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The Swiss Industrial Biocatalysis Consortium (SIBC): Past, Present and Future

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Abstract: Since its inception in 2004, the Swiss Industrial Biocatalysis Consortium (SIBC) has brought together scientists from the Pharma, Fine Chemicals, Agrochemicals and Flavor and Fragrance Industries with the goal of promoting biocatalysis inside and outside of Switzerland as well as providing mutual benefits in the form of pre-competitive knowledge sharing. One of the 'founding fathers' of the SIBC was of course Oreste Ghisalba, whom we are honoring here in this special edition. The history of the SIBC as well as current activities and future challenges will be presented.

Keywords: Biocatalysis · Swiss Industrial Biocatalysis Consortium (SIBC)

Dr. Steven Hanlon is Senior Scientist in the Catalysis Group at F. Hoffmann-La Roche Ltd in Basel, Switzerland and is currently President of the SIBC. He studied biology before completing a PhD focused on molybdenum-containing bacterial oxidoreductases under the supervision of Dr. Alistair McEwan at the University of East Anglia, UK. He heads a lab responsible for preparing drug metabolites and chiral intermediates using whole-cell biocatalysts with particular emphasis on oxidations.

1. Founding and History of the SIBC

The SIBC was initiated in 2004 with the main goal of promoting biocatalysis as an efficient, economically and ecologically attractive technology for industrial applications. Although the driving force behind the founding of the consortium was Hans-Peter Meyer of Lonza, the first colleague Hans-Peter contacted was Oreste Ghisalba to ensure his active support in establishing such a unique organization. Oreste's extensive network in academia, industry and particularly in the political arena became a very important factor in the success of the consortium. His ability to bridge the divide between these different worlds was invaluable in strategically positioning the SIBC and biocatalysis in general. His great success in employing the SIBC as a vehicle to improve understanding between industry and academia is one of his most outstanding achievements. Even after his retirement from Novartis, Oreste continued to play an active part in SIBC meetings, providing his usual valuable support and advice.

In drawing up the SIBC Agreement, there was a focus on being as pragmatic as possible; for instance, there was no financial commitment involved in joining or membership, with the only financial outlay being associated with consortial projects. This rather unusual arrangement exemplified the high degree of trust between the founding members and made the legal discussions involved with drawing up the contracts much simpler. Although there was some 'back and forth' exchange between the various legal teams, thanks to the hard work of the core team consisting of Thomas Keppler (Lonza), Franz Kaufmann (Ciba), Oreste Ghisalba (Novartis), Thomas Münch (Givaudan), Roland Wohlgemuth (Sigma-Aldrich), Hans-Peter Meyer (Lonza), Beat Wirz (Roche) and Volker Jungmann (Syngenta), the tremendous goodwill between the main players ensured that the negotiations ran smoothly.

The consortium was open to any Swiss company actively involved in biocatalysis and the agreement was signed in 2006 by six companies, Ciba, Givaudan, Lonza, Novartis, Roche and Sigma-Aldrich. The main goal of the SIBC was broadening the range of reaction types applicable to biocatalysis and to create win-win situations by promoting pre-competitive knowhow exchange. Integral to this was the creation of a database containing strains which had been successfully applied in biotransformations by the member companies and a physical exchange of strains under a bilateral MTA was envisaged. One important point was not insisting on each company contributing an equal number of entries for the database (and indeed this varied widely); further emphasizing the degree of trust and goodwill involved. Under the terms of the Consortium Agreement, the database could not be shared with third parties, thus providing a safeguard for the companies' proprietary information. The SIBC was committed to supporting academia, industry and the authorities by acting as consultants on issues relating to biocatalysis and also developing a roadmap for Biocatalysis in Switzerland in cooperation with the Swiss Biotech Association and ScienceIndustries. In addition, an SIBC homepage hosted by the SBA was established.

It was always the goal of the SIBC to expand the membership and in 2010, Cerbios (a Ticino-based Pharma CRO) and DSM both joined to be followed by Syngenta in 2012. In 2009, Ciba left the consortium after the company was taken over by BASF. The remaining eight companies therefore represented the Pharma, Fine Chemicals, Fragrance and Flavor and Agrochemicals sectors, and this diversity certainly represents a major strength of the SIBC.

Consistent with the SIBC mission of promoting biocatalysis; several well-received workshops were held at the Biotrans conferences in Oviedo, Spain (2007), Bern, Switzerland (2009), Giardini Naxos, Italy (2011) and Budapest, Hungary (2017). These workshops provided a discussion forum for academia and industry with the aim of improving mutual understanding between the two groups, and to find ways of addressing the most

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important challenges in the field. Since its founding the SIBC has also contributed to a number of reviews on biocatalysis.[1a–c]

2. Current Status

SIBC meetings take place twice a year and typically include presentations from guest speakers from academia or industry and in this way the SIBC is informed about new developments in the field of biocatalysis. A 'Tips and Tricks' round has also been introduced in which members can pose questions on technical and regulatory issues relating to biocatalysis and thus benefit from the wide knowledge and experience present. The sharing of experiences with CROs has also featured prominently in these discussions

Having realized that the exchange of wild type strains was largely not possible due to constraints relating to commercial strain collections, an alternative strategy was sought for obtaining new enzymes on a consortial basis. In recent times, the SIBC has favored exchange of recombinant strains expressing industrially relevant enzymes. In 2013, a CYP450 subgroup involving Novartis, Roche, Givaudan and DSM was formed and embarked on a program to jointly obtain five microbial CYP450s. The cloning and expression was handled by DSM with each company contributing equally to the costs. A subsequent project entitled 'Minienzymes Exchange' involved each participating company to select five IP-free enzymes of interest to them and express them in *E. coli* with validation of the enzyme activity. These recombinant strains would then be exchanged with those from the other companies. Five companies took part and received twenty enzymes for an outlay for only five, a definite win-win! The rapidly decreasing costs associated with ordering synthetic genes has greatly facilitated this approach, although some of the companies employed CROs for cloning and expression of the enzymes. Even though the enzyme exchange was considered a success, the lengthy process involved with finalizing the contracts made the completion of a subsequent enzyme exchange round prohibitively difficult. More recently, we have taken the approach to exchange sequence information, again involving IP-free enzymes, rather than a physical exchange of strains and such a project involving ketoreductases has been finalized and follow-on exchanges are currently in discussion. These developments reflect major trends in the industry; 20 years ago wild type strains were the norm in industrial biotechnology. With the explosion of numbers of genes in public databases and plummeting costs associated with ordering them, *in silico* information has become increasingly important.

The SIBC is pledged to promote biocatalysis by acting as consultants for industry and academia. Currently, several members are serving on the Scientific Board and Working Groups of the 'Innovationsraum Biokatalyse', a project with research and educational aspects funded by Swiss Universities, with ZHAW in Waedenswil as leading house. The SIBC was involved in selection of the projects to be funded and several member-companies initiated projects which were accepted for funding

At the most recent SIBC Biotrans Conference Workshop, held in Budapest (2017), the SIBC Lecture entitled 'From mgs to Kgs; Industrial Biocatalysis from an SIBC Perspective' was presented. This lecture consisted of real-world examples from each company in which biocatalysis is applied in diverse processes ranging from preparation of milligram amounts of drug metabolites to production of bulk chemicals on multi-tonne scale. This lecture has also been presented twice to students on the Masters Biocatalysis Course at the ZHAW Zurich University of Applied Sciences; emphasizing the commitment of SIBC to educating the next generation of scientists.

3. Future of the SIBC

Of course, we want to build on the vision of Oreste Ghisalba and the other founding members and increase the scope of pre-competitive information exchange started 15 years ago. This will undoubtedly include further exchange of sequence information as the number of genes available in public databases continues to increase rapidly. We will also look to expand the membership and promote biocatalysis by further assisting in projects such as Innovationsraum Biokatalyse. It is vital that industrial biocatalysis groups in Switzerland retain sufficient 'critical mass' in order to continue innovating and retain their competitive edge. We believe that a vibrant and thriving SIBC acting as an advocate for biocatalysis can be a major contributor in achieving this.

One significant trend expected in the next years is the development of the 'Bioeconomy', *i.e.* the sustainable use of renewable biological resources, which was the subject of a recent review.[2] Although Switzerland has not finished the work on its own Bioeconomy strategy, there are already a number of initiatives including a recent Sustainability Call in connection with the Innovationsraum Biokatalyse Project. This aims partly to 'establish a roadmap for the contribution of biocatalysis to a Swiss Bioeconomy'. One specific area in which biocatalysis might contribute is the use of CO_2 as a renewable feedstock for generation of high-value chemicals. A recent review highlighted a number of carboxylases, dehydrogenases as well as Rubisco to give a flavor of the enzymes which might be employed.[3] Although currently, the vast majority of biocatalytic processes use fossil fuel-based precursors, one can imagine this will change in the coming decades. It is the responsibility of SIBC and similar organizations to keep abreast of these developments and encourage their adoption in the industry.

A recent boost to Swiss catalysis research is the funding of the NCCR SUCHCAT (Sustainable Chemical Processes through Catalysis) project, a multi-center, interdisciplinary, long-term program which aims to accelerate discovery of novel catalytic processes using the most up to date digital and experimental methods. The emphasis will be on utilizing sustainable raw materials to promote a carbon-neutral chemical industry. A biocatalysis module will be hosted at ZHAW under the responsibility of Prof. Rebecca Buller. The SIBC is also part of the SUCHCAT community and will assist in networking between the industrial and academic partners. As such, the program is a great opportunity to embed biocatalysis as part of a future sustainable chemical industry.

4. Perspectives on the Future of Industrial Biocatalysis: An SIBC view

The members of the SIBC were polled on the following questions:

What do you see as the major bottlenecks in the development of improved biocatalysts and how will these likely be overcome?

Education was seen to be critical, especially that of chemists, in the use of biocatalysis. Currently, biocatalysis is seen as complex and expensive in companies with a strong chemistry background and is poorly understood by chemists in general. Improved 'cross-training' of bioscience and chemistry students would produce more open-minded scientists in the future. Installation of equipment for biocatalysis in industrial chemistry labs and appropriate training of staff would also go some way to address these issues. In addition, senior management and decision makers should also be better informed about biocatalysis. If biocatalysis is to fully benefit from the trend towards green, sustainable processes, then education of the public is important as there is currently great opposition to the use of GMOs. From a Pharma perspective, lack of regulatory guidelines and therefore analytical methods for remaining DNA/protein may cause a lack of uptake of biocatalysis in API synthesis. Establishing a regulatory framework for use of enzymes in API synthesis is therefore a priority. Long delivery times for larger amounts of enzyme after a hit is

found in screening is a severe problem in a research environment where timelines are very short. Therefore speeding up large-scale production of enzymes is considered a priority. In crop protection, the high initial investments needed are seen to limit implementation of biocatalysis and unless significant improvements, *e.g.* a reduction in step count, improvement of chemo, stereo-selectivity and a high space-time yield are achieved, the process won't be cost-competitive with chemical approaches especially on >100 T per year products. Nevertheless, the desire and need to run more sustainable processes, the increasing prices of some metals, the diversification of the portfolio to new types of active ingredients (AIs) as well as the need to synthesize metabolites on scale are strong drivers for reconsidering biocatalysis as an economically viable and greener alternative to current processes. Decreasing the time and costs needed for enzyme improvement and application on scale was also seen as very important and will likely be addressed by improved enzyme engineering and prediction tools and high throughput screening technologies. The relatively limited reaction types covered by the commercially available enzymes were also seen as a limiting factor and expanding the biocatalytic toolbox is a necessity. In addition, biocatalysis should be applied as early as possible in process development to allow efficient route scouting, and not after a chemical route has already been established. Increased awareness of downstream processing issues specifically relating to biocatalysis also need to be addressed routinely at an early stage in projects.

What do you see as the major trends in biocatalysis in the next 10 years?

Developments in bioinformatics including artificial intelligence and machine learning have the potential to drive the expansion of the biocatalytic toolbox although they are largely unproven at present. The expectation is for faster development of a broader palette of reaction types that can be applied on large scale. *De novo* protein design and prediction of protein folding are two topics that may also be addressed by these technologies. Improvement in predictive tools will likely reduce the risks involved with applying biocatalysis at an early stage of development. Increased automation of screening and other lab procedures will allow faster progress and higher output without increasing headcount which is very important considering the pressures on costs being applied in most industries. Implementation of enzyme cascades, either in whole cells, or *in vitro*, will further increase the scope of biocatalysis and allow production of high value products from cheap starting materials. Application of retrosynthetic approaches to route scouting will facilitate optimal enzyme selection in conjunction with readily available starting materials.

For information on SIBC, please contact Steven Hanlon directly.

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[1] a) H.-P. Meyer, T. Münch, *BioWorld Europe* **2005**, *1*, 14; b) M. Kittelmann, H.-P. Meyer, B. Wirz, R. Wohlgemuth, *Chimia* **2011**, *64*, 780; c) C. Coppolechia, E. Eichhorn, S. Hanlon, S. Lütz, H.-P. Meyer, M. Schürmann, R. Wohlgemuth, *Catal. Sci. Technol* **2013**, *3*, 29.

[2] A. Aguilar, T. Twardowski, R. Wohlgemuth, *Biotechnol. J.* **2019**, *14*, 1800638.

[3] A. Alissandratos, C. Easton, *Beils. J. Org. Chem.* **2015**, *11*, 2370.

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