Glyco-Forum section

Letter to the Glycoforum

Transforming Glycoscience: An Australian Perspective

Deirdre R Coombe1, Christopher Davis2, Geoff Fincher3, Malcolm J McConville4, Nicolle Packer5, Keith A Stubbs6, Spencer J Williams7, and Anne Dell8

1School of Biomedical Science, Curtin University, Perth, Australia; 2Institute for Glycomics, Griffith University, Australia; 3ARC Centre of Excellence in Plant Cell Walls, University of Adelaide, Australia; 4Department of Biochemistry and Molecular Biology and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Australia; 5Department of Chemistry and Biomolecular Sciences, Macquarie University, Australia; 6School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Australia; and 7Department of Life Sciences, Imperial College London, UK

A visit by Anne Dell (Imperial College London) in September 2013 to the University of Western Australia (UWA) under the “Professor-at-Large” scheme run by UWA’s Institute of Advanced Studies provided an opportunity to bring together a selection of students and postdocs from the Perth area with some of Australia’s leading glycoscientists to participate in a workshop: “One year on from the launch of the US National Academies’ Transforming Glycosciences Roadmap: Would Australian glycoscience benefit from enhanced networking?”. After a day of enthusiastic discussion, the title question posed by the workshop received an unequivocal “Yes”. This Letter seeks to capture the essence of the workshop’s roundtable discussions, with the aim of stimulating glycoscientists worldwide to join a debate as to how best to engage with the Roadmap’s recommendations (http://www.nap.edu/catalog.php?record_id=13446) (Hart 2012) for prioritisation of funding for:

- Transformative methods for carbohydrate and glycoconjugate synthesis
- Transformative tools for detection, imaging, separation and structure determination
- Transformative capabilities for perturbing carbohydrate and glycoconjugate structure, recognition, metabolism and biosynthesis
- Development of robust, validated informatic tools
- Establishment of a long-term-funded, stable, integrated, centralized database

Plus:

Integrating glycoscience into relevant disciplines in high school, undergraduate and graduate education.

Workshop Topic 1: Databases and Glycoinformatics

The US National Academy of Sciences report “Transforming Glycoscience: A Roadmap for the Future” argues that an important factor in broadening the appreciation of glycomics is the necessity to develop robust, scalable and standardised bioinformatic platforms to acquire and disseminate information-rich data collections. Whilst important discoveries have been made in the individual disciplines of glycoscience, it is generally recognised that future successes will rely on multi-institutional and multi-disciplinary research initiatives, which have sufficient tools and resources to answer complex questions in biology. The challenge for glyco-biology and glycomics is to address the problem of data analysis, data distribution and the fragmentation of knowledge. This can be achieved by integrating many sources of information into a single and systematic informatics infrastructure entity. As in genomics and proteomics, wide adoption, interest and progress in the glycoscience field will only happen if such resources are made freely available and easily accessible. Equally important is the requirement for data quality – provision of inaccurate, incomplete and unvalidated data will only impede the entry of new researchers into the field and hold back innovation and discovery.

Historically, there have been many initiatives to develop informatics resources for glyco-biology, beginning with the pioneering efforts in 1991 at the Complex Carbohydrate Research Center in the development of CarbBank. Unfortunately their fate has uniformly been the same – when funding support ceases they disappear. This is not unique to glycoinformatics: it took from 1986 to 2003 for the Swiss-Prot proteomics database to become fully established as the invaluable universal protein knowledgebase (UniProt) supported by major NIH funding of a global consortium of European, Swiss and US informatics resources. In the wake of this example, identical challenges exist in the development of an informatics knowledgebase for the glycosciences – as was entertainingly described by Bairoch et al (2004).

In Australia in 2011, funding from the National eResearch Collaboration Tools and Resources (NeCTAR) seeded the

9To whom correspondence should be addressed: e-mail: a.dell@imperial.ac.uk

© The Author 2013. Published by Oxford University Press. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com
development of the UniKarbKB infrastructure for a glyco-
ciences knowledgebase. This initiative built upon the pre-
viously successful glycan structural databases, the Australian
developed GlycoSuiteDB (discontinued 2005) and the EU-
funded EUROCarbDB (discontinued 2010), to offer a
broad, publicly accessible glycomics knowledgebase, derived
from diverse datasets and analytical approaches. We are aiming
at a broadly supported international, world-wide initiative, with
the curated central oligosaccharide structure database (through
which all other information on each glycan structure is linked)
located on the ExPASy server at the Swiss Institute of
Bioinformatics. The model for UniCarbKB is based on the suc-
cessful Swiss-Prot “gold standard” protein database and the
subsequent UniProt international consortium established in pro-
teomics bioinformatics.

The collection, curation, storage, archiving, integration and
deployment of data collections is an immense challenge that
cannot be handled by a single organisation or suite of tools and
databases, but requires international coordination and leverage
of existing capabilities and planned investments. As outlined
above, the major challenge now is obtaining continuing
funding to sustain this knowledgebase and international effort.
Various strategies were discussed including approaches to EBI
and NIH, but it was recognised that such organisations have dif-
ferent research funding priorities and that bioinformatics is dif-
ficult to put into the traditional research grant context. The
shorter term solution may be to continue the current strategy
in which motivated glycobiology research groups, who recognise
the value of the development of such a resource, apply to their
national funding bodies for grants to conduct informatics
aspects as a component of their projects. This approach has
proved successful with our current partners in Switzerland,
Germany, Sweden and Japan, and although relatively small in
dollar value, is already providing the impetus for significant
developments to UniCarbKB based on unified underlying
infrastructure and user interfaces.

**Workshop Topic 2: Synthesis and tools**

The Academies Roadmap highlights the central role that
chemistry plays in providing reference and study materials for
enhancing our understanding of glycoscience. Recognizing the
significant advancements in chemistry required to underpin
future expansion in the discipline, the Roadmap provides ambi-
tious targets to drive enhancements in our capability to chemically
synthesize glycans and glycoconjugates including: targets of
any octasaccharide within 7 years, and any carbohydrate or gly-
coconjugate in milligram to gram amounts within 15 years.

A shortcoming of the Roadmap is that it is short on detail in
suggesting how these targets are to be met. Generally, it is
recognized that while Australia has significant expertise in
carbohydrate chemistry, it is difficult to see how it can play a
leading role in achieving the Roadmap goals, particularly as
this will require industrialization of solid-phase and large-scale
synthesis capabilities. Notably, previous efforts to develop
automated oligosaccharide synthesis technologies (Seeberger
and Werz, 2005; Wu and Wong, 2011) have been achieved
through academic-industry partnerships.

It is noted that Australian scientists have important niche
capabilities in synthesis and tools development, in particular in
carbohydrate recognising protein inhibitor design and synthesis
as exemplified by the role played by the von Itzstein group
in the discovery of the first anti-influenza drug, Relenza®
(zanamivir), marketed by GSK. Moreover, the vibrant
Glycoscience community within Australia provides opportunities
for chemists to be involved in partnerships with glycobiologists
active in the health and plant sciences to deliver bespoke carbo-
ydrate materials "on demand" for specialist projects. This nexus
will be of growing importance to help unravel the burgeoning in-
formation being accumulated from genomics and proteomics,
and to an increasing extent metabolomics, initiatives. In particu-
lar there is a growing need for homogeneous, chemically-derived
reference and study materials that can be used to investigate and
manipulate the biological processes that mono- or polysacchar-
ides orchestrate in cellular and organismal processes.

The recent opening, to industry and academia, of the glyc
array facility at Griffith University’s Institute for Glycomics
may provide additional opportunities for Australian carbohy-
drate chemists to be involved in synthesis of array glycans and
associated study materials. Consideration needs to be given as
to whether a capability to establish solid-phase automated
oligosaccharide synthesis should be established within
Australia, as the carbohydrate synthesizer pioneered by the
Seeberger group may soon become more widely available to
the research community. The challenge here is whether this
capability will be superseded by commercial suppliers, as for
(most) peptide and oligonucleotide synthesis.

**Workshop Topic 3: Development of analytical tools for
glycan characterization**

The Academies Roadmap highlighted the need to develop
transformative tools for detection, imaging and high resolution
structural determination of glycan/carbohydrate structures
derived from biological samples. The challenges of determin-
ing the fine structures of glycan moieties found in glycopro-
teins, glycolipids and proteoglycans, as well as peptide site
occupancy, are well rehearsed. While recent technological
advances in mass spectrometry and NMR have the potential to
make this goal achievable, the workshop identified a number of
challenges. In particular, it was noted that the push behind the
development of biological mass spectrometry and NMR is
coming from the related fields of proteomics and metabolomics,
with the latter “discipline” in particular, having to deal with
similar issues of structural and chemical complexity as the gly-
coscience community. While these advances are beginning to
allow comprehensive profiling of all glycan structures in
complex biological extracts, the rapid rate at which current
mass spectrometry (and to a lesser extent NMR) instrument
platforms are being developed means that it is almost impos-
sible for individual research groups or even institutional core fa-
cilities to maintain state-of-the art analytical facilities as well as
the expertise for these analyses.

This challenge has been partially addressed in Australia with
the establishment of national facilities that provided researchers
from academia, Government and industry with access to the
latest technology and expertise in the ‘omics’, including gen-
omics, proteomics and metabolomics, with the latter two cover-
ing expertise in glycomics. A major, and highly successful
feature of this model, is the distributed nature of these facilities
with each having a hub and several nodes distributed around the country. Funding for both instrument upgrades and personnel is provided from Federal (under the National Capability Research Infrastructure Strategy (NCRIS)) and State governments, as well as host institutions. Similar ‘distributed national facilities’ have been established in the Netherlands, Canada and more recently in the USA (see the NIH Common fund initiative for metabolomics). The further development of core facilities that provide researchers beyond a single institution with state-of-the-art facilities and, particularly in the case of the glycosciences, specialist expertise is likely to be crucial to achieving the Academies Roadmap goal of improving researcher access to transformative analytical tools.

While access to high end mass spectrometry and other analytical technologies is crucial, our group also noted other challenges specific to the glycosciences. In particular, there is anecdotal evidence that major suppliers of biochemical reagents are cutting back on their range of existing speciality glycan reagents, such as linkage-specific enzymes and antibodies. This ‘market gap’ is not being filled by boutique suppliers, leading to a contraction, rather than expansion of the current glycocientist’s tool kit. Such reagents are clearly complementary to mass spectrometry approaches and are likely to assume even greater utility with the emergence of new mass spectrometry imaging techniques where the assignment of structures will require more than just accurate mass.

Another challenge for the glycoscience field that has been highlighted by advances in metabolomics is the need to go beyond the measurement of steady state glycans to structures to measuring rates of synthesis and turnover under different physiological conditions. As an enzyme-directed process, glycosylation is likely to be acutely sensitive and responsive to changes in the availability of sugar nucleotides that are, in turn, reflective of nutrient level, energy state and physiology of cells. Metabolic dynamics can be readily assessed using stable isotope labeling and coupled to existing analytical (mass spectrometry and NMR) techniques. Workshop participants believe that the use of stable isotope labeling to measure the metabolic dynamics of both precursors and mature glycans will increasingly become an area of great activity in the future and that there will be a need to develop flux and mathematical modeling approaches, similar to those being developed within the metabolomics field.

**Workshop Topic 4: Education**

Glycans are one of the four building blocks of life and are involved in virtually all biological processes, and yet students at all levels are taught almost nothing about them. Many of the workshop participants are involved in science teaching and training activities at various levels including biology and chemistry demonstrations for high school students, professional training of high school science teachers, community activities for all age groups, and specialist talks to politicians for funding support. The view was expressed that while these types of activity are important for raising the profile of science in general terms, to attract students into a career specifically within the glycosciences we should focus our attention at the university level. The following points were made about glycosciences in the tertiary education system:

- The fundamental carbohydrate chemistry that underpins glycosciences is often presented at first year level in a workmanlike fashion.
- For biological sciences students, the lecturers are often from chemistry departments and have no interest in or inclination for presenting the chemistry in a biological or functional context.
- Context was considered to be crucial in inspiring student interest in glycosciences given day-to-day applications in fields such as cancer research, other human diseases, human health and nutrition and renewable biofuels. Workshop participants agreed that it should be relatively easy to attract the attention and hence interest of university students in glycoscience-related disciplines in this way.
- Many participants felt that it would be very difficult indeed to change existing curricula to accommodate special sections or lecture blocks on glycosciences.

Specific suggestions as to how the university teaching and curricula problems might be addressed included:

- Use of guest lecturers to excite interest in glycosciences as a way of breaking into established curricula to raise the profile of, and interest in, glycosciences among students
- Capitalizing on opportunities that might present themselves during major changes in undergraduate course structures, as seen in the changes from traditional Honours year courses to coursework and coursework/research M.Sc. degrees.

As a first step in implementing some of the ideas emerging from the workshop, the decision was taken to revitalize The Australia and New Zealand Glycosciences Group (ANZGG) with the view of holding a specialist glycoscience conference in 2014. This not-for-profit organization was originally formed to promote glycoscience in the Australia and New Zealand region. The conference would serve as a focus for educational activities and would assist in highlighting glycoscience as a viable discipline that is well worth supporting. A resurgent ANZGG and regular specialist conferences would help promote a greater understanding of the glycosciences and the importance/relevance of this field to the wider Australian research community and local funding bodies, and may improve future funding opportunities for research with a glycoscience flavour. In addition such an organization may provide a more formal vehicle to provide the Australian perspective to other initiatives being undertaken in the glycoscience area in the US, Europe and Asia.

**References**


