Potential Impact

This project has brought together biotechnological scientists as well as microfluidic and modeling experts. This interdisciplinary interaction was at the beginning not straightforward but it resulted in a highly valuable rapid **development** and progress in the investigated field. This can be observed for instance by the development of **new microfluidic products** (i.e. the design of 17 new micro-reactors resulting in 24 different micro-reactor prototypes), 24 **mass fabrication compatible micro-reactors** for further commercial application, **standardization of device formats**, making the systems applicable with standard laboratory equipment, the development of 6 **new chemical products**, by using screening of ATA against a library of potential substrates, **novel LentiKats® particles** with immobilized ATA for the production of fine chemicals, as well as **new enzyme products**.

Impact on biotechnology Industries

This project has a realistic probability that the developed microfluidic tools will have a much broader potential application market in other biotechnolgoical industries and will therefore not only be targeted to biocatalytic processes. The main idea of the project was based on the idea to accelerate with help of miniaturized systems the process development tasks during the product development. Other chemical and biochemical branches will therefore also use the advantages of such accelerated systems. Assuming the successful applicability of such tools it can be anticipated that considerable faster developments can be achieved and the time-to-market horizon will be substantially reduced. This will improve the competitive edge of European companies and hence strengthen the European position in a global competitive market

Social-economic impact

Considering the technological developments of the next decades it can be for sure assumed that the transition of the petrol based industries will shift to a more sustainable use of raw materials. It is therefore not unrealistic to assume that more and more production in Europe will take the advantage of bioprocesses or at least part processes, which will use biotechnological production principles. Therefore the efficient and fast characterization of enzymes, cells or other biological materials might decide in the future about the economic viability of a product or a company. It is therefore expected that the developed and investigated technology will find its way into development processes of highly valuable products as well as into bulk products. The time frame for such developments will however be decades here.

Wider societal implications of the project

The project has shown it´s potential to use the developed technology especially in the field of technology education. The developed educational animation videos on microfluidic principles have so far registered a real interest in the internet. In the education of chemical engineers the miniaturized systems offer a real alternative to classical laboratory teaching classes, where e.g. typical design and build courses can often not be offered due to the high risk that chemical reactions in the laboratory, without a full control of the students, might go wrong. This is especially true, when working with organic synthesis or similar chemical challenges, where often toxic or health damaging

solvents have to be used and special precautions must be taken. Here the developed technology offers a real alternative, due to the small amounts used in the system.

Main dissemination activities

The partners of the project have been highly active in the dissemination of the results. The high amount of peer reviewed scientific publications (31) as well as an impressive number of oral and poster presentations at scientific conferences (163) are a good indicator for the scientific dissemination. Additionally, two international conferences on the Implementation of Microreactor Technology in Biotechnology – IMTB (2013 and 2015) were organized within the project. Finally an explanatory animated video about the project has been produced addressing a broader public audience.

Exploitation of results

The exploitation of the products is essential for the participating SMEs and companies of the project. A more extensive overview is given in the separately submitted document describing the submitted patent application and the exploitable foreground. But in the following a more detailed description of some of the developed sensors, microreactors, the integration of sensors into other platforms, microplate based screening assays and consumables as well as chemical products is given in the following:

Optical Oxygen and pH sensors

GUT has elaborated new synthesis and preparation routes for sensor materials and components and published in scientific journals. This know-how and the materials are exploitable in commercial products in sensor technology. GUT has strong interest in commercialization of the findings. During the project the sensors have been tested in various applications. Based on these finding GUT will search for commercialization partners of the technology.

Within the project we already demonstrated potentially new products (microfluidics, microreactors) with integrated sensors. Partner Chipshop has adapted the technology and is planning to launch a product with integrated oxygen sensors soon. Partner iX-factory GmbH has adapted the methodology, which enables the integration of sensor spots down to 100 µm in silicon-glass micro reactors and is also interested in further collaboration with GUT to expand this technology. In addition, GUT has a deep collaboration with the German company Pyroscience GmbH (SME). Scientific results of GUT from other national and international projects have been successfully commercialized by Pyroscience. GUT has also collaborations with other companies and various fields of applications.

Micro reactor toolbox

During the project different micro reactors were developed, which can be applied for rapid screening and characterization of biocatalysts and biochemical process options. After defining requirement specifications for these micro reactors in close cooperation with the project partners, prototypes were fabricated and fluidically characterized. Finally, fabrication processes for mass

production of the most promising candidates were established. The developed microfluidic modules – especially devices such as meander micro reactors, packed bed micro reactors, the biocatalyst screening micro reactors and the 96 channel microfluidic plate represent valuable tools for further use in biocatalysis process development. A detailed overview over the single modules, which have been developed within BioIntense project, was given in deliverable D1.5.

Due to the fact that a later production scale of the developed single micro reactors and the fact that microfluidic ChipShop GmbH covers the whole technology chain for fabrication of these reactors, further exploitation of the project's results can and will be enforced by implementation of the new microfluidic building blocks into the unique international Lab-on-a-Chip Catalogue of microfluidic ChipShop GmbH.

The microfluidic chips from glass and silicon developed within the micro reactor toolbox will be further implemented into the online-Shop of iX-factory GmbH to enable the overcome of the challenge of reducing time and investment costs to move from a research prototype device to a production device.

Integration of optical sensor technology into microfluidic devices

Integrated optical oxygen sensors represent valuable tools for online analysis of catalyst and process screening. While the development of sensor materials was part of WP 3, their integration into microfluidic devices is one of the highlights within WP 1. Starting from simple investigations of material compatibility, the major outcomes of the project comprise the fabrication of micro reactors especially suited for sensor integration for oxygen or pH, new processes to integrate these sensors into microfluidic devices and the optimization of automated sensor integration regarding spot appearance and reproducibility of the fabricated oxygen sensors. Furthermore, assembling technologies have been adapted to maintain the functionality of integrated sensors.

The sensor material developed within BioIntense as well as the automatization of sensor integration directly into microfluidic channels make integrated oxygen sensors interesting candidates for product development. Therefore, the know-how generated within previous investigations was transferred to microfluidic ChipShop GmbH, where automated fabrication of oxygen sensors into polymer based devices was further optimized regarding spot appearance and reproducibility of the fabricated oxygen sensors.

Further exploitation of the project's results is planned to be achieved by establishing a new product line comprising different microfluidic devices with integrated oxygen sensors. The know-how generated within BioIntense project is transferable also to applications different from biocatalytic process development, such as microfluidic cell culture and Organ-on-a-Chip applications and therefore has the potential to address research and industry customers on a broad range of subjects.

The improvements in process methodology can and will be further used by SMEs iX-factory GmbH and microfluidic ChipShop GmbH on a technology level to increase the performance of new microfluidic product development.

Microplate-based screening assay and associated consumables (eg microplates with integrated oxygen sensors and plate sealing lids)

A screening assay was developed on low volume 96 well plates measured on a time-resolved fluorescence plate reader with Z' values in excess of 0.7, thereby demonstrating screening-level performance. The data produced also correlated with the HPLC-based reference method and facilitated high-throughput characterisation of a panel ATA enzymes and convenient assessment enzyme enatioselectivity and heat stability. Solutions were developed using dispensable oxygen sensitive probes and solid-state oxygen sensors integrated into the base of the microtiter well for instances where interference between assay components and the oxygen reporter might occur. Solutions were also develop for oil-free sealing of microtitre plates using a sealing lid fabricated by partner Chipshop. The data surrounding these developments are confidential and the technologies are being further developed towards marketing of future products.

Low volume screening – plates

Low-volume screening tools were also developed on (i) glass chips custom designed by partner iXFactroy and (ii) on polymeric chips custom designed by partner Microfluidic Chipshop. These platforms facilitated activity measurement in volumes as low as 5 µL and involved optimisation of channel geometry, and polymer choice to facilitate both good O2 barrier properties and enable accurate measurements on fluorescence plate reader platforms. These data are confidential and the resulting applications show commercial potential. This is underscored by the fact that the polymeric solution is currently being be developed further in collaboration with partner Chipshop with plans for production and product launch in 2016.

Substrates, Intermediates and Final Products

The substrates, intermediate and final products which have been developed in the Biointense-project are in different stages of commercialization as listed above with the purpose of making it available to the research and applied field. Whereas one final product has already been commercialized, others will become commercially in the course of the year 2016 and for some susbtrates and final products additional research and development or analytical work is required to make it commercially available, as indicated in the table. Substrates also will be commercialized after finalization of the analytical quality control work, while the intermediates and the Kanosamin diasteromer require further research and are therefore still on hold.