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Synthetic strategies for production of carbohydrate vaccines

In this project we will develop new approaches for the preparation of glycoconjugate vaccines in which multiple different carbohydrates are attached to specific sites on protein carriers.

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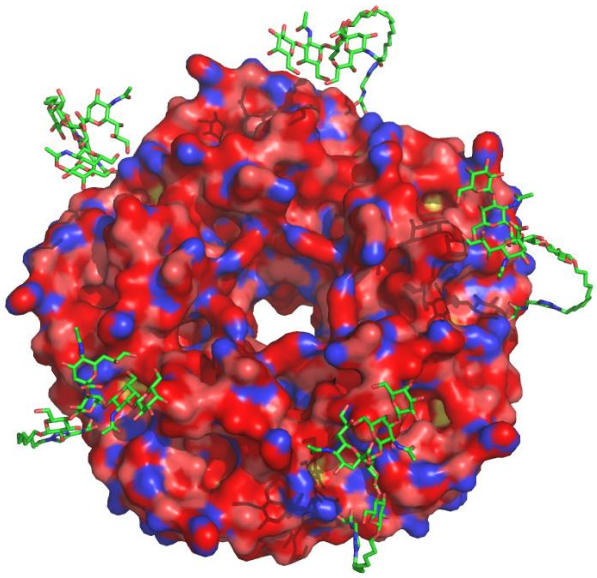
http://www.icenidiagnostics.com/

Cell surface carbohydrates have many biological functions are the unique carbohydrate structures on the surface of bacteria make them good targets for vaccine development.[1] So-called glycoconjugate vaccines for infectious diseases represent a strong emerging market, as evidenced by the recent GSK acquisition of Glycovaxyn and Novartis Vaccines. The use of bacterial capsular polysaccharides as vaccine components has general applicability as prophylactic treatments to protect human and animal health. However, carbohydrates generally make poor immunogens and glycoproteins/glycoconjugates are difficult to manufacture in the homogenous form necessary to pass regulatory scrutiny. **In this project we will develop new approaches for the preparation of glycoconjugate vaccines in which multiple different polysaccharide epitopes are attached to specific sites on protein carriers.**

We have recently developed methods to make chemically defined glycoproteins based on the cholera toxin B-subunit protein.[2] We will use both the cholera toxin B-subunit and reengineered virus capsids as protein scaffolds on which to make the glycoconjugates vaccines. We will use the first automated oligosaccharide synthesizer in the UK to make bacterial glycans for conjugation using complementary chemical and enzymatic conjugation methods. For example, we recently developed a highly efficient enzymatic reaction using the sortase transpeptidase and ester-linked depsipeptide substrates.[3,4] We will investigate if the sortase methods can be combined with two other orthogonal methods already implemented in our lab (oxime ligation and alkyne-azide cycloaddition),[2] to allow introduction of multiple different carbohydrate antigens to the carrier protein at specific sites.



Please contact Dr. Bruce Turnbull (W.B.Turnbull@leeds.ac.uk) for further details about this opportunity.

References

1. The Complex Life of Sugars https://www.youtube.com/watch?v=9uT9dQ-s1yo
2. T. R. Branson, T. E. M^{c}Allister, J. Garcia-Hartjes, M. A. Fascione, J. F. Ross, S. L. Warriner, T. Wennekes, H. Zuilhof and W. B. Turnbull, A protein-based pentavalent inhibitor of the cholera toxin B-subunit, *Angew. Chem. Int. Ed*. **2014**, *53*, 8323-8327.
3. D. J. Williamson, M. A. Fascione, M. E. Webb and W. B. Turnbull, Efficient N-terminal labeling of proteins by use of sortase, *Angew. Chem. Int. Ed*. **2012**, *51*, 9377-9380.
4. D. J. Williamson, M. E. Webb, W. B. Turnbull, Depsipeptide substrates for sortase-mediated N-terminal protein ligation. *Nat. Protoc*. **2014**, *9*, 253-262.