Developing Therapeutics to Reduce Cryptosporidium Morbidity and Mortality Among Children in Low-Resource Settings

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Introduction

- Cryptosporidium is an intestinal protozoan parasite that is a major cause of diarrheal disease among young children in low-resource settings.1,2
- Beyond diarrheal disease, cryptosporidiosis is associated with other chronic conditions, including growth faltering, enteric dysfunction, and possibly impaired cognitive development.3
- Current therapeutic options are limited, with only one drug, nitazoxanide, approved by the United States Food and Drug Administration. Metronidazole is not approved for children under 1 year of age and has limited efficacy in malnourished children.4
- There is only one drug in clinical trials against Cryptosporidium: clofazimine, a repurposed leprosy drug developed more than three decades ago. There are no vaccines for Cryptosporidium approved or in clinical development.

PATH Cryptosporidium Portfolio

PATH actively engages with academic and industry partners to advance anti-Cryptosporidium drug development projects. Some of our current projects include:

1. Calcium-dependent protein kinase 1 (CDPK1) “bumped kinase inhibitors,” with the University of Washington (Van Voorhis lab).
2. Methionyl-tRNA synthetase (MetRS) inhibitors, with the University of Washington (Fan and Buckner labs), the University of Vermont (Huston lab), and Takeda Pharmaceutical Company Limited.
3. Celgene phenotypic screen, with Celgene Global Health, the University of Washington (Van Voorhis lab), and the University of Vermont (Huston lab).
4. Symposium on Innovative Therapeutics for Cryptosporidium, a biannual gathering of Cryptosporidium researchers from around the world.

Crypto Target Product Profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ideal</th>
<th>Minimum essential</th>
<th>Nitazoxanide (NTZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Cryptosporidiosis, diarrhea-associated or asymptomatic</td>
<td>Cryptosporidiosis resulting in diarrhea (acute or persistent)</td>
<td>Diarrhea due to C. parvum (or Giardia)</td>
</tr>
<tr>
<td>Target age</td>
<td>Children ≥2 months and adults</td>
<td>Children ≥2 months and adults</td>
<td>Children ≥2 months and adults</td>
</tr>
<tr>
<td>Target population</td>
<td>Malnourished, immunocompromised, and/or HIV-positive</td>
<td>Malnourished, immunocompetent</td>
<td>Malnourished, immunocompetent</td>
</tr>
<tr>
<td>Regimen</td>
<td>Single dose</td>
<td>BID x3 days</td>
<td>BID x3 days</td>
</tr>
<tr>
<td>Clinical efficacy (Cessation of diarrhea)</td>
<td>≥90% of patients in 2 days</td>
<td>Superior to NTZ in malnourished children</td>
<td>Malnourished children: ≥50% in 7–10 days Non-malnourished children: ≥90% in 7–10 days</td>
</tr>
<tr>
<td>Microbiological efficacy (Cessation of shedding)</td>
<td>≥90% of patients in 2 days</td>
<td>Non-inferior to NTZ in immunocompetent adults</td>
<td>≥90% of patients in 7–10 days</td>
</tr>
<tr>
<td>Safety</td>
<td>Safe for syndromic treatment of diarrhea in patients ≥2 months</td>
<td>Safe in patients ≥2 months</td>
<td>Safe in patients ≥2 months</td>
</tr>
<tr>
<td>Cost</td>
<td>US$1.00</td>
<td>US$2.00</td>
<td>US$3.00 (generic)</td>
</tr>
</tbody>
</table>

Table 1. Target Product Profile (TPP) for a new treatment for cryptosporidiosis. This TPP is the consensus result of discussions among the members of the Bill & Melinda Gates Foundation Cryptosporidium Drug Accelerator.

Figure 1. Schematic of interferon gamma knockout mouse model (IFN-γ KO) with Nluc-expressing C. parvum.5 Mice (N=3 per treatment group) are infected with 1,000 oocysts on day 0 and then dosed with test compounds by oral gavage on days 6–10. Fecal samples are collected daily during the dosing period, and then every 2-3 days until day 20. Parasite levels are determined by relative luciferase units (RLU) normalized to mass of the stool samples.

Figure 2. Structures of representative MetRS inhibitors compounds.

Figure 3. CpMetRS inhibitors 2093, 2114, and 2259 are active in the IFN-γ KO mouse model. Y-axis: relative luciferase units in pooled fecal samples collected from mice infected with Nluc-expressing C. parvum. Untreated control mice were euthanized on day 10 post-infection (PI) due to morbidity. 1369 is a CDPK1 bumped kinase inhibitor used as a positive control.

Figure 4. CELG-001 is active in the IFN-γ KO mouse model. Y-axis: relative luciferase units in pooled fecal samples collected from mice infected with Nluc-expressing C. parvum. Untreated control mice and mice treated with CELG-001 at 5 mg/kg QD were euthanized on day 13 post-infection (PI) due to morbidity. 1369 is a CDPK1 bumped kinase inhibitor used as a positive control.

Conclusions

PATH and collaborators have developed a promising portfolio of lead optimization stage drug candidates against Cryptosporidium with potential to meet Target Candidate Profile and Target Product Profile criteria.

References


Acknowledgments

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