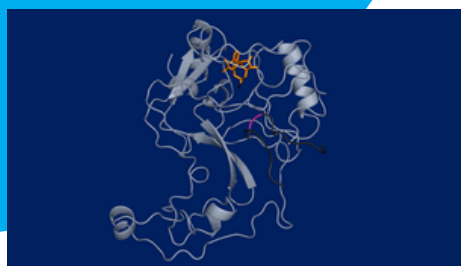
Design and optimization process for the production of specific protein lysine methyltransferases inhibitors

Technologie-Lizenz-Büro
der Baden-Württembergischen
Hochschulen GmbH

Design and optimization process to produce specific protein lysine methyltransferases inhibitors based on super-substrates as lead structures.

- Predictable cost-efficient pathway to the design of super-substrates
- Super-substrates can be used as lead structures to generate small molecule PKMT inhibitors
- This approach dramatically reduces the search space for small molecule inhibitors
- By design, super-substrate derived inhibitors are PKMT specific



Fields of application

Design of specific PKMT inhibitors for applications in clinics and basic research

Background

Protein lysine methyltransferases (PKMTs) constitute a large family of epigenetic writers that catalyse the transfer of a methyl group from the cofactor S-adenosyl-L-methionine (SAM) to histone- and non-histone-specific substrates. In this way, PKMTs mediate a wide variety of chromatin-controlled processes such as transcription, DNA repair and DNA replication. Impaired expression and activity of these enzymes have been linked to cancer, developmental disorders and other pathologies. Therefore, therapeutic compounds targeting specific PKMTs are of greatest interest, although overall drug discovery in this field is relatively underdeveloped.

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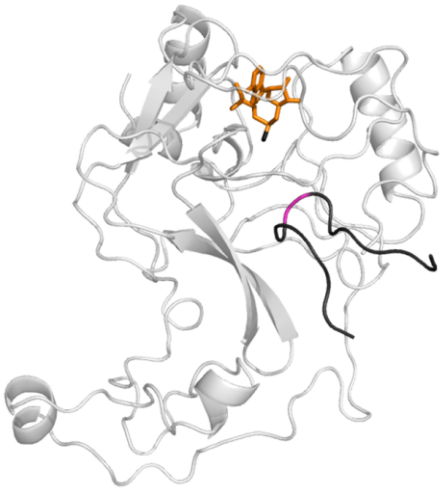
Service
Technologie-Lizenz-Büro GmbH has been entrusted with exploiting this technology and assisting companies in obtaining licenses.

Problem

In conventional approaches to inhibit PKMTs, attempts are often made to disrupt the interaction between PKMT and the cofactor SAM. However, the use of SAM inhibitors is problematic with regard to the specificity of the molecules, as the cofactor is also a methyl group donor for other methyltransferase families. It is therefore necessary to find inhibitors that specifically regulate or inhibit only the desired PKMT, ideally those PKMT that are involved in cancer and other diseases. Screening methods are often blindfold-shot gun approaches with a high screening demand. Lead structures as starting points can highly reduce screening costs.

Solution

Prof. Jeltsch's research group at the University of Stuttgart has developed a new concept for the inhibition of specific PKMTs based on so-called super-substrates. Super-substrates are peptide sequences designed and optimized to be methylated by the PKMT of interest much more efficiently than natural histone sequences. In the next step, they could be converted to PKMT specific inhibitors, used as lead structure for the development of small molecule PKMT inhibitors. This new class of inhibitors binds to the part of the PKMT active site where substrate peptides normally bind. Therefore, the super-substrate derived inhibitors could act as competitive inhibitors and block the access to the histone peptides or the binding pocket. As a result, the methyl groups can no longer be transferred to external substrates and the (hyper)activity of the PKMT is reduced. The mechanistic basis for the improved binding of this new class of inhibitors lies in a hairpin conformation that allows easier access to the active site of the enzyme. The advantage of this approach is the expected high PKMT specificity, as the substrate binding regions of different PKMT active sites are very different, in contrast to SAM binding sites, which are similar in all Methyltransferases. Therefore, these peptide inhibitors do not interact with other families of methyltransferases and only with certain PKMTs. Super-substrates for SETD2 and NSD2 have already been found, and the development of inhibitors based on these peptides has been shown in proof on concept experiments. The search for further super-substrates for other PKMTs are underway.



Structure of the SETD2 PKMT (grey) in complex with a bound peptide inhibitor (black, target lysine in pink) and SAM (orange). Source: IBTB/Uni Stuttgart.

Literature and links

Schnee P. et al., Communications Chemistry (2022)5:139, *Mechanistic basis of the increased methylation activity of the SETD2 protein lysine methyltransferase towards a designed super-substrate peptide.* https://doi.org/10.1038/s42004-022-00753-w