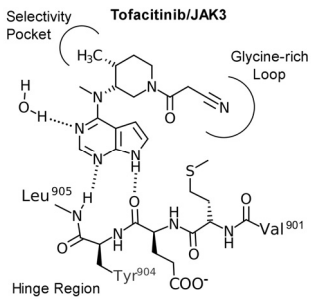
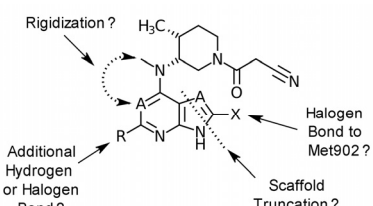
IS01-1 **Raising the Gold Standard: Novel Bioisosteric Hinge-Binding Motifs for Tofacitinib-Derived JAK3 Inhibitors**

M GEHRINGER[2], E PFAFFENROT[2], M FORSTER[2], S. M BAUER[2], ○Stefan LAUFER[1,2]
[1]ドイツ薬学会, [2]テュービンゲン大

Janus kinases (JAKs) are cytosolic tyrosine kinases consisting of four members JAK1-3 and TYK2. While the other JAK family members are ubiquitously expressed, JAK3 is exclusively found in hematopoietic cells, providing a rationale for therapeutic inhibition to suppress inflammation. The current gold standard, pan-JAK inhibitor Tofacitinib, was recently approved by the for treating rheumatoid arthritis.[1] Being poorly selective within the JAK family, this drug suffers from an unfavorable side effect profile which led to its rejection by the European Medicines Agency. Tofacitinib shows narrow SARs. Only one of four stereoisomers is active. The pyrrolopyrimidine core of Tofacitinib binds to the hinge region of the kinase via a bidentate hydrogen bond. As the key promoter of kinome selectivity, the chiral methyl group on the piperidine side chain is buried in a small hydrophobic pocket while the cyanoacetyl residue stacks against the glycine rich loop.[1] Aiming towards more JAK3- selective Tofacitinib analogues with similar potency, we applied a plethora of modifications to its hinge-binding motif. Finally, a rigidization approach led to inhibitors bearing a tricyclic core free- zing the Tofacitinib side chain into its active conformation. Within this series, inhibitors derived from a 3-methyl-1,6-dihydrodo-pyrrolo[2,3-b:2',3'-d]-pyridine scaffold proved to be extremely potent against JAK3. Subnanomolar IC_{50}'s, >10-fold selectivity within the JAK family and good cellular activity were achieved.[2]





[1] J. E. Chrencik *et al.*, *J. Mol. Biol.* **2010**, *400(3)*, 413-433, [2] M. Gehringer *et al.*, *ChemMedChem* **2014**, *9(2)*, 277-281.