PYRROLOPYRIMIDINES AND PURINES AS CSF1R INHIBITORS.

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The colony-stimulating factor 1 receptor (CSF1R) is a tyrosine kinase expressed among others on monocytes, macrophages, microglial cells, and bone resorbing osteoclasts. Activation of CSF1R and downstream signalling, is necessary for normal function of these cell types. However, in some diseases, overexpression of CSF-1 and/or elevated activity of CSF1R cause a misbalance of the immune cell phenotypes. Thus, CSF1R inhibitors might be relevant in cancers, CNS and bone diseases. We have investigated pyrrolopurimidines and purines as CSF1R inhibitors [1-4]. An X-ray co-crystal structure of one of the front runner inhibitors allowed for rational design and indentification of a high number of compounds being more active than the reference drug PLX3397 in enzymatic studies. Hurdles for progressiong these inhibitors into lead compounds will be discussed, alongside their kinase activation state preferences.

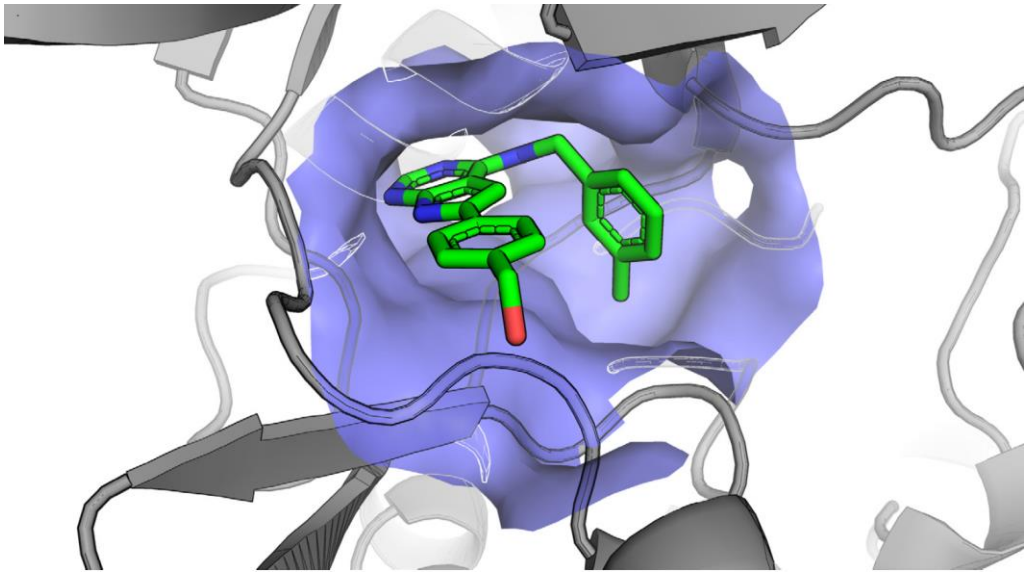

Figure 1: Front view of CSF1R inhibitor co-crystallesed with the CSF1R kinase domain.

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