IN BRIEF

ANTICANCER DRUGS

Gefitinib-sensitizing *EGFR* mutations in lung cancer activate anti-apoptotic pathways.

Sordella, R. *et al. Sciencexpress* 29 Jul 2004 (doi:10.1126/science.1101637)

Recent findings associating clinical responses in non-small-cell lung cancers (NSCLCs) to the drug gefitinib (Iressa; AstraZeneca) — which inhibits the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) — with activating mutations within the EGFR kinase domain have attracted considerable attention. Sordella *et al.* now provide insight into the underlying mechanism by showing that these mutant EGFRs selectively transduce survival signals on which NSCLCs become dependent.

NEUROLOGICAL DISORDERS

P2X7 receptor inhibition improves recovery after spinal cord injury.

Wang, X. *et al*. *Nature Med.* **10**, 821–827 (2004)

Treatments for spinal cord injury represent a major unmet medical need. Wang and colleagues show that spinal cord injury is associated with prolonged purinergic receptor activation that results in excitotoxicity-based neuronal degeneration, and that the inhibition of this process with antagonists of the P2X7 purine receptor can improve functional recovery after spinal cord injury.

IMAGING

In vivo cancer targeting and imaging with semiconductor quantum dots.

Gao, X. *et al. Nature Biotechnol.* **22**, 969–976 (2004)

The development of highly sensitive and specific probes that lack the inherent limitations of organic dyes and fluorescent proteins could be valuable in molecular imaging and medical diagnostics. Gao *et al.* describe the development of nanoparticle probes based on semiconductor quantum dots that are suitable for *in vivo* targeting and imaging of human prostate cancer cells growing in mice.

BIOTECHNOLOGY

Discovery of an allosteric site in the caspases.

Hardy, J. A. *et al. Proc. Natl Acad. Sci. USA* 16 Aug 2004 (doi:10.1073/pnas.0404781101)

Allosteric regulation of proteins by conformational change is a key means of biological control, but identifying and characterizing novel allosteric sites — which might provide opportunities to develop small molecules that therapeutically regulate protein function — has proved challenging. Hardy and colleagues describe the application of an approach known as 'Tethering', which is based on the reversible formation of disulphide bonds between thiol-containing small molecules and accessible cysteine residues in protein targets, to identify a novel allosteric site in caspases, which are promising drug targets owing to their key role in apoptosis and inflammation.

VACCINES

Sweetness synthesized

It's a sweet approach indeed: extracting the carbohydrate-based fragments from the surface of bacteria and viruses has produced vaccines that have brought much-needed protection against several infectious diseases to millions of people worldwide. Given that the growth methods can be imprecise in terms of controlling the size and configuration of the fragments, and that the purification methods are expensive, rectifying these issues would allow these vaccines to reach more of those people who desperately need them.

Synthesizing polysaccharide fragments efficiently is one option, but because carbohydrate chemistry is so complex it has been difficult to successfully develop a synthetic polysaccharide vaccine until now. Reporting in *Science*, groups from Cuba and Canada describe the first large-scale production and testing of a synthetic polysaccharide vaccine — one that targets the bacterium *Haemophilus influenzae* type B (HiB), a major cause of meningitis in children.

The key to the creation of this vaccine lies in streamlining an existing synthesis process. The multistep process used by a handful of laboratories to synthesize short polysaccharide antigens containing five repeated units of ribosylribitol phosphate (sPRP) was redesigned to include a synthetic pathway with a reduced number of reaction and chromatography purification steps. The group also simplified the method for oligomerization of the repeating units, so that the polysaccharide fragment encompassing the key conformational epitope could be obtained in a single step, as opposed to the previous 16-step process. sPRP was conjugated to a tetanus toxoid (TT) protein, as this stimulates a strong, sustained and specific response.

The sPRP-TT conjugated vaccine was tested in several Phase I trials, culminating in a Phase II trial on 1,141 infants in Cuba, who received sPRP-TT, sPRP-TT mixed with aluminium phosphate (which stimulates the synthesis of PRP-specific antibodies) or a marketed vaccine. Almost all infants receiving sPRP-TT reached antibody titres that indicate long-lived protection against HiB, showing that, at least in this respect, it is comparable to existing HiB vaccines.

All clinical development steps as required by the World Health Organization have been concluded; consequently, the vaccine was registered by Cuban National Control Authorities in November 2003 and is now commercially available under the trade name Quimi-Hib. More than one million doses have already been produced and used in children in Cuba, and larger-scale production is now under way. So synthesis of effective polysaccharide vaccines is a feasible approach: the stage could be set for the development of similar vaccines for other conditions, which would be great news for those currently denied access to existing treatments.

Simon Frantz

References and links

ORIGINAL RESEARCH PAPER: Verez-Bencomo, V. *et al.* A synthetic conjugate polysaccharide vaccine against *Haemophilus influenzae* type B. *Science* **305**, 522–525 (2004)