

From Selectivity to Polypharmacology: Computational Design of Phosphodiesterase Inhibitors

Phosphodiesterases (PDEs) constitute a structurally related enzyme family in which subtle differences in binding-site structure, dynamics and hydration can determine inhibitor potency and selectivity. This makes PDEs an attractive model system for developing and applying computational approaches in medicinal chemistry.

We first illustrate this using inhibitor design for *Trypanosoma brucei* PDEB1 (TbrPDEB1), where activity against the closely related human PDE4 represents an important anti-target liability. Free-energy perturbation calculations were used to rationalize and predict inhibitor activity profiles across these highly homologous proteins, while molecular dynamics-based approaches provided additional insight into experimentally observed differences in binding kinetics. In particular, analysis of ligand dissociation and binding-site water networks revealed how hydration of a conserved inhibitor–protein interaction can profoundly affect residence time and selectivity.

These studies also illustrate the value of systematically combining structural and ligand information across the PDE family. Building on the original PDEStrIA structure and ligand interaction database, we have recently developed PDEStrIA 2.0 to exploit the expanding structural and chemical information available for phosphodiesterases.

Finally, we show how these computational concepts translate to a different design challenge: rather than maximizing selectivity, we aim to deliberately balance activity at human PDE4 and PDE7 as a potential therapeutic strategy for Alzheimer's disease. Integration of structural bioinformatics, molecular dynamics, free-energy calculations and prospective compound design provides a framework for navigating this transition from selective inhibition to rational polypharmacology.

Curriculum vitae of Prof. Dr. Iwan de Esch

Iwan de Esch is Professor of Medicinal Chemistry (Drug Design & Synthesis) and Head of the Department of Chemistry & Pharmaceutical Sciences at Vrije Universiteit Amsterdam. His research combines computer-aided and structure-based drug design, fragment-based drug discovery, medicinal chemistry and pharmacology to discover and optimise novel small-molecule ligands. After obtaining his PhD at Vrije Universiteit Amsterdam and the University of Cambridge, he conducted postdoctoral research in the Cambridge Drug Design Group before returning to VU Amsterdam in 2003. His work covers several important drug-target classes, including GPCRs and phosphodiesterases, and ranges from computational molecular design to the identification of preclinical drug candidates. He is also co-founder of several drug discovery biotechnology companies.

