Application of a quantitative systems pharmacology (QSP) model to evaluate xCT inhibition as a target for central nervous system diseases.

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Introduction

• Neuronal excitotoxicity, often mediated by glutamate, has been implicated as a factor in a number of central nervous system (CNS) diseases.
• In order to improve the understanding of the role of the cysteine-glutamate transporter (xCT) in excitotoxicity and CNS diseases and the potential utility of xCT inhibitors, Sanofi and Rosa collaborated in the development of a CNS PhysiPDR® Research Platform, a QSP model that supported hypothesis generation and testing.

Objectives

• Evaluate the degree of xCT inhibition required to reduce CNS glutamate levels below neurotoxic levels and retain normal microglial phagocytic function.
• Provide guidance on the CNS indications most likely to respond to this mechanism of action.

Methods

The CNS PhysiPDR® Research Platform is an ordinary differential equation-based Platform that represents:
• Cell dynamics of microglial activation, neuronal stress and death.
• Synthesis/expression and metabolism of mediators and surface markers.
• xCT function (amino acid transport) and dysfunction in processes associated with multiple sclerosis (MS) and Alzheimer’s disease (AD).
• Glutathione (GSH) metabolism in healthy white and gray matter.
• Effects of treatment by xCT inhibitors.

Publicly available literature were analyzed to provide guidance for the representation of white and gray matter in health, multiple sclerosis (MS) and Alzheimer’s disease (AD) (References 1-11).

Properties of xCT inhibitor compounds were provided by Sanofi for representation in the Platform.

Results

• The CNS Platform reproduced in vitro results, supporting current understanding of biological mechanisms of action.
• Simulation research informed key recommendations:
  – In vitro experiments to resolve material uncertainties and reduce risk.
  – Prioritization of MS as lead therapeutic indication.

In Vivo Simulation Results

Different versions of the Platform were created to represent in vivo white matter (relevant for MS) and in vivo gray matter (relevant for AD). Administration of Sanofi’s xCT inhibitor compounds was simulated to assess potential in vivo efficacy.
• MS simulations (white matter) of xCT inhibition suggested dose-dependent reductions in glutamate release, axonal injury, and death of oligodendrocytes (Figure 5).
• AD simulations (gray matter) of xCT inhibition suggested limited benefits on glutamate release and neuronal death (Figure 6).
• Decreased glutamate release and GSH production in response to xCT inhibition increased oxidative stress (Figure 7). Similar results were seen in MS simulations (not shown).

Conclusions

• Results from simulated xCT inhibition in the CNS PhysioPDR Research Platform supported the prioritization of MS over AD as the lead therapeutic indication.
• In MS, glutamate is increased and leads to excitotoxicity of oligodendrocytes and axonal damage, and xCT is likely to contribute significantly to extracellular glutamate concentration.
• For AD, the therapeutic rationale is mixed. While glutamate is locally and transiently increased, xCT contribution appears to be initially limited.
• Simulation research and insights led to focused recommendations for in vitro experiments to resolve material uncertainties in the understanding of xCT function and to reduce risk in the development program.
• The research illustrates the key role that QSP modeling can play in providing quantitative integration of internal and external knowledge, mechanistic insight and decision support in early stage drug discovery.

References


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