IN BRIEF

NEURODEGENERATIVE DISEASE

Inhibiting β-secretase in humans

The β-secretase-mediated generation of amyloid-β peptide (Aβ) is involved in the pathogenesis of Alzheimer's disease. This paper describes the characterization of the first orally available non-peptidic β-secretase inhibitor, LY2811376. The β-secretase 1 (BACE1) inhibitor, which was identified by fragment-based screening, lowered Aβ levels in a mouse model of Alzheimer's disease as well as in normal dogs. In healthy volunteers LY2811376 was safe and well tolerated and produced long-lasting reductions in Aβ levels. Although the authors note that non-target-related toxicology prevented the compound from progressing to clinical development, this study shows that BACE1 is a tractable target in humans.

ORIGINAL RESEARCH PAPER May, P. C. *et al.* Robust central reduction of amyloid-β in humans with an orally available, non-peptidic β-secretase inhibitor. *J. Neurosci.* **31**, 16507–16516 (2011)

COMPUTATIONAL CHEMISTRY

Crowd-based enhancement of chemical diversity

Hack *et al.* described a novel approach for enhancing the diversity of chemical libraries. Compounds for potential acquisition (filtered to remove non-drug-like compounds) were added to those in a corporate library, and the overall group was organized into clusters using an algorithm that emphasized common substructures. Clusters that were populated exclusively by external compounds were then presented to medicinal chemists, who used community voting to prioritize which clusters should be acquired. The authors noted that the goal of enhancing the diversity of the chemical library was met, and the voting preferences reflected current views on lead-likeness.

ORIGINAL RESEARCH PAPER Hack, M. C. *et al.* Library enhancement through the wisdom of crowds. *J. Chem. Inf. Model.* 31 Oct 2011 (doi:10.1021/ci200446y)

KINASE INHIBITORS

Analysing kinase inhibitor selectivity

Most small-molecule kinase inhibitors interact with multiple members of the protein kinase family; achieving selective inhibition of specific protein kinases is challenging. These two papers describe studies of kinase inhibitor selectivity. Anastassiadis *et al.* profiled the activity of 178 kinase inhibitors against a panel of 300 protein kinases. They identified kinases that were inhibited by many compounds, as well as kinases that were resistant to small-molecule inhibition, and showed that many off-target interactions occur with seemingly unrelated kinases. They also identified potential lead compounds for orphan kinases and for the development of multitargeted kinase inhibitors. Davis *et al.* tested the interaction of 72 kinase inhibitors with 442 kinases. They showed that, as a group, type II inhibitors — which bind adjacently to the ATP site and prefer an inactive kinase conformation — were generally more selective than type I inhibitors but several individual type I inhibitors were among the most selective identified. Furthermore, they identified a class of inhibitors that was broadly active against a single subfamily of kinases but selective outside that subfamily, and several compounds that were active against orphan kinases. Together, these papers provide information that could aid the identification of selective kinase inhibitors for use as tool compounds, and assist in kinase inhibitor drug discovery.

ORIGINAL RESEARCH PAPERS Anastassiadis, T. *et al.* Comprehensive assay of kinase catalytic activity reveals features of kinase inhibitor selectivity. *Nature Biotech.* **29**, 1039–1045 (2011) | Davis, M. I. *et al.* Comprehensive analysis of kinase inhibitor selectivity. *Nature Biotech.* **29**, 1046–1051 (2011)