EDITORIAL

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"Automated Glycan Assembly Enables the Glycoscience" lecture by Dr. Peter Seeberger at IQS

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The Spanish Royal Society of Chemistry (RSEQ) and the German Chemical Society established in 1990 the Elhuyar-Goldschmidt Award to recognize the achievements of outstanding chemists from both countries. In 2023, the Spanish award was presented to Prof. Dr. Peter Seeberger from the Max-Planck Institute for Colloids and Interfaces, Potsdam, Germany. The Carbohydrates Group of the RSEQ organized a tour in Spain where Prof. Dr. Seeberger delivered a lecture entitled "Automated Glycan Assembly Enables the Glycosciences" in Madrid (November 27th), Sevilla (28th), Bilbao (29th), San Sebastian (30th) and Barcelona (December 1st).

Dr. Seeberger pioneered the field of automated glycan assembly in 2001 (1) and continues with improvements and optimization to deliver automated synthesizers for the preparation of complex glycans. Compared to polynucleotides and polypeptides that are linear polymers, polysaccharides are more diverse, complex and often branched. Whereas automated synthesis of oligonucleotides, genes and peptides has enabled fasts developments in molecular biology, the complexity of carbohydrates has been the bottleneck for investigations into glycan synthesis that hampered access to pure glycans and hence impeded progress in the glycosciences. Automated Glycan Assembly (AGA) is a powerful solid phase-based technology for the construction of homogeneous oligosaccharides, where the growing oligosaccharide is bound to a resin and elongated from reducing end to non-reducing end (2)(3). The general strategy is summarized in Figure 1.

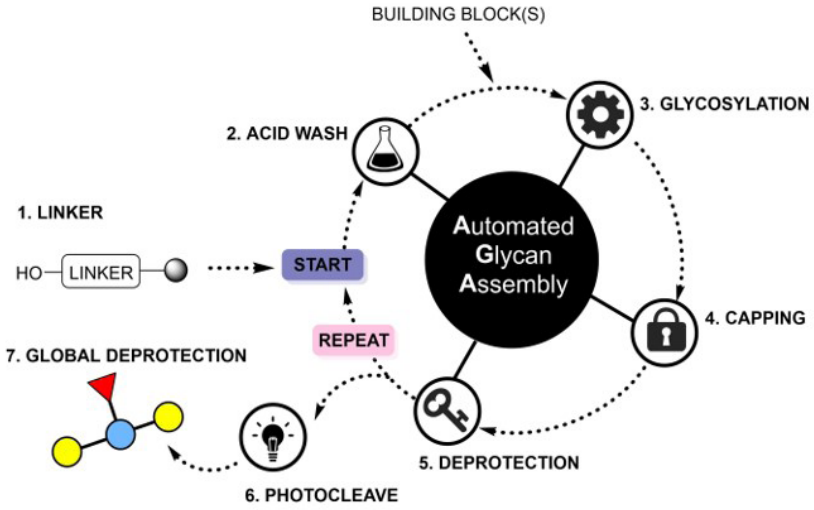

Figure 1. *The automated glycan assembly workflow. Reproduced from (2) with permission of the publisher.*

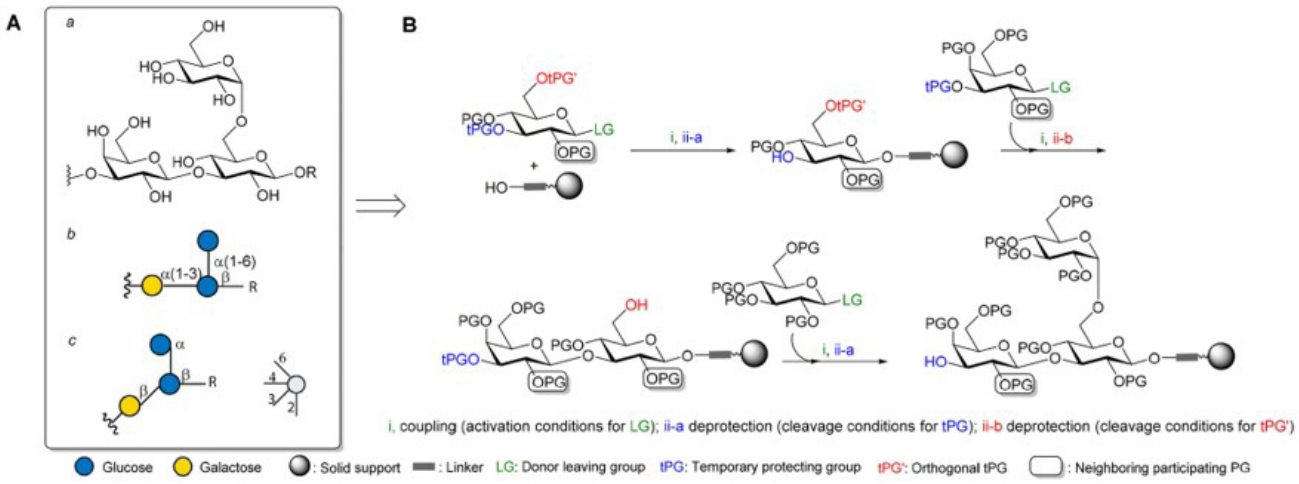

Figure 2. *Segment of a branched oligosaccharide represented with (A.a) chemical structure, (A.b,c) symbol representation. (B) Steps and building blocks required for the assembly of the branched oligosaccharide segment using solid-phase synthesis. Reproduced from (3) (open source).*

It starts with an acidic wash of the resin with a reactive linker to remove any residual base, and the first building block (electrophilic donor), corresponding to the reducing-end sugar of the target glycan to be synthesized, is added to glycosylate the resin. The unreacted electrophile is capped by acetylation and washed out. Next, a temporary protecting group at the intended place of elongation is selectively removed (deprotection) and the cycle is repeated by adding the next building block. When the glycan chain is completed, it is released from the resin and deprotected to remove all the temporary protecting groups to end up with the final glycan structure. The challenge is the proper selection of the protecting groups on the building blocks as they affect the reactivity of the donor and the temporary groups need to be placed at the desired points of elongation. Besides, each building block requires specific conditions for the glycosylation reaction. Figure 2 illustrates an example for the synthesis of a segment of a branched oligosaccharide.

In the last two decades the technology has been improved following significant optimizations in product yields and reaction times since the first proof-of-concept using a modified peptide synthesizer in 2001 to the first commercial Glyconeer 2.1 synthesizer by Dr. Seeberger. Other technologies recently introduced in AGA developments are microwave radiation and flow chemistry. The conventional AGA system requires rapid changes of temperature since glycosylation occurs at sub-zero temperature while deprotection reactions take place at higher temperatures. Introduction of microwave-assisted solid-phase automated glycan assembly accelerates the overall cycle time and expands the temporary protecting group portfolio. On the other hand, flow chemistry reactors have enabled the screening of glycosylation conditions for different building blocks to set up the optimized temperature and reaction times to improve each individual combinations of coupling reactions.

Dr. Seeberger highlighted in his lecture at IQS that the combination of automation platforms, flow chemistry and digital tools for carbohydrate chemistry are enabling technologies in glycan synthesis, yet often investigated in isolation, but with many possible synergies by combining them. All of them will further advance the field, with progress toward the realization of a self-driving lab for glycan synthesis. He presented several applications to the synthesis of complex glycans as target molecules in a broad variety of fields such as polysaccharide materials, vaccines and diagnostics.

About Prof. Dr. Seeberger

Prof. Dr. Peter Seeberger studied chemistry at the University of Erlangen-Nuremberg and completed his PhD in biochemistry in 1995 at the University of Colorado at Boulder. After a postdoctoral stay at the Sloan Kettering Institute for Cancer Research in New York, he was appointed assistant professor at Massachusetts Institute of Technology (MIT) in 1998 and promoted to Firmenich Associate Professor of Chemistry in 2002. After six years as Professor at the Swiss Federal Institute of Technology (ETH) Zurich he assumed positions as Director at the Max-Planck Institute for Colloids and Interfaces in Potsdam and Professor at the Free University of Berlin in 2009. In addition, he serves as honorary Professor at the University of Potsdam. From 2003-2014 he was Affiliate Professor at the Sanford-Burnham Institute for Medical Research (La Jolla, USA). Since 2021, he is a Vice President of the German Research Foundation (DFG), the main funding body in Germany. He is a member of the governing body of the

Max-Planck Society ("Senate") and the Veterinary University (TiHo) Hannover ("Stiftungsrat").

Professor Seeberger's research on the chemistry and biology of carbohydrates, carbohydrate vaccine development and continuous flow synthesis of drug substances spans a broad range of topics from engineering to immunology and has been documented in over 650 peer-reviewed journal articles, four books, more than 60 patents, over 200 published abstracts and more than 950 invited lectures. He is one of the editors of the standard textbook "Essentials of Glycobiology". His work was recognized with more than 40 international awards.

Peter H. Seeberger greatly supports the idea of open access publishing as the Editor-in-Chief of the Beilstein Journal of Organic Chemistry and serves on the editorial advisory boards of many other journals.

Through his work in the area of neglected diseases, Peter Seeberger has become involved in philanthropic causes. He is a co-founder of the Tesfa-Ilg "Hope for Africa" Foundation that aims at improving health care in Ethiopia that recently helped to build a bed-net factory and established an IT training center.

The research in the Seeberger laboratory has given rise to nine successful companies in the USA, Switzerland, Denmark and Germany.

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