signature sequence of K^+ channels. But this result did not explain how the channel could maintain such a precise geometry in spite of thermal fluctuations and whether a rigid channel could enable fast conduction.

Unsatisfied by the classic explanation, Noskov *et al.* [5] pushed the study of permeation to another level. Realizing that the difference in size between K^+ and Na^+ ions is much less than the structural changes within the diameter of the selectivity filter – a deviation of 0.15 Å per subunit within the selectivity filter would be sufficient to abolish the preference for K^+ – they addressed the issue of protein flexibility and its influence on ion selectivity directly.

The authors showed, via a series of careful computations, that selectivity is partly controlled locally by the intrinsic carbonyl–carbonyl repulsion in the selectivity filter, and that there is no need for rigidly maintaining a precise pore geometry. This result demonstrates that accounting for the microscopic physical properties is crucial for understanding biological mechanisms in detail.

5 Noskov, S.Y. *et al.* (2004) Control of ion selectivity in potassium channels by electrostatic and dynamic properties of carbonyl ligands. *Nature* 431, 830–834

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Targets and Mechanisms

Bisthiazolium prodrugs with strong oral antimalarial activity

With widespread drug resistance to common antimalarial drugs, much current research is focussed on new compounds unrelated in structure to existing drugs and that act against novel drug targets. Quaternary ammonium compounds that resemble acetylcholine are active against parasite phospholipid biosynthesis. Given that the parasite has to synthesize large quantities of lipid membrane in the course of its 48-hour blood cycle, this represents a potentially excellent target. Unfortunately however, quaternary ammonium compounds are poorly suited as drugs owing to their permanent positive charge and hence low oral bioavailability. Now Vial and co-workers [6] have prepared prodrug precursors of two thiazolium compounds that are rapidly metabolised by human blood plasma enzymes to produce highly active compounds.

Acyclic thioester precursors of the thiazolium target molecules were synthesized and shown to be cyclized to the desired products by esterase enzymes. The metabolites exert powerful antimalarial activity *in vitro*. This ranges from 15 times greater than chloroquine in a chloroquine-sensitive parasite strain, to 200 times in a chloroquine-resistant strain. The prodrugs are similarly active, but an analogue lacking the thioester group that cannot be metabolized to a thiazolium product is essentially inactive. These compounds were found to accumulate in parasites, apparently through interaction with haem. Impressively, they show potent *in vivo* oral antimalarial activity.

6 Vial, H.V. *et al.* (2004) Prodrugs of bisthiazolium salts are orally potent antimalarials. *Proc. Natl. Acad. Sci. U. S. A.* 101, 15458–15463

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Business

Collaborations

Dynavax establishes collaboration with Riken Institute for development of cedar allergy therapeutics for Japanese market

Dynavax Technologies Corporation (http://www.dynavax.com), a biopharmaceutical company developing treatments for allergy, infectious disease and chronic inflammatory disease, has announced the establishment of a collaboration with the Riken Institute for the development of novel cedar tree allergy therapeutics utilizing the company's proprietary immunostimulatory sequence-(ISS-) based therapeutics platform. Cedar tree allergy is a serious public health challenge in Japan, which afflicts >15M sufferers, representing approximately 12% of the country's total population, and is increasingly prevalent.

The principal investigator from the Riken Institute in this collaboration will be Masahiro Sakaguchi, Japan's leading researcher in cedar tree allergy. 'We are honored to collaborate with Dr Sakaguchi and the prestigious Riken Institute with the goal of developing a new approach to treating cedar allergy,' said Dino Dina, President and Chief Executive Officer of Dynavax Technologies. 'Based on data we have generated in multiple clinical trials for ragweed allergy, and the broad application of our proprietary ISS-based technology to a wide range of allergic disorders, we are optimistic that our efforts will lead to development of a safe and effective cedar allergy treatment that provides long-lasting relief from this serious health problem. Considering the pervasiveness of this disorder in Japan, and the need for new interventions, we believe that this collaboration has significant therapeutic as well as commercial potential for our company.'

Under the terms of the two-year collaboration, Dynavax will apply its expertise in the discovery and development of immunostimulatory sequence (ISS)-based allergy therapeutics and develop a cedar antigen-ISS conjugate product. Dr. Sakaguchi, who has performed early animal testing of these therapies with promising results, will further test these therapeutic candidates in his advanced, proprietary animal models of

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cedar pollinosis. In the 1950s, Japan embarked upon a program of widespread reforestation efforts. Cedar trees were chosen due to their rapid rate of growth. Today, cedar trees cover over 12% of the landmass in Japan and produce vast amounts of pollen, which can be seen wafting over the forests in great clouds during the allergy season. Japan today is the world's second largest market for prescription and over-the-counter drugs for treatment of allergy, with over $2 billion in sales of these drugs annually representing approximately 20% of global sales.

Xantos Biomedicine signs service agreement with Serono

Xantos Biomedicine AG (http://www.xantos.de), a leading functional biology and drug discovery company announced that it has signed an agreement with Serono (http://www.serono.com/index.jsp), Europe's leading biotechnology company, to discover new secreted proteins for diagnostics and drug candidates. The terms of the deal were not disclosed.

Xantos will analyse proteins encoded by Serono's proprietary cDNA libraries and apply a cellular assay allowing the identification of only secreted factors. This program will be employed in XantoScreen™, a high-throughput, fully automated gene isolation, transfection and assay system. Xantos will deliver to Serono a cDNA collection with single clones encoding these extracellular molecules with therapeutic and diagnostic relevance.

Michael Kazinski, Xantos' CTO commented: 'we are delighted that a company of Serono's calibre has recognized the value of Xantos technology. Most approaches towards identifying secreted proteins are dependent on bioinformatic annotation, which predicts these molecules based on their leader sequence. However it is known that many of these proteins do not have defined signature sequence and therefore cannot be identified by a bioinformatics approach. Our unbiased, functional approach enables identification of all types of secreted proteins.

Serge Halazy, Head of the Serono Pharmaceutical Research Institute (SPRI) commented: 'we are impressed with Xantos' high-throughput library screening capabilities and extensive experience in assay development, which allows functional analysis of around 100,000 genes in just one month. The identification of therapeutically relevant secreted proteins is key to the success of this project. The collaboration with Xantos enables the realisation of our idea in a time and cost effective manner.'

Roche and Pharmasset join forces to develop new generation hepatitis C therapies

Roche and Pharmasset today announced a partnership to develop nucleoside polymerase inhibitors for the treatment of chronic hepatitis C virus (HCV) infections. Pharmasset will receive an upfront fee, research and development support, and milestone payments that could total $168 million for PSI-6130, the lead nucleoside compound of the partnership. In addition, Pharmasset will receive royalties on product sales and retain certain co-promotion rights in the USA.

PSI-6130 has the potential to offer greater efficacy and activity against the hepatitis C virus, especially when used in combination with Roche's Pegasys and Copegus. For patients not responding to today's standard of care therapy, the addition of nucleoside polymerase inhibitors to their treatment regimen may offer benefit.

'Pharmasset's expertise in nucleoside drug discovery and early stage clinical development combined with Roche's proven track record in bringing new and improved hepatitis C therapies to market is a formula for success,' stated Schaefer Price, Pharmasset's President and CEO. 'The economics of this deal are significant. In addition, this partnership will support Pharmasset's activities toward establishing a commercial infrastructure for our HIV and HCV clinical candidates.'

'We believe that nucleosides are likely to be an important class of drugs in HCV treatment,' said Jonathan K.C. Knowles, President of Global Research. 'PSI-6130 fits perfectly within our virology portfolio. When used in combination with Pegasys and Copegus, this therapy may offer significant benefit to patients who have previously been resistant to treatment, especially those with a difficult to treat virus.'

Business was written by
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People

Appointments

MedImmune Promotes Edward Connor to Executive VP and Chief Medical Officer and Appoints New Senior Executives

MedImmune (http://www.medimmune.com) has announced the promotion of Edward Connor, formerly senior Vice President of clinical development and Chief Medical Officer, to Executive Vice President and Chief Medical Officer. In addition, the company has appointed George Kemble to Vice President, viral vaccines research and development, and general manager of MedImmune's California facilities, and Dirk Reitsma to Vice President, clinical development, oncology. MedImmune has also recently expanded its management team with the additions of Mark Spring, Vice President, finance and controller, and Sam Yonren Vice President, product safety.

'Ed's promotion reflects his many contributions to MedImmune's success over the past 10 years,' said David M. Mott, president and Chief Executive Officer at MedImmune. 'His dedication as a physician to our corporate mission of advancing science for better health has helped to solidify MedImmune's position as a leader in the biotech industry and in bringing innovative and improved products to market.'

'As MedImmune has grown, so has the breadth and depth of our management

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