The impact of computational design in the discovery of novel NIK and DHODH inhibitors for the treatment of cancers – Dr. Edgar Jacoby

Computer-Assisted Drug Design (CADD) has evolved from a supportive role into a driving force within modern drug discovery. In this presentation, we highlight two case studies where in silico methods played a pivotal role in the identification and optimization of novel small-molecule inhibitors targeting cancer-related enzymes.

The first example focuses on the discovery of azaindoline-based inhibitors of NIK kinase for the treatment of multiple myeloma. During the hit-to-lead phase, a striking stereochemical SAR switch was observed and successfully modelled using free-energy perturbation (FEP+) calculations. Crystallographic and computational analyses revealed that both stereoisomers could establish comparable contacts with the binding pocket, making this an intriguing system from an interaction-energy perspective.

The second case addresses the development of N-heterocyclic 3-pyridyl carboxamide inhibitors of DHODH for acute myelogenous leukaemia. Here, virtual screening combined with traditional hit-finding strategies accelerated assay development and expanded SAR understanding. During lead optimization, in silico FEP+ and WaterMap calculations, together with crystallographic studies, guided the design of improved analogues. Notably, the identification of a key water molecule whose excess binding free energy significantly influenced potency provided an important optimization vector.

Together, these examples illustrate how computational approaches are increasingly integral to drug discovery, enabling more efficient hit identification, mechanistic understanding, and lead optimization.

Curriculum vitae of Dr. Edgar Jacoby

Edgar Jacoby holds a Licence en Sciences Chimiques from Louvain and a Dr.rer.nat. in Computational Chemistry from RWTH Aachen. He conducted postdoctoral research in Molecular Biophysics at Harvard Medical School and the University of Chicago before joining Servier in 1995 as Cadre de Recherches in Molecular Modeling.

In 1999, he moved to Novartis Central Technologies, leading the in silico design of combinatorial compound libraries within the Combinatorial Chemistry group. From 2002 to 2012, he directed the Molecular and Library Informatics group at the Novartis Center of Proteomic Chemistry in Basel. Since 2013, he has been at Johnson & Johnson Innovative Medicine in Beerse as Senior Principal Scientist II in Computer-Aided Drug Design (CADD).