Plenary 14

Automated Glycan Synthesis Inspired from Biosynthetic Systems and Their Use in Drug Discovery Research

Shin-Ichiro Nishimura

Graduate School of Advanced Life Science, Hokkaido University, Japan

It is clear that sufficient amount of structurally defined homogeneous samples of nucleic acids and peptides have greatly promoted basic researches and pharmaceutical/medical applications of these biomolecules. Solid-phase chemical synthesis for peptides proposed by Merrifield [1] was utilized for oligonucleotide synthesis, and automated synthesizers based on this methodology were subsequently set afloat. As is the case of glycans, which is the third major class of biopolymers next to nucleic acids and proteins, solid-phase synthesis of oligosaccharide has also been studied [2] since the first report by Frechet and Schuerch [3] in 1971, and Seeberger *et al*. have developed the first automated carbohydrate synthesizer based on solid-phase chemical strategy in 2001.[4] However, solid-phase synthesis of oligosaccharide still involves a longstanding characteristic problem. Although many researchers have developed practical chemical synthetic methods since advent of powerful glycosylation techniques, stereoselective and regioselective glycosylations require multistep syntheses for selective protections/deprotections of hydroxyl groups. Taking access to homogeneous glycans into account, these disadvantages are serious for sequential chemical synthesis on supporting polymer because purification of intermediates are impossible until final cleavage from supporting polymer in order to remove multiple by-products attached on solid support such as α/β isomers, unreacted compounds and so on.

Enzyme-assisted synthesis is an attractive alternative to chemical synthesis because there is the advantage of accomplishing regio- and stereoselective glycosylations for versatile glycoconjugate acceptors according to the substrate specificity inhered to enzymes. As they fundamentally require hydrophilicity for both donor and acceptor substrates, we therefore have developed an enzyme-based strategy applying water-soluble supporting polymers for the construction of various glycoconjugates such as oligosaccharides, sugar derivatives, sphingoglycolipids, and glycopeptides.[5] Herein, we would like to show an improved protocol using dendrimer-based automated synthesis and

the feasibility of some synthetic glycopeptide library in the epitope mapping of anti-KL-6 mAb [6], a clinically important probe for interstitial pneumonia, lung adenocarcinoma, breast cancer, colorectal adenocarcinoma, and hepatocellular carcinoma.

[1] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

[2] Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 19-28.

[3] Frechet, J. M., Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492-496.

[4] Plante, O. J., Palmacci, E. R., Seeberger, P. H. *Science*, **2001**, *291*, 1523-1527.

[5] (a) Nishimura, S.-I., Matsuoka, K., Lee, Y. C. *Tetrahedron Lett.* **1994**, *31*, 5657. (b) Nishimura, S.-I., Yamada, K. *J. Am.Chem. Soc.* **1997**, *119*, 10555. (c) Fumoto, M., Hinou, H., Matsushita, T., Kurogochi, M., Ohta, T., Ito, T., Yamada, K., Takimoto, A., Kondo, H., Inazu, T., Nishimura, S.-I. *Angew. Chem. Int. Ed*. **2005**, *44*, 2534. (d) Fumoto, M., Hinou, H., Ohta, T., Ito, T., Yamada, K., Takimoto, A., Kondo, H., Shimizu, H., Inazu, T., Nakahara, Y., Nishimura, S.-I. *J. Am. Chem. Soc.* **2005**, *127*, 11804-11818.

[6] Oyabu *et al*, submitted.