Targeting neglected parasitic diseases with human EGFR inhibitor chemotypes

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ABSTRACT
Neglected tropical diseases affect over 1 billion people and collectively result in 550,000 deaths each year. The family of trypanosomatid parasites is responsible for a range of diseases, including African sleeping sickness (T. brucei), Chagas disease (T. cruzi) and leishmaniasis (Leishmania sp.). The current treatments for these diseases are suboptimal; many are toxic, have poor oral bioavailability, and resistance to many of these drugs is emerging. Consequently, there is a dire need for new chemotherapeutics that target neglected tropical diseases. We have applied a target class repurposing approach and identified that the tyrosine kinase inhibitor lapatinib has a GI50 of 1.84 µM against T. brucei. Notably, despite the observation of tyrosine phosphorylation within trypanosomes, the parasite does not express receptor tyrosine kinases. Therefore, the parasite must have a dual-specificity kinase that binds the lapatinib chemotype. Based on this, we have developed structure activity relationship (SAR) studies on a range of other established human EGFR inhibitor scaffolds and three protozoan parasites: Plasmodium falciparum, Leishmania major, and T. cruzi.

SYNTHETIC ROUTE

TARGET REPURPOSING

PARASITIC DISEASES

Human African trypanosomiasis - T. brucei gambiense and T.b. rhodesiense
Malaria - Plasmodium falciparum
Chagas Disease – T. cruzi
Leishmaniasis - Leishmania major (cutaneous) and L. donovani (visceral)

Four tropical and neglected diseases transmitted by protozoan parasites:
• Transmitted by insect bite mainly in tropical, developing countries
• Collectively lead to 47.6 million disability-adjusted life-years (DALYs)
• Current drugs toxic, not orally bioavailable, and resistance emerging
• Pharmaceutical companies avoid due to lack of financial incentives

Tyrosine kinases in protozoa:
• No receptor tyrosine kinases in trypanosomatids (Trypanosoma, Leishmania)
• Tyrosine phosphorylation likely achieved by dual-specificity kinases
• The human epidermal growth factor receptor (EGFR) inhibitor lapatinib binds to four T. brucei kinases and the chemotype inhibits parasite growth in multiple protozoan pathogens

Question: Can related tyrosine kinase inhibitor chemotypes show similar effects?

LAPATINIB & RELATED COMPOUNDS

SYNTHETIC ROUTE

INHIBITION PROFILES

Malaria

Leishmaniasis

T. Cruzi

SUMMARY AND FUTURE PLANS

This study successfully used a drug repurposing approach to cross-screen both [3,2-d] and [2,3-d] thienopyrimidines against four parasitic diseases and found several analogs with sub-micromolar potency. The future of the project is to optimize these potent compounds for cellular selectivity and pharmacokinetics. Overall, these analogs need improved properties for site-specific targeting (eg CNS exposure for HAT).

REFERENCES & ACKNOWLEDGEMENTS


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