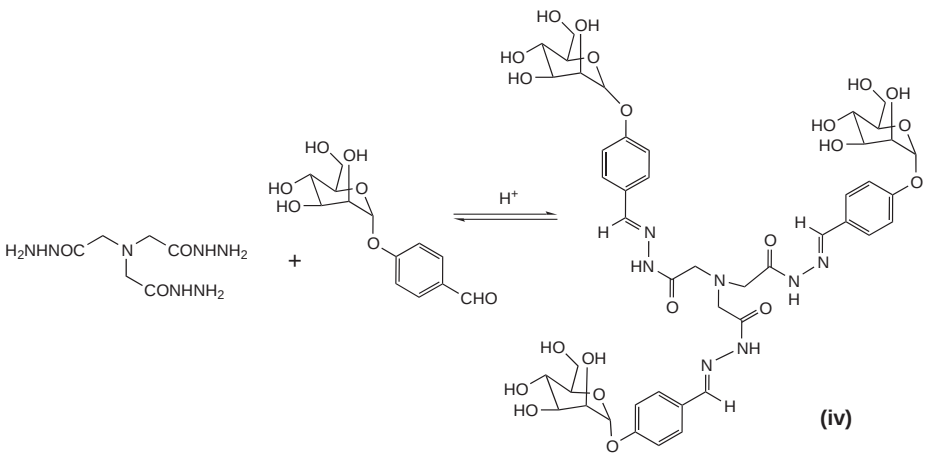

these problems, particularly in forming libraries of dynamically interchanging carbohydrate clusters. To explore the use of DCC in glycobiology, dynamic libraries of constituents that are susceptible to binding to the plant glycoprotein concanavalin A (con A), using the hydrazidecarbonyl–acylhydrazone interconversion as reversible chemistry, has been undertaken [6]. Acylhydrazone libraries were generated from the dynamic assembly of a series of oligohydrazide core building blocks (used to arrange the interactional components in a given geometry) with a set of aldehyde counterparts capable of interacting with the binding site of the target species: this is exemplified by the synthesis of (**iv**). Six naturally occurring carbohydrates were used to generate a library of 474 constituents. To screen the library against con A, an enzyme-linked lectin assay was adopted based on yeast mannan as the immobilized ligand. Several active components were identified from the screening of the library. To pinpoint the active constituents, a deconvolution process relying on the dynamic features of the library was used. Single building blocks were removed from the complete library, resulting in a redistribution of the remaining compounds incorporating that moiety and suppression from the equilibrating pool of all constituents containing the removed components. For each component of the dynamic combinatorial library, a sublibrary was prepared from which all library constituents based on this element were removed. A decrease in inhibitory effect reveals the importance of the removed component in the generation of active compounds in the dynamic library. From the deconvolution process, several active components were identified, of which (**iv**) was one of the most potent with an IC_{50} of 22 μM in binding to con A. This research has demonstrated that lectin ligands can be generated by acylhydrazone formation and exchange, enabling the efficient generation of dynamic combinatorial libraries in aqueous media. The data also indicate that, in the first stage of component selection for establishing dynamic combinatorial libraries, it is beneficial to introduce flexible components to allow for adaptation to the target of the dynamic combinatorial library constituent generated. This research has shown the potential of DCC to refine the preliminary constituents identified as active to more precisely defined structural components.

4 Ganesan, A. (1998) Strategies for the dynamic integration of combinatorial synthesis and screening. *Angew. Chem. Int. Ed. Engl.* 37, 2828–2831

5 Bertozzi, C.R. and Kiessling, L.L. (2001) Chemical glycobiology. *Science* 291, 2357–2364

6 Ramström, O. *et al.* (2004) Dynamic combinatorial carbohydrate libraries: probing the binding site of the concanavalin A lectin. *Chem. Eur. J.* 10, 1711–1715

Paul Edwards

paul.edwards@santhera.com

NEUROSCIENCE

A novel single-strand DNA-repair process has implications for neurodegenerative disease

Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) is a neurodegenerative disease caused by mutations in tyrosyl phophodiesterase 1 (Tdp1). This enzyme removes DNA topoisomerase I peptides from DNA ends during repair, but it is not clear how mutations in this enzyme cause neurodegeneration. El-Khamisy *et al.* have shown that Tdp1 is required in a novel repair process for DNA single-strand breaks (SSBs), which is important in neuronal cells not undergoing DNA repair [1].

Strand breaks were compared in normal and SCAN1 cells after treatment with the topoisomerase I inhibitor, camptothecin (CPT). Unlike normal cells, the SCAN1 cells continued to accumulate strand breaks. These breaks were not repaired even when the cells were moved to a CPT-free medium, showing that SCAN1 cells can't repair CPT-induced DNA breaks.

The authors tested whether strand breaks could occur in cells not undergoing DNA replication. Mimosine was added to the cells to reduce the level of DNA replication. It prevented the accumulation of DNA breaks in normal cells, but only reduced DNA breaks in SCAN1 cells by twofold, showing that half the breaks in SCAN1 cells occur independently of DNA replication. The authors further showed that a large proportion of the breaks were caused in a transcription-dependent manner.

The authors proposed that the SCAN1 cells lacked a Tdp1-dependent SSB repair process. To test this they showed that cell lines with known defects in SSB repair also accumulated CPT-induced strand breaks. The authors also reconstituted Tdp1-dependent SSB repair *in vitro* and showed that extracts prepared from SCAN1 cells were defective in this activity.

It is not clear why defects in single-strand DNA repair only cause phenotypic effects in neurons. It could be due to the high level of oxidative stress in neurons. Consistent with this, the authors also showed that strand breaks persisted in SCAN1 cells in response to oxidative damage, but were repaired in normal cells. Clearly further research is required to fully understand the functions of this pathway.

1 El-Khamisy, S. F. *et al.* (2005) Defective DNA single-strand break repair in spinocerebellar ataxia with axonal neuropathy 1. *Nature* 434, 108–113

Christian Noble

cnoble@nimr.mrc.ac.uk

New insight on the acetylcholine receptor

The nicotinic acetylcholine receptor (AChR) is a neurotransmitter-gated ion channel consisting of a ring of five membrane-spanning subunits. It is found in a variety of tissues, including the autonomic nervous system, the neuromuscular junction and the brain in vertebrates. Agonists such as acetylcholine (Ach), carbamylcholine and nicotine produce an influx of sodium through a ligand-gated ion channel that is associated with nicotinic cholinergic activation. A recent atomic model determined by Nigel Unwin [2] via

1359-6446/05/$ – see front matter PII: S1359-6446(05)03444-6

electron microscopy gives a detailed description of the entire receptor in the closed-channel form at a 4 Å resolution.

This new structure includes the ligand-binding and an intracellular domain allows an unprecedented understanding of the coupling between Ach binding and pore opening. To open the channel ACh has to bind at two sites of widely different affinities. At rest, the receptors possess a relatively low affinity for acetylcholine, but the affinity increases during activation. These functional observations can be explain by the EM structure; in the closed conformation, the ACh-coordinating amino acid side-chains of the a subunits are far apart, which indicates that a rearrangement resulting in the closure of two important loops around the bound ACh molecule is implicated in channel gating. Entry vestibules at both ends of the channel seem to be organized to influence permeation and selectivity and screen out ions other than sodium.

These findings are important for structural biologist and open the door to the study of many mammalian channels and receptors. Electron microscopy is a technique that allows the study of membrane protein under conditions that are close to physiological.

2 Unwin N. (2005) Refined structure of the nicotinic acetylcholine receptor at 4A resolution. *J. Mol. Biol.* 346, 967–989

Muriel Laine
mul2001@med.cornell.edu

IMMUNOLOGY

ABO blood group antigens and HIV-1 transmission

Although many studies have been devoted to searching for genetic factors that confer resistance to HIV-transmission, little is known about the role that blood group antigens may play in viral transmission. A new study published in *Blood* is giving new insights on this matter.

ABO blood groups are carbohydrate antigens that are synthesized by allelic forms of a single glycosyltransferase that catalyses the addition of N-acetylgalactosamine (A) or D-galactose (B) to a core oligosaccaride. The O group is found in individuals homozygote for a truncated form of the ABO transferase and displays the H phenotype, without A or B. ABO antigens are incorporated into the surface glycoproteins and glycolipids of red blood cells. Individuals develop antibodies against the antigens they do not synthesize. This leads to transfusion incompatibility, mediated by complement fixation by these antibodies. Stuart Neil and colleagues addressed the question of whether ABO antigens can be incorporated into the envelope of HIV-1 virions and analyzed the sensitivity of the latter to complement-mediated antibody-dependent inactivation [3].

To this end, the authors produced HIV-1 based vectors pseudotyped with the HXB2 envelope in 293T co-transfected with H (giving the O blood group) and A or B transferases. They showed that the ABO transferases add blood group antigen to the viral envelope protein, gp120. In addition, the authors observed that HIV vectors derived from cells expressing ABO antigens displayed sensitivity to fresh human serum analogous to ABO incompatibility. Furthermore, the authors extended the analysis by showing that HIV-1 grown in primary lymphocytes supplemented with autologous serum acquire ABO antigens. In other words, HIV-1 derived from donor PBMC, a primary cell target of the virus, acquired the 'blood group of the donor', thus confirming that ABO antigens can be passively acquired by PBMC from serum and thus possibly by virions derived under these culture conditions.

Further investigations demonstrated that both active complement and specific anti-AB antibodies play a role in virions' sensitivity to serum. This sensitivity could have implications for the relative risk of transmission between individuals of different blood groups.

3 Neil, S.J.D. *et al.* (2005) HIV-1 incorporates ABO histo-blood group antigens that sensitise virions to complemented-mediated inactivation. *Blood* DOI: 10.1182/blood-2004-11-4267 (Epub. ahead of print; http://www.bloodjournal.org)

Mariam Andrawiss
Mariam_andrawiss@hotmail.com