IN BRIEF

DRUG METABOLISM

MetaSite: understanding metabolism in human cytochromes from the perspective of the chemist.

Cruciani, G. *et al*. *J. Med. Chem.* **48**, 6970–6979 (2005)

During lead optimization, a major consideration of medicinal chemists is predicting the metabolism of the lead compound based on potential sites of degradation. A new computational tool called MetaSite has been developed by Cruciani *et al.* to make it easier for chemists to predict the possible positions at which a chemical could be metabolized and which cytochrome P450 isoforms are likely to be involved. The fully automated method can be used for all cytochrome P450 isoforms for which the three-dimensional structure is known, and should prove invaluable in drug and prodrug design.

HIV

From nonpeptide toward noncarbon protease inhibitors: metallacarboranes as specific and potent inhibitors of HIV protease.

Cigler, P. *et al*. *Proc. Acad. Natl Acad. Sci.* **102**, 15394–15399 (2005)

Currently used HIV pseudopeptide protease inhibitors have limited bioavailability and stability, and are expensive to manufacture. Cigler *et al.* have developed a group of inorganic icosahedral metallacarboranes that potently, specifically and selectively inhibit HIV protease. The most active compound showed promise in antiviral tests and caused no toxicity in tissue culture.

CARDIOTOXICITY

Phosphodiesterase 4D deficiency in the ryanodine-receptor complex promotes heart failure and arrhythmias.

Lehnart, S. E. *et al*. *Cell* **123**, 25–35 (2005)

Phosphodiesterase (PDE) inhibitors are being developed for several major diseases but have been associated with increased mortality from heart failure and arrhythmias in some clinical trials. Lehnart and colleagues show that knocking out the *PDE4* gene in mice results in a phenotype that is more susceptible to progressive cardiomyopathy and arrhythmias. They established that PDE4D3 forms an essential part of the ryanodine-receptor (RyR2) complex required for excitation–contraction coupling in the heart, and that lack of PDE4D in mice results in a 'leaky' channel phenotype known to predispose individuals to heart failure.

INFECTIOUS DISEASES

Small-molecule inhibitor of *Vibrio cholerae* virulence and intestinal colonization.

Hung, D.T. *et al*. *Science* **310**, 670–674 (2005)

A novel approach to developing antibiotic agents is to target the genes involved in bacterial virulence. Hung *et al.* used this strategy to discover potential drugs for cholera. A high-throughput phenotypic screen was used to search for inhibitors of *Vibrio cholerae* virulence factor and identified a small-molecule inhibitor called virstatin. Virstatin prevents the expression of two essential virulence factors in *V. cholerae* and can protect infant mice from intestinal colonization by the pathogen.

ION CHANNELS

Stopping the flow

Ion channels have proven value as drug targets, but the function of many potential targets in this class is unknown. Traditional approaches to elucidating their function, and blocking or enhancing the activity of the channel proteins, have mainly used natural compounds or genetic means, which are laborious, slow and expensive. Reporting in *Nature Biotechnology*, Xu *et al.* present a method to rapidly develop ion-channel inhibitors based on a new systematic antibody design strategy.

An obvious key to developing an effective inhibitory antibody is to direct it to the right spot on its target protein. In their report, the authors tested the idea that pattern recognition in the commonly used Kyte–Doolittle (KD) hydrophobicity analysis of the amino-acid sequence provides a simple, readily accessible and effective basis for identifying target sequences in established as well as uncharacterized ion channels.

On a KD plot, ion-pore-forming channel subunits, such as those comprising the voltage-gated potassium channel family or the transient receptor potential (TRP) calcium channel family, show six predicted membrane-spanning segments (S1–S6). The retrospective analysis of the binding sites of existing inhibitory antibodies led the authors to identify a common localization to the E3 domain, a hydrophilic region situated between S5 and S6 — close to the predicted ion pore. The hydrophobicity pattern allows the identification of E3, but the actual peptide sequence is diverse between different proteins, suggesting that highly specific inhibitory antibodies can be developed.

To test this hypothesis the authors generated polyclonal antibodies that were targeted against the E3 region of four different ion channels, including a TRP- and even a voltage-gated Na^+ channel, which shows greater complexity compared with voltage-gated potassium channels or TRP calcium channels. For all channels the authors managed to produce highly specific antibodies on first attempt that were capable of blocking 50–60% of the respective ion current.

These results suggest that conventional KD plots can successfully predict hot spots for antibody targeting to create ion-channel inhibitors, to provide new specific tools for linking genes to function and possibly for therapeutic uses. Other patterns on KD plots are evident in more distantly related proteins, such as ligand-gated ion channels and transporters, and should provide the foundations for related antibody strategies. These findings could pave the way for the wider adoption of antibody strategies for therapeutic drug development, with the potential to add to the successes of current antibody-based immuno-modulatory and anticancer therapies.

Alexandra Flemming

References and links

ORIGINAL RESEARCH PAPER Xu, S-Z. *et al*. Generation of functional ion-channel tools by E3 targeting. *Nature Biotechnol.* **23**, 1289–1293 (2005)