reference: 634942
Coordinator: Fundació Centre de Regulació Genómica (Spain)
Website: http://www.mycosynvac.eu/

Exploiting native endowments by re-factoring, re-programming and implementing novel control loops in *Pseudomonas putida* for bespoke biocatalysis - EmPowerPutida

As a tightly intertwined and multidisciplinary team of nine academic and industrial partners, the **EmPowerPutida** consortium aims to fill major technical and scientific gaps that, to this day, have limited the full-fledged application of contemporary synthetic biology to large-scale industrial biotechnology in Europe.

It will do so by developing innovative workflows for the tailored engineering of the lifestyles of *Pseudomonas putida*, a bacterium with remarkable metabolic endowment and stress tolerant capabilities that make it superior to potential competitors. The ultimate goal of the project is thus to provide a robust platform for the generation of versatile, high performance *P. putida* chassis directed at the sustainable biotechnological production of bulk and specialty chemicals.

The well-characterized, streamlined and re-factored microbial platform will offer easy-to-use plug-in opportunities for novel, DNA-encoded functions under the control of orthogonal regulatory systems. The game-changing innovations will provide strong versatility, enhanced efficiency and efficacy to the production processes, thereby overcoming current bottlenecks, matching market needs and fostering high-level research growth and development.

EmPowerPutida addresses and contributes to three major drivers in biotechnology: (1) enabling the shift from a petrochemical to a bio-based economy, (2) creating diversity and new products, processes and markets and (3) providing a solid, higher-level platform to enable entrance to new industrial players, for which established technologies are too onerous or otherwise uncompetitive.

Project starting year: 2015
Project reference: 635536
Coordinator: Wageningen University (The Netherlands)
Website: www. http://relaunch-empowerputida.blauserver.de/

From Plastic waste to Plastic value using *Pseudomonas putida* Synthetic Biology - P4SB

The objective of **P4SB** is the biotransformation of non-sustainable plastic waste into sustainable value-added alternative materials by the utilization of the conceptual and material tools of contemporary synthetic biology.

These tools will be used to design tailor-made enzymes for the bio-depolymerization of PET (polyethylene terephthalate) and PU (polyurethane), but also for the custom design of a *Pseudomonas putida* Cell Factory capable of metabolizing the resulting monomers. *P. putida* will undergo deep metabolic surgery to channel these diverse substrates efficiently into the production of polyhydroxyalkanoates (PHA) and derivatives.

In addition, synthetic downstream processing modules based on the programmed non-lytic secretion of PHA will facilitate the release and recovery of the bioplastic from the bacterial biomass.

P4SB and **EmPowerPutida** are complementary projects which will share their corresponding improvements in order to advance both projects.

Project starting year: 2015
Project reference: 633962
Coordinator: Rheinisch-Westfaelische Technische Hochschule Aachen (Germany)
Website: www.P4SB.eu

BIOTEC 3. Widening industrial applications of enzymatic processes

Expanding the industrial use of Robust Oxidative Biocatalysts for the conversion and production of alcohols - ROBOX

The **ROBOX** project is focused in oxidative biocatalysts for the conversion of starting material (both renewal and fossil resources) to broader the application of theses enzymes to the whole spectrum of products in the chemical industry.

In order to achieve the widening of industrial application **ROBOX** will demonstrate the techno-economic viability of bio-transformations of four types of robust oxidative enzymes: P450 monooxygenases (P450s), Baeyer-Villiger MonoOxygenase (BVMOs), Alcohol DeHydrogenase (ADH) and Alcohol OXidase (AOX) for which target reactions have already been validated on lab-scale in pharma, nutrition, fine and specialty chemicals and materials applications. **ROBOX** will demonstrate 11 target reactions on large scale for these markets in order to prepare them for scale up to commercial scale plants.

Since the April 2015 kick-off efficient bacterial P450s expressed in *Escherichia coli* for diclofenac metabolites production were identified. Reaction engineering is ongoing for the first demonstration on 100 litres pilot-plant scale at DSM (scheduled November 2015). To regio-selectively oxidise lactols to flavour and pharma lactones suitable ADHs and AOXs have been identified by HTP screening at c-LEcta and Fraunhofer Institute. Dyadic has first generation AOX fungal production strains. BVMOxygenations to synthesise high-performance monomers were identified jointly by the universities Maastricht and Groningen together with ChemStream.

Project starting year: 2015
Project reference: 635734
Coordinator: DSM Chemical Technology R&D BV (The Netherlands)
Website: www.h2020robox.eu/

Sustainable industrial processes based on a C-C bond-forming enzyme platform - CarbaZymes

The **CarbaZymes** project is about making new carbon bonds. This is a specific technology that needs specific enzymes and intensive reaction development. Nature has evolved catalysts that can steer such reactions with perfect stereocontrol under very mild conditions, but that offer only a limited scope for practical applications. The aim of the project is the implementation of a biocatalytic carboligation platform by making stable, diverse and efficient catalysts for new processes. With inherent safety advantages over traditional chemical methods, this biocatalytic carboligation platform aspires to replace the current use of hazardous components for the industrial scale manufacturing of products with high economic and societal value. In particular, the focus is on the industrial production of important pharma and bulk chemicals, including polymer precursors, in an environmentally friendly mode.

CarbaZymes will promote innovation in the field of biocatalytic C-C bond formation at large scale, and thus the global competitiveness of the European chemical and pharmaceutical industries.

Project starting year: 2015
Project reference: 635595
Coordinator: Technische Universitaet Darmstadt (Germany)
Website: www.carbazymes.com/

BIOTEC 4. Downstream processes unlocking biotechnological transformations

Sustainable downstream processing of vaccines through incorporation of nanobiotechnologies: novel affinity ligands and biomimetic membranes - DiViNe

DiViNe is based on an industrial consortium and its main goal is to improve the downstream process of vaccine production in order to reduce the cost of vaccines. **DiViNe** will tackle these costs and environmental issues with technological answers.

The partners will combine two major nano/biotechnology innovations to develop an integrated purification platform amenable to the different natures of vaccines: glycoconjugates, protein antigens and enveloped viruses. They will implement Nanofitins (novel affinity capture ligands) and aquaporin-based membranes (energy-saving nano-biomimetics), for a positive purification approach. High yields are expected at affordable cost of goods and with a sustainable approach of water recycling.

Project starting year: 2015
Project reference: 635770
Coordinator: Instituto de Biologia Experimental e Tecnologica (Portugal)
Website: www.divineproject.eu

Next-generation biopharmaceutical downstream process - NextBioPharmaDSP

The scope of the project is the optimization of downstream process (DSP) for the production of biopharmaceuticals, since the downstream part of the manufacturing process involves substantial costs and is also a bottleneck from the perspective of efficient production. The main objective of **NextBioPharmaDSP** is to implement a fully integrated manufacturing platform for biosimilar monoclonal antibodies based on continuous chromatography in combination with disposable single-use techniques for all unit operations of the DSP sequence together with incorporation of advanced analytical tools. The structure of the consortium with three large companies combined with expertise from academic partners is a guarantee that the project goals can be reached.

The main benefits of the project are reduction of production costs and efficiency improvement, which will ultimately lead to expanded accessibility of patients to these highly efficient drugs. Another important aim is lowering the environmental footprint and moving to more sustainable technologies. With these goals achieved, also EU competitiveness on the fast growing field of biopharmaceutical drugs production will increase.

The project successfully started in March 2015 and all main steps of DSP, such as various primary separation alternatives, continuous capture step, flow-through purification steps and in-line advanced analytical tools are being developed on smaller scale.

Project starting year: 2015
Project reference: 635557
Coordinator: Lek Farmacevtska Druzba DD (Slovenia)
Website: www.nextbiopharmdsp.eu

7. KET BIOTECHNOLOGY IN EUROPE: INDUSTRIAL AND SOCIETAL NEEDS

1) EuropaBio

Speaker: Joanna Dupont-Inglis

Director, Industrial Biotechnology

Mrs Dupont-Inglis discussed the needs of the biotech industry and how they are closely related to the needs of society as a whole. Biotechnology can hold the key to solving several important issues around the depletion of fossil fuels, waste management and the concern of a growing global population.

In addition to the needs of society, Mrs Dupont-Inglis also spoke of the need for a supporting framework for science and industry in relation to job growth, investments and regional policies. Even though there is plenty of cutting-edge technology and scientific knowledge in the EU, Mrs Dupont-Inglis argued that there is still an issue with the slow commercialization of products that are derived from this vast scientific knowledge base.

According to EuropaBio, five areas need to be addressed in order to bring Europe to the forefront of the biotechnology race:

1) Policy framework

2) Dialogue between different sectors of the bioeconomy

3) Information, standardisation, certification and adopting measures to create new markets

4) Attracting and fostering investments

5) Access to competitively priced feedstock

2) SusChem

Speaker: Reiner Grimbergen

Royal DSM, SusChem Board Member

Mr Grimbergen stressed the need for a circular economy and emphasized that sustainable feedstock must be available at world market prices (i.e. level playing field with oil and gas). Through smart and efficient use of resources the aim should be to produce food, feed and biochemicals. Energy was mentioned as one of the key points; indeed, one of the advantages of bio refineries is that they can be operated on zero carbon footprint bio-energy (e.g. bio-steam) as a by-product generated from the waste streams. The most important point, however, relates to process efficiency and industrial symbiosis, where a lot can be learned from the fossil industry of the last century. Finally, there is a need for innovative products such as functional molecules and intermediates, which can have a great impact on society and the industry. The downstream processing (DSP) is also considered to be a critical step in the production of bio-based products, since this can represent up to 80% of the production cost.

3) European Federation of Biotechnology

Speaker: Philippe Corvini

Professor, University of Applied Sciences and Arts, Northwestern Switzerland

Vice President and Chairman, Section of Environmental Biotechnology of the EFB

Speaking from an academic perspective, Prof Corvini focused on environmental issues as well as the convergence of biotechnology with other disciplines.

Regarding the environment, Prof Corvini addressed, besides the needs for bioremediation/bioaugmentation approaches, the issue of climate change in relation to agricultural production, farmer´s income and rising food prices. In this regard, he pointed to the importance of advancing our understanding of soil microbiology in order to improve plant and soil properties such as water storage capacity. Advancing the knowledge of microbial ecosystems will go a long way in helping plants resist such stress factors as drought, heat waves and salinity, helping us restore plant ecosystems and increase food production for a growing population.

Microbial photosynthesis was another topic discussed with regard to maintaining environmental balance and helping us maximise available resources. In this aspect, photosynthesis through microorganisms could help reduce the emission of greenhouse gases, control soil erosion and even lead to the production of novel chemicals and biofuels.

Microbial electro-chemical technology was also mentioned as a method to manipulate microbial metabolism through the use of solid-state electrodes. Even though this technology has already been applied successfully for wastewater treatment, it is still costly to implement. Fortunately, there have been some developments in this field such as microbial electrosynthesis based on methane molecules and electrofermentation, which uses small organic molecules to produce chemicals.

Even though the up-scaling of these processes will be a challenge for developing marketable products, Prof Corvini spoke of a real need to understand microbial metabolism in order to help microorganisms to achieve a high bio-electric and catalytic activity. If successful, this type of research could lead to control greenhouse gas emissions and decreasing the use of fossil fuels.

Finally, Prof Corvini mentioned the need to produce robust "immortal" enzymes and novel biocatalytic processes with the use of nanotechnology, for instance through immobilization of enzymes onto nanomaterials in order to tune enzyme characteristics such as the biocatalytic turnover and substrate specificity. This requires improving reactor design for the implementation of biocatalysts in continuous processes.

8. A VISION OF KET BIOTECHNOLOGY IN 2030

A vision: KET Biotechnology in 2030

Speaker: Roland Wohlgemuth, Senior Scientist at Sigma-Aldrich

Mr Wohlgemuth gave an overview of the impacts of fundamental innovation, creating value for industry and understanding and building systems as key drivers for the bioeconomy.

The biotechnology industry in Europe is based on the fundamental sciences of biology, chemistry and engineering. In asking what Key Enabling Technologies (KET) really mean, Mr Wohlgemuth stated that it is essential to enable people to create the economic values of the future through education.

The main needs that arise from KET Biotechnology can be subdivided into three main parts: (1) health applications; (2) food applications, and (3) chemicals and materials.

Resource efficiency was considered by Mr Wohlgemuth as a very important issue in both chemistry and biotechnology, since a lot of waste is created as by-product of production processes. Waste reduction can be achieved either by new and improved production processes with high molecular economy or by finding novel applications for a by-product while creating an additional product from what was previously considered waste, thereby transforming waste into a raw material.

Fundamental innovation was also mentioned by Mr Wohlgemuth as essential to transform our fossil based economy into a bio-based economy. The first steps have already been taken in this direction, but it is a task that will take more than a century to complete in order to make a full transition to a bio-based economy.

According to Mr Wohlgemuth it is important to create value by navigating innovation pathways and addressing the following actions:

1) Becoming aware of important problems;
2) Selecting and bundling new developments;
3) Advancing critical enabling technologies by identifying bottlenecks;
4) Creating well-balanced sustainable value and anchoring it in science-industry-society;
5) Using sustainably limited resources as a driving force;
6) Converting abundant and inexpensive raw material into high value products;
7) Creating jobs;

Finally, the main challenges remain:

1. The Enzyme Function frontier and the creation/standardisation of a global protein database reporting enzyme functions
2. Advancing the manufacture of relevant molecules when and where needed
3. Studying the metabolite frontier and closing the gap between known and available metabolites

4. Innovation, manufacture and analysis by scaling reaction, space and time in medicine and industry

From sectorial to systematic research innovation and education

Speaker: Lucia Gardossi

Prof Università degli Studi di Trieste, Italy

Even though it is difficult to predict which disruptive biotechnological innovations might occur by 2030 and how they might impact on industry and society, previous foresight studies indicate that we should concentrate in strengthening the resiliency of both the society and the educational systems. This would mitigate our vulnerability towards many urgent challenges, such as environmental degradation and population changes.

Nevertheless, there are certain disciplines that like to use models in order to predict a possible future outcome, such as economics. In certain models, it is predicted that globalisation will decrease in the future due to lacking natural resources and we will go back to a more local based economy. If we take into account that Europe is rich in waste and CO_2, we should focus on a circular based economy by optimising processes and reducing waste as well as creating novel uses for both waste and CO_2. Moreover, the utilisation of non-conventional resources (e.g. insects) might also be explored with the intent of relieving the pressure on soil exploitation.

The needs of a new bio-economy are well addressed in the current calls and many projects make very good contributions to this field. But, there is a real need to **develop an integrated multi-KET approach** for solving highly complex problems that cannot be addressed through a simple assembling of discrete steps of innovation. Biotechnology is expected to demonstrate the practical applicability of bio-conversion of renewable carbon and CO_2 into chemicals, plastics and fuels: however, the achievement of such objective requires novel approaches able to integrate not only the massive amount of scientific data available, but also information coming from economic, social, legislative and environmental analysis. Therefore, the global constraints and objectives should be made explicit from the beginning of the research and optimisation processes leading to more efficient biotechnological tools and processes.

This change of paradigm in biotechnology research and innovation represents a **challenge for academia,** which is expected to maintain European competitiveness and innovation through universities and institutions as strategic points for multidisciplinary thinking. In this respect, corporatism represents one of the major bottlenecks to be overcome by academia because sectorial interests not only hamper effective knowledge integration but also cause exclusion.

9. PANEL DEBATE - MAXIMISING THE IMPACT OF KET BIOTECHNOLOGY

Speakers: Ana Segura (Abengoa), Dirk Carrez (BBI), Markus Schmidt (Biofaction) and Laure Baillargeon (European Commission).

The workshop closed with a panel discussion about maximising the impact of KET Biotechnology. The questions addressed to the panellists were the following:

1. What is the added-value of cooperation outside the consortium to maximise the project success (*e.g.* clustering of projects, international cooperation)?
2. What are the barriers to maximise impact? Can you share best practices on exploitation? How has your project addressed IPR, patenting and contribution to standards?
3. What could help to further ensure that the projects generate breakthrough exploitable results?

Each panellist presented its views, based on its experience and not necessarily representing the organisation to which everyone belonged. These were followed by interventions of the audience.

Ana Segura mentioned that research industry does not always know precisely what it needs, as its main driver has an economic nature. She stressed that in generic terms cooperation is always necessary; however, given that issues of confidentiality and intellectual property are always a concern when linking different entities, industry may not always be as open to cooperation as the scientific community. From a different perspective, she pointed out that education is an essential component when trying to innovate and develop new technologies. Unfortunately science and engineering education are often not convergent and opportunities are therefore missed.

Dirk Carrez stated that it is always important to have a clear idea of the different uses that biotechnology can have in our society. He stressed that it is essential to bring all the actors together and create a coherent plan from the beginning of the project in order to maximise the desired results. This is one of the main challenges, integrating the value chain with all the different sectors focusing on deployment. This would attract investors who are willing to take a chance on future technologies.

Markus Schmidt focused on the importance of developing standards that can be utilised by interested parties in order to enable better cooperation and communication and to capitalise on results. He noted that unfortunately there are no real incentives to develop any such standards, an issue that must be addressed in future proposals if cooperation between sectors and institutions is to be improved. He went on to recommend the European Committee for Standardisation (CEN) as a suitable partner to create such protocols. The CEN should be included in proposals as a key participant in order to achieve the desired goals. Finally, Mr Schmidt stated that given that Horizon 2020 projects are of great importance to scientific and industrial development, they should aim to have a real economic impact and therefore they should be a part of a long term strategy to bring Europe to a leading position.

Finally, Laure Baillargeon stressed the need for better communication between industry, academia and policy makers, since they need to work together to shape the policies of the future. She stated that in order to keep Europe at the forefront of scientific and industrial innovation, more attention should be given to SMEs, since they have the highest potential to drive real innovation. She mentioned that science and technology were the game changers and that from scientific researchers in academia, through industrial partners, stakeholders, policy makers and finally consumers, everyone should play a role to drive a meaningful change in society.

A summary of the issues brought up during the debate is as follows:

- Why Europe is less competitive compared to the United States? Why does Europe not exploit what Europeans invent? Why does Europe not invest in new products and new markets? Is Europe less risk-averse?

- Are comparisons between Europe and the USA possible? The political and social settings and culture are different. Europe decided long ago to be different. In the end, do Europe and the USA need to be similar?
- There is no correlation between quality, number of scientific publications and successful technology transfer. The national systems should change the performance methods of scientists, which now emphasised publishing and the number of publications.
- One of the main barriers in European industrial biotechnology is trying to attack too many fronts simultaneously, which is a problem when trying to maintain focus on increasing the competitiveness. Instead of trying to diversify into different branches such as academic research, ecology, biofuels or health, it would be better to build cooperation and governing organizations that help European industry to be more competitive.
- It is important to recognise the many success stories that have been a product of European science and help disseminate the results, giving our scientific research the importance and prominence in the world it deserves. At the same time, it is important to understand the necessities of the biotechnological industry and help policy makers act according to those needs.
- In addition to those needs, it is also important to examine our resources to learn to work with what is available to us and focus our efforts in a realistic and constructive manner.

Closing the workshop, there was a contribution by Mr Waldemar Kütt (European Commission), who gave a short presentation about the future of the Bio-based institutionalised PPP in Horizon 2020, placing biotechnology at the heart of the three main pillars within Horizon 2020 (Fig. 2).

Fig. 2. Biotechnology in Horizon 2020

Mr Kütt shared his views about the expected growth of the bio-based industries in the next decades and the reliance of the EU bioeconomy strategy on strengthening rural economies through re-industrialisation and sustainable growth. He explained that the objectives of the **BBI Joint Undertaking**[9] consist in developing at least five new bio-based value chains for Europe based on advanced biorefineries, thus increasing economic growth and employment. Finally, Mr Kütt used the example of the Bio-based Industries Consortium —consisting of 77 full members and 142 associate members that range from educational institutions to technology platforms— to highlight how clustering leads to a close interaction across related industries, while stimulating and supporting each other and enabling a wide societal impact.

[9] http://www.bbi-europe.eu/

Appendix 1: Agenda

22 September 2015, Tuesday

Venue: Centre Conference Albert Borschette, Room 5B, 1040 Brussels

09:00-09:20 **Registration**

Chair: José-Lorenzo Vallés, Head of Unit, DG RTD/D2

09:20-09:30 **Welcome address**

Clara de la Torre, Director, RTD/D

09:30-10:30 **FP7 KBBE Biotechnology projects** (IB2Market, Indox, Metacode, Synpol, Transbio)

Focusing on exploitation of results and maximising impact

10:30-11:00 ***Coffee break***

11:00-11:15 **KET Biotechnology in Horizon 2020**

José-Lorenzo Vallés, Head of Unit, DG RTD/D2

11:15-12:45 **Horizon 2020 projects in KET Biotechnology** (Carbazymes, Divine, Empowerputida, Mycosynvac, NextbiopharmDSP, P4SB, Robox)

12:45-13:45 ***Lunch***

13:45-14:15 **KET Biotechnology in Europe - industrial and societal needs**

Speakers: Joanna Dupont from EuropaBio, Reinier Grimbergen from SusChem and Philippe Corvini from EFB.

14:15-14:45 **A vision of KET Biotechnology in 2030**

Speakers: Roland Wohlgemuth and Lucia Gardossi

14:45-16:00 **Panel debate - Maximising the impact of KET Biotechnology**

Moderator: Andrea Gentili

Panellists: Ana Segura, Dirk Carrez, Markus Schmidt and Laure Baillargeon

16:00-16:30 **Conclusions and next steps**

Rapporteur: Outcome of the workshop

Waldemar Kütt: Future BBI opportunities

Andrea Gentili: Outlook in Horizon 2020

16:30 ***Networking Coffee***

Appendix 2: List of participants and contacts

Name	Affiliation	Project
Anders Jonas	Merck	NextBioPharmDSP
Baillargeon Laure	EC DG Growth, F3	
Beauprez Joeri	Inbiose NV	IB2Market
Benedito Flavio	CEFIC/Suschem	
Bernauer Hubert	ATG:biosynthetics GmbH	MycoSynVac
Budisa Nediljko	TU Berlin	Metacode
Carrez Dirk	Biobased Industries (BBI) Consortium	
Carrondo Manuel	IBET	DiViNe
Corvini Philippe	EFB/FHNW	
de Bont Karen	EC DG for Research and Innovation, D2	
de Vicente Coll Carmen	EC DG for Research and Innovation, D2	
Doce Capeans Alberto	EC DG for Research and Innovation, D2	
Dupont Joanna	EuropaBio	
Fernández Gutiérrez María	EC DG for Research and Innovation, F2	
Fessner Wolf-Dieter	Technical University of Darmstadt	CarbaZymes
Gardossi Lucia	Universita' degli Studi di Trieste	
Gentili Andrea	EC DG for Research and Innovation, D2	
Gómez Sala Beatriz	Teagasc Food Research Centre	
Gray Claire	EuropaBio	
Grimbergen Reinier	SusChem/DSM	
Gutiérrez Ana	IRNAS	Indox
Hoflack Lieve	Bio Base Europe Pilot Plant	IB2Market
Kaluzna Iwona	DSM	ROBOX
Kenny Shane	Bioplastech	P4SB
Kitten Olivier	AFFILOGIC	DiViNe
Kütt Waldemar	EC DG for Research and Innovation, F2	
Lluch María	CRG	MycoSynVac
López García José Luis	CIB, CSIC	Synpol
Lorenzo Vallés José	EC DG for Research and Innovation, D2	
Lund Henrik	Novozymes	Indox
Martins dos Santos Vítor	Wageningen University	EmPowerPutida
Marzano Carmine	EC DG for Research and Innovation, D2	
Noorman Henk	SusChem/DSM	
Novak Marjan	Sandoz	NextBioPharmDSP
Oven Matjaž	Site Head Biopharmaceuticals	NextBioPharmDSP
Pop Bianca	Tritecc SRL	TRANSBIO
Schmidt Markus	Biofaction	
Schurmann Martin	DSM	ROBOX
Segura Ana	Abengoa	
Spiros Agathos	UCL, Louvain la Neuve	
T. Martínez Angel	CIB, CSIC	Indox
Takors Ralf	University of Stuttgart	EmPowerPutida
Wardenga Rainer	Enzymicals AG	CarbaZymes
Wierckx Nick	Aachen University	P4SB
Wohlgemuth Roland	CATV	

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The main objective of the EC-Workshop "Maximising the Impact of KET Biotechnology" was to contribute to maximise the impact of KET Biotechnology projects through fostering the creation of an Industrial Biotechnology community and exploring in particular the potential of clustering. To reach this objective, the Workshop brought together representatives of ongoing biotechnological projects, both from FP7 KBBE and Horizon 2020 calls, as well as stakeholder representatives and experts from industry and academia. The Workshop allowed the exploration of opportunities for synergies and cooperation by giving participants a chance to network, to discover common interests and to share the challenges encountered throughout the development of their projects. All participants shared their views and concerns in order to maximise the impact of KET Biotechnology and to drive long term sustainability leading to growth across a variety of economic sectors.

Studies and reports

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