

# conference report

suppressants fenfluramine and dexfenfluramine. These drugs had been among the most widely prescribed medications for obesity when combined with phentermine. Known as 'fen-phen', their success appeared unassailable, but the combination was found to cause malfunction of the heart valves in approximately 30% of patients. After this setback, the number of appetite suppressants under development is again rising: development of obesity therapeutics has increased 453% over the past decade.

The more cautious increase of recent years could be the result of the regulatory difficulties observed with other launched anorectic drugs (Figure 2). Before its approval and launch as Meridia®, Abbott's sibutramine (a serotonin and norepinephrine reuptake inhibitor) had been rejected by the FDA's Endocrinologic and Metabolic Advisory Committee as a result of concerns that the potential risk of elevated blood pressure outweighed the benefits of weight loss; safety and efficacy issues were also raised in Europe, particularly in Belgium and Italy. Roche's widely launched orlistat (Xenical®) inhibits lipase, an enzyme found in the gastrointestinal tract that aids digestion of dietary fat. This results in a marked increase in the amount of

triglycerides excreted in the faeces, rendering it unsuitable for treatment of patients with irritable bowel syndrome or Crohn's disease, and disagreeable for non-sufferers because it results in steatorrhea.

## Continuing research

Although obesity has existed since humans first developed agriculture (the earliest known representation of the human form is the Venus of Willendorf, a 25,000-year-old sculpture of an obese woman), it is only within the past half-century that it has become a widespread medical catastrophe. This is a consequence of advances in the treatment of more traditional killers (e.g. smallpox, cholera and tuberculosis), coupled with an ageing population, and thus it is only recently that weight loss has become vital for health, rather than stylistic, reasons. Because, at the molecular level, obesity does not have one simple, straightforward cause, it is difficult to know how to combat it pharmacologically. The pharmacological approaches through which the appetite suppressants currently in preclinical development mediate their effects are varied (Figure 3), with the pharmacologies of the largest proportion unknown. Many are psychologically active, with serotonin,

neuropeptide Y and even cannabis receptor modifiers present.

The burgeoning market for these drugs and the vast sums of money at stake guarantee that research in this therapeutic area will not slow within the foreseeable future. The notion of a pill that will result in cessation of hunger, and hence easy weight loss, is an extraordinarily beguiling one. Unfortunately, all currently marketed anorectic drugs require dietary modification to have maximum effect with minimal side effects – patients treated with Xenical® must ensure that no more than 30% of the calories in their diets come from fat.

According to the WHO, over one billion adults worldwide are overweight. Nearly five million US adults used prescription weight-loss medication between 1996 and 1998, and half the population of the USA will be obese by 2030. Unless appetites are tamed by medication, or people finally learn to resist temptation, the future looks bleak.

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# conference report

## Glycomics: coming of age across the globe

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Post-translational modifications (PTMs) have been recognized as underlying much of the diversity of the human proteome superimposed on the relatively limited peptide sequence repertoire encoded by the genome [1]. Although comparatively simple PTMs, such as phosphorylation or acylation,

have been targeted extensively for drug discovery, by far the greatest repertoire of structural and functional diversity on proteins is created by another process of PTM, known as glycosylation. Glycosylated proteins (glycoproteins) and other glycoconjugates occur in all compartments of the living cell, and carbohydrate structures are of particular importance on the cell surface, where they

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mediate fundamental processes underlying cell–cell and cell–matrix interactions, cell proliferation and infection. The science of biologically relevant complex carbohydrates has been unified under the term glycobiology [2].

In the USA, many glycobiologists are organized in the Society for Glycobiology (SfG), the annual meetings of which have

# conference report

become a prime venue for the presentation and discussion of cutting edge glycobiology data. The second most important community of glycobiologists exists in Japan under the umbrella of the Japanese Society for Carbohydrate Research (JSCR). The idea of a joint meeting of these societies was conceived about five years ago by Vernon Reinhold (University of New Hampshire, USA), the then President of SfG, and Naoyuki Taniguchi (University of Osaka, Japan). The plan came to fruition when *USA/Japan Glyco 2004* was held 17–20 November 2004, in Honolulu, HI, USA.

This one-track conference, chaired by Marilyn Etzler (University of California, Davis, CA, USA), who was President of SfG in 2004, and Taniguchi, was organized into nine plenary sessions and three poster sessions, followed by a joint session of the US and Japanese Consortia for Glycomics.

## A new direction

From the viewpoint of both the Japanese and US communities, glycomics – the system-wide high-throughput profiling of the human glycosylation and carbohydrate-binding protein repertoire – has emerged as the most exciting new direction in glycosciences. In a session chaired by James Paulson (Scripps Research Institute, CA, USA), who heads the US Consortium for Functional Glycomics (CFG), Ola Blixt (Scripps), Jun Hirabayashi (Research Center for Glycoscience, AIST, Tsukuba, Japan) and Peter H. Seeberger [ETH Zurich and Massachusetts Institute of Technology (MA, USA)] presented various approaches to glycome analysis using both glycan and lectin microarrays. Carolyn Bertozzi and members of her group at the University of California, Berkeley, discussed novel methodologies to specifically label cell-surface glycans *in vivo*, towards the goal of advanced imaging methodologies and potentially novel cancer therapies targeting labeled glycans on tumor antigens [3].

In a related session, high-throughput MS-based approaches to system-wide glycan analysis were discussed by Anne Dell (Imperial College of Science, London, UK) and Akihiko Kameyama (AIST). These topics were expanded on in the joint session of the glycomics consortia. CFG is a large research initiative funded by an NIH core grant to understand

the role of carbohydrate–protein interactions at the cell surface in cell–cell communication. It provides a variety of free resources and tools for glycome analysis to the general research community. CFG has inspired similar initiatives overseas, such as the Japan Consortium for Glycobiology and Glycotechnology – CREST – funded by the Japan Science and Technology Agency. Both initiatives integrate, fund and track research across overlapping disciplines and sets of expertise in the glycosciences.

## Lessons learned: glycosylation in disease

Another exciting session at this conference covered the roles of glycosylation and glycosylation defects in health and disease. Tamao Endo (Tokyo Metropolitan Institute of Gerontology) presented specific glycosyl transferase deficiencies that underlie genetic muscular disorders associated with the dystroglycan complex at the neuromuscular junction, such as Walker–Warburg Syndrome (WWS) and muscle-eye-brain disease (MEB). A novel disease mechanism in cystic fibrosis was proposed by Thomas Scanlin (University of Pennsylvania, PA, USA), wherein the absence of functional cystic fibrosis transductance regulator from the Golgi compartment leads to aberrant glycoprotein processing through mislocalization of essential glycosyltransferases within the Golgi.

Data on cell migration to the bone marrow and skin, mediated by specific protein–carbohydrate interactions, were reviewed by Robert Sackstein (Harvard, USA). Detrimental leukocyte homing to the skin occurs in graft-versus-host disease (GVH) and is mediated through the interaction of E-selectin with cutaneous lymphocyte antigen (CLA), which comprises sialyl Lewis x-capped polylactosamine structures. 4-Fluoro-*N*-acetylglucosamine is a cell-active inhibitor of polylactosamine extension that could be useful in treating GVH [4].

Nobuhiro Yuki (Dokkyo University, Japan) presented *in vivo* evidence proving that antibodies against the GM1 ganglioside elicited by an aberrant immune response to *Campylobacter jejuni* lipo-oligosaccharide cause Guillain-Barré syndrome [5]. Motohiro Kobayashi, from Minoru Fukuda's lab at the Burnham Institute (CA, USA), showed

induction of sulfated sialyl Lewis x-type glycans in *Helicobacter pylori*-infected mucosa that support L-selectin mediated leukocyte recruitment to, and chronic inflammation of, the inner lining of the stomach.

## Making glycoconjugates

Great strides have been made recently in chemoenzymatic synthesis of biologically important glycoconjugates. Seeberger and colleagues used an automatic carbohydrate synthesizer adapted from an Applied Biosystems oligonucleotide synthesizer to generate chemical quantities of a complex hexasaccharide that is produced as a toxin by *Plasmodium falciparum*. Immunizations with this toxin substantially protected mice against malarial acidosis, pulmonary edema, cerebral syndrome and fatality [6]. A vaccine derived from this synthetic malaria toxin is currently being advanced into clinical trials.

Yasuhiro Kajihara (Yokohama City University, Japan) described the total synthesis of a 4972 Da glycopeptide derived from cytotoxic T-lymphocyte antigen-4 with two branched complex sialylated glycans that maintains biological activity and has improved pharmacokinetic properties. In other instances, specific glycosylation can be detrimental to biological half-life and/or efficacy. Taniguchi and colleagues have found that removal of a specific 2-fucosylation from *N*-linked glycans in therapeutic antibodies improves antibody-dependent cell-mediated cytotoxicity by >10-fold.

## Awarding rewarding work

This year's Karl Meyer Award of the Society for Glycobiology for widely recognized major contributions to the field went to the biochemist William J. Lennarz from Stony Brook University (NY, USA) to honour the pioneering studies performed in his laboratory on the biosynthesis and catabolism of glycoproteins and the role of cell surface glycoproteins in fertilization and early development. In his award lecture, Lennarz reviewed the biochemistry of early *N*-glycosylation in the endoplasmic reticulum, which is catalysed by the oligosaccharyl transferase (OT) multiprotein complex. Lennarz summarized a wide spectrum of recent work in this area, including genetic,

# private prescription

biochemical and chemical studies into the catalytic mechanism of OT, as well as the function of each of its subunits [7].

## The pharmaceutical industry's perspective

In summary, *USA/Japan Glyco 2004* provided an exciting snapshot of the state-of-the-art in the field of glycobiology. Glycomics, the system-wide analysis of glycosylation, is maturing rapidly through the use and further development of standardized high-throughput microarray and MS methodologies adapted from cDNA profiling and proteomics. Although most of the cutting-edge basic research in glycobiology is still being done by academics, the potential of glycosylation to improve pharmacokinetic and pharmacodynamic properties of existing recombinant therapeutics has thus far been the focus of pharmaceutical companies (e.g. Amgen,

Neose and Seikagaku). However, the industry is rapidly becoming aware of the potential of glycosylation in drug discovery, specifically glycan-derived drugs [Arixtra™ (Fonda BV), neuraminidase inhibitors and selectin inhibitors] and vaccines (malaria vaccine and 2G12 epitope of HIV gp120), glycosyl and sulfotransferase inhibitors, therapeutic antibodies to disease-relevant carbohydrate epitopes (glycotopes) and unnatural carbohydrate precursors for use in imaging and cell-targeting. Much of this work is being pioneered by small 'biotech' startups, including Abaron Pharmaceuticals (CA, USA), Ancora Pharmaceuticals (MA, USA), Glycomimetics (MD, USA), Selexys (OK, USA) and Thios Pharmaceuticals (CA, USA). We wait with anticipation for the next annual meeting of the Society for Glycobiology, which is to be held 9–12 November 2005, in Boston (MA, USA).

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## A soft approach to hard science?

In a recent article [1], I dealt with the penetration of cartoons into the field of science, the backgrounds of several science cartoonists and their endorsement by eminent scientists. I also alluded to the use of cartoons in the teaching of science. The two tenets on which this is based are: (i) a picture is worth ten thousand words; and (ii) every picture tells a story. Hence, it would be expected that to be successful in this means of visual communication would require an intimate knowledge of both the art of cartooning and the science behind the subject matter. An analysis of the work of an expert in this area should provide some answers.

## Larry Gonick

Probably the most well-known and respected of cartoonists who have applied their craft to unravelling the mysteries of science is Larry Gonick. Born in 1946, he originally studied mathematics at Harvard University, obtaining an MA in 1969. He then spent an academic

## 'Uncovering the mysteries of science with cartoon guides'

year at the Tata Institute of Fundamental Research, Bombay, India, and another year teaching calculus at Harvard before leaving to take up cartooning. After a series of jobs in newspapers in the early 1970s, during which

A thought-provoking tonic on the lighter side



Column by Raymond C. Rowe,  
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Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

he produced comic style columns explaining politics and history, he decided to commit himself to creating a series of non-fiction comic books or cartoon guides. Over the intervening years, he has worked with co-authors to produce the highly successful cartoon guides to genetics (1981) (Figure 1),