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SUMMARY & MISSION STATEMENT

We develop and apply methods for computer-aided drug design. We are currently interested in epigenetics targets (bromodomains) and RNA-binding proteins (m6A readers).

OVERVIEW

We use a set of computational in-house tools to find novel lead compounds and for lead optimization. The most important of these tools is a program for protein structure-based virtual screening based on docking. A second area of current emphasis is a virtual coupling tool (AutoCouple) to exploit feasible synthesis pathways. This tool is designed to foster the collaboration with Prof. Cristina Nevado's group at the University of Zurich who are experts in organic synthesis. Together, we try to optimize the pharmaceutically relevant properties of candidate molecules. Using the strategies outlined above, we have developed a number of highly active compounds targeting proteins important for the growth of malignant tumors. These include tyrosine kinases, bromodomains, and RNA-binding proteins as the most important protein classes.

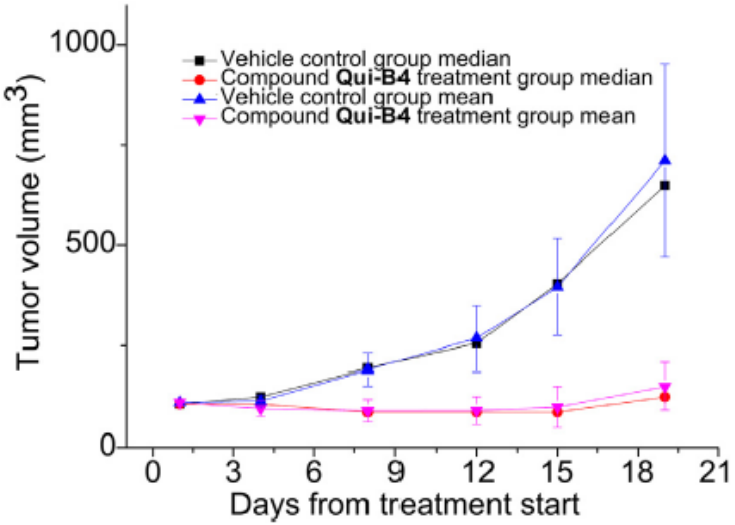
SELECTED CANCER RELATED PUBLICATIONS

Chemical Space Expansion of Bromodomain Ligands Guided by in Silico Virtual Couplings (AutoCouple). Batiste, L., Unzue, A., Dolbois, A., Hassler, F., Wang, X., Deerain, N., Zhu, J., Spiliotopoulos, D., Nevado, C., Caflisch, A. **ACS Cent. Sci.** 2018; 4 180-188

Specificity and mechanism-of-action of the JAK2 tyrosine kinase inhibitors ruxolitinib and SAR302503 (TG101348). Zhou, T., Georgeon, S., Moser, R., Moore, D.J., Caflisch, A., Hantschel, O. **Leukemia** 2014; 28 (2) 404-407.

Pharmacokinetic properties in mice.

Compound	Qui-B4		Qui-C2		Qui-C7	
	IV	PO	IV	PO	IV	PO
Dose (mg/kg)	1	5	1	5	1	5
Cl (mL/min/kg)	42	–	32	–	31	–
V_{ss} (L/kg)	1.6	–	2.2	–	2.2	–
$T_{1/2}$ (h)	1.7	1.7	1.2	5.0	1.1	2.8
AUClast (h ng/mL)	392	493	506	263	533	803
F(%)	–	25	–	10	–	30



(Top) Pharmacokinetics of three tyrosine kinase inhibitors originally discovered in the Caflisch group (UZH, Biochemistry) and optimized in the Nevado group (UZH, Chemistry).
(Bottom) The lead compound Qui-B4 shows cytostatic effects in mice on a tumor xenograft of triple-negative breast cancer cells (MDA-MB231).