Discovery of selective diacylglycerol lipase β inhibitors

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Propositions

Accompanying the thesis

Discovery of selective diacylglycerol lipase β inhibitors

1. Selective inhibitors for DAGLα and DAGLβ are essential to harness their therapeutic potential from both safety and efficacy perspectives.

   This thesis, Chapter 1.

2. KT109, initially promoted as a selective DAGLβ inhibitor, lacks the anticipated selectivity.

   Hsu, K.-L. *et al. Nat. Chem. Biol.* **8**, 999–1007 (2012); This thesis, Chapter 2.

3. Acid/base properties are often overlooked during prospective design unless it has been established that a certain ionization state (e.g. carboxylic acid or quaternary base) is required for activity.

   This thesis, Chapter 3.

4. The inability to detect the enzyme DAGLα does not necessarily negate its existence and functional significance.

   This thesis, Chapter 5.

5. Location plays a critical role in modulating metabolic enzymes, thereby driving signaling.

   Jung, K. M. *et al. Mol. Pharmacol.* **80**, 60–67 (2011); This thesis, Chapter 5.

6. Allosteric modulators offer a distinct advantage over orthosteric modulators by enabling a level of selectivity that is often hard to achieve with many orthosteric modulators.

7. Drug repositioning/repurposing offers a valuable alternative way for the discovery of effective treatments.
   Gounder, M. *et al. N. Engl. J. Med.* **388**, 898–912 (2023).

8. The COVID-19 pandemic has shown how sharing data and fostering collaboration can expedite the development of medicines and treatments.

9. The generation and publication of negative data are fundamental to the scientific enterprise, yet there is often an overwhelming emphasis on positive findings.

10. Reading about others' experiences helps you know yourself a little better.

Na Zhu

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