News in brief

New plan to tackle HIV/AIDS

The National Institutes of Health (NIH) are creating an Executive Committee to produce an integrated plan for AIDS drug discovery and development. This group of ten [including Ellen Feigal [Deputy Director of the National Cancer Institute's (NCI) Division of Cancer Treatment], Carl Dieffenbach [National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS] and Edward Sausville (Associate Director of the NCI's Developmental Therapeutics Program)] will initially set the parameters for determining what additional resources, if any, are required for the program. The group will then consult the Director of the NIH Office of AIDS Research (OAR), Neal Nathanson, concerning allocation of the resources. Existing resources will come from the NCI, the NIAID and the OAR.

The plan aims to optimize utilization of all the NIH resources for the discovery and development of new and improved therapeutics and microbiocides for HIV and its associated complications. The NCI can bring repositories in informatics to the project, as well as research and developments in toxicology, pharmacology and screening. Meanwhile, the NIAID has had successes in developing new concepts in therapeutics and initiating Phase III clinical trials, and has focused on *in vitro* and *in vivo* pathogenesis and developing testing methods.

The NCI and NIAID have also identified research priorities that could be improved. These included the establishment of the NCI's own AIDS research department to coordinate HIV/AIDS research throughout the Institute and the entire NIH. This was later rejected because it would create an overlap with the present NIH OAR. However, this suggestion has led to the NCI coordinating AIDS research activities, with particular focus on therapeutic development in areas not pursued by industry, and to the establishment of an official NCI/NIAID discovery plan. The NCI Developmental Therapeutics Program AIDS Review Group produced a report suggesting the discovery plan, and recommended research into three main pathways not currently pursued by industry, these being TAT (transactivator of transcription), REV (a transdominant negative inhibitor of HIV) and NEF (a down-regulator of CD4 expression that enhances HIV infectivity in peripheral blood lymphocytes).

Epidermal growth factor repeat gene: a new target for brain and lung cancers?

A new human epidermal growth factor (EGF) repeat superfamily member has been identified by researchers at Hyseq (Sunnyvale, CA, USA) using high-throughput screening by hybridization[1]. The *EGFL6* gene maps to human chromosome X and encodes a predicted signal peptide, suggesting that it is secreted. The gene contains 4.5 EGF-like repeat domains, two N-linked glycosylation sites, an integrin association motif (RGD) and a tyrosine phosphorylation site. The EGF repeat superfamily of genes often encodes proteins that control cellular proliferative responses. The transcripts of *EGFL6* are expressed in brain and lung tumour and fetal tissues, but are generally absent from normal adult tissues. This selective expression makes the gene and its expressed protein potential targets for pharmaceutical intervention, as well as potential diagnostic markers for brain and lung cancers.

1 Yeung, G. *et al.* (1999) Cloning of a novel epidermal growth factor repeat containing gene *EGFL6*: Expressed in tumor and fetal tissues. *Genomics* 62, 304–307

Artificial human corneas

An artificial human cornea has been constructed by researchers from the University of Ottawa Eye Institute, Ottawa Hospital (Ontario, Canada), University Laval (Quebec, Canada), University of Tennessee (TN, USA) and Proctor and Gamble (OH, USA), mimicking the three main layers of the cornea, namely the epithelium, stroma and endothelium[2]. Each of these cellular layers was constructed around a biomatrix (cellular scaffolding) using immortalized human corneal cells isolated from the three layers of the human cornea, and were screened for morphological, biochemical and electrophysiological similarity to their human counterparts. The cells in the cornea were then made to replicate indefinitely by using virus genes. The resulting cornea was found to have a high degree of similarity in morphology, biochemical marker expression, transparency, ion and fluid transport and gene expression compared with human corneas.

The production of these artificial corneas should not only reduce, and hopefully eliminate, the need for live animals for toxicity testing of new drugs and potential irritants, but should also provide a much closer model for such tests than current non-primate models. Furthermore, these corneas could help overcome a possible future shortage of corneas for transplantation into patients with injured or diseased corneas.

2 Griffith, M. *et al.* (1999) Functional human corneal equivalents constructed from cell lines. *Science* 286, 2169–2172

Potassium channel interacting proteins: involvement in CNS disorders?

A family of potassium channel interacting proteins (KChIPs) have been

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identified by researchers at Millennium Pharmaceuticals (Cambridge, MA, USA) and Wyeth-Ayerst Research (St Davids, PA, USA) that are thought to associate with, and regulate, the activity of certain potassium ion channels, called A-type channels[3]. These rapidly-inactivating voltage-gated A-type channels are thought to control the electrical signals of the brain and other excitable tissues and, hence, abnormalities in the signals lead to disorders such as anxiety, depression, ischaemia and epilepsy.

It is hoped that this discovery will enable the development of drug screens to identify compounds that modulate the A-type channels in a tissue-selective manner. Hopefully, these compounds might then enable the development of therapies for CNS disorders that do not produce the common cardiac side effects associated with many current therapies. Frank An (Millennium Pharmaceuticals) said, 'We have found that KChIPs restore many important features of the physiological properties of native A-type potassium channels. KChIPs might modulate specific potassium currents and therefore also regulate the excitability of key neurons in the brain. This discovery could prove important to understanding the molecular basis of a wide range of CNS diseases.'

3 An, F.W. *et al.* (2000) Modulation of A-type potassium channels by a family of calcium sensors. *Nature* 403, 553–556

Death signal discovered for *Streptococcus pneumoniae*

Signal transduction via a two-complement system called VncS–VncR has been shown to trigger multiple death pathways in *Streptococcus pneumoniae*, a bacterial strain that is the leading cause of mortality in children. Researchers from St Jude Department of Infectious Diseases (St Jude Children's Research Hospital, Memphis, TN, USA) have shown that the signal sensed by VncS–VncR is a secreted peptide, namely Pep27 (Ref. 4). New antibiotics and other therapies could be targeted to stimulate this death pathway. However, some pneumococci have emerged that can inhibit the pathway, and there is currently no available test to determine whether the bacterial strain is antibiotic tolerant. This new information regarding the death pathway could therefore be used to develop a test to predict tolerant bacteria.

Current antibiotics bind to bacteria to inhibit bacterial growth but do not cause the death of the bacteria, this second process being triggered by the release of certain enzymes from the bacteria itself. Elaine Tuomanen, Chair, St Jude Department of Infectious Diseases, said, 'The newly discovered peptide, Pep27, and death pathway are an integral part of this process. The key to stopping bacterial infections is to determine what causes certain bacteria to grow out of control. What we are getting closer to doing is putting the pneumococcus in a box and it is not going to be able to get out of it. Once we define the box, then we can understand why some bacteria escape and specifically direct the therapy at how bacteria get out of the box.'

4 Novak, R. *et al.* (2000) Signal transduction by a death signal peptide: Uncovering the mechanism of bacterial killing by penicillin. *Mol. Cell* 5, 49–57

Bioflavonoids for chronic prostatitis

A recent study has shown that the bioflavonoid, quercetin, can significantly reduce pain and improve the quality of life of patients with chronic prostatitis syndromes such as nonbacterial chronic prostatitis and prostatodynia[5]. Initial studies with quercetin were disappointing because of the poor bioavailability of the compound. However, reformulation by researchers in the Institute for Male Urology, UCLA School of Medicine (Encino, CA, USA) produced Prosta-Q, for which 82% of patients recorded an improvement in their National Institutes of Health pain and quality of life symptom score of at least 25%.

5 Shoskes, D.A. (1999) Quercetin in men with category III chronic prostatitis: A preliminary prospective, double-blind, placebo-controlled trial. *Urology* 54, 960–963

Project to construct the first high-density SNP map of a human chromosome

A collaboration has been formed to construct the first high-density single nucleotide polymorphism (SNP) map of a human chromosome and corresponding test panel. This project, which will be carried out by Third Wave Technologies (Madison, WA, USA) and the Sanger Centre (Hinxton, Cambridge, UK), will focus on SNPs located on the human chromosome 22, the chromosome for which the complete DNA sequence was recently identified by the Sanger Centre[6].

The study will examine approximately 2000 unique SNPs positioned at ≈40 Kb intervals along the chromosome. David Bentley, Head of Human Genetics at the Sanger Centre, said, 'The utility of SNP maps and disease association studies depends largely on the extent of linkage disequilibrium (LD) or the non-random association of genetic variations across the human genome. This will be the first LD map of any human chromosome, and will provide the paradigm for the use of high-density SNP-based approaches to study complex disease associations and genetic variation.'

6 Dunham, I. (1999) The DNA sequence of human chromosome 22. *Nature* 402, 489–495

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