Discovery and Development of Novel Benzoxaboroles to Treat Kinetoplastid Diseases

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Boron has a Unique Bonding Orbital Configuration: An Empty P-Orbital

- Boron has an empty P-orbital & can form a new bond under specific conditions
- The new bond forms a tetrahedral structure
- Exploitation of P-Orbital Expands Drug Design Possibilities

History and Overview of Boronic Acid Drug Discovery Efforts

- Design of boronic acid enzyme inhibitors initiated in 1970s

\[
\text{RBOH} + \text{HO-Enz} \rightleftharpoons \text{RBO(Enz)}^{-} \quad \text{Mimic of} \quad \text{RCONH(Enz)}^{-}
\]

- Multiple disease targets have been pursued

- Velcade® (bortezomib) was approved by FDA in 2008 for use in multiple myeloma

- KERYDIN™ (tavaborole) topical solution, 5% was approved by FDA in 2014 for topical treatment of onychomycosis

Summary of Modes of Interaction of Anacor Boron Compounds with Biological Targets

All shown by X-Ray Crystallography

Covalent Boron Interaction with Activated Cis-diol

LeuRS Inhibitor

Covalent Boron Interaction with NAD⁺ OH

Oxidoreductases

Covalent Boron Interaction with Activated OH of Serine

Serine Protease

Oxaborole Metal Chelating Interaction

PDE4

Novel chemistry
Broad target applicability
High selectivity

Covalent Bonding
Metal Interaction
Hydrogen bonding

Conventional Hydrogen Bonding Interaction

Kinase Inhibitor

Anacor’s Boron Chemistry Pipeline for Neglected Diseases

Parasitic Diseases

- African Sleeping Sickness (HAT)
- Visceral Leishmaniasis
- Chagas disease
- Malaria – Lead Series
- Malaria (New Scaffolds)
- River Blindness (Macrofilaricide)
- River Blindness (Wolbachia)
- African Animal Trypanosomiasis
- Cutaneous Leishmaniasis

Bacterial Diseases

- Tuberculosis (TB) LeuRS
- TB (non-LeuRS)
- TB new targets

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Anacor’s Boron Chemistry Technology Has Delivered 8 Drug Candidates

**Clinical Candidates**

- **Antifungal**
  - KERYDIN™
  - FDA Approved

- **Anti-inflammatory**
  - AN2728
  - Phase 3

- **Antibacterial**
  - AN3365
  - Phase 2

- **Antitrypanosome**
  - SCYX-7158 (AN5568)
  - Phase 1 completed

**Preclinical Candidates**

- **Antibacterial**
  - Preclinical Candidate

- **Antitubercular**
  - Preclinical Candidate

- **Antimalarial**
  - Advanced Lead

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Human African Trypanosomiasis (HAT): “Sleeping Sickness”

- Caused by the single cell parasite *Trypanosoma brucei* sp.
- Transmitted through bite of tsetse fly
- 55 million at risk in 36 countries in sub-Saharan Africa\(^1\)
  - Estimated 10-20 thousand deaths per year
- Disease progresses through two stages; timing dependent upon parasite strain
  - Stage 1 HAT: Parasites restricted to blood, symptoms are mild
  - Stage 2 HAT: Parasites have invaded the brain, symptoms are more severe, ultimately leads to coma and death\(^2\)

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HAT Collaboration: Partners

- **Anacor (Palo Alto, California)**
  - Founded in 2002; drug discovery company based on a boron chemistry platform; products and clinical candidates in anti-fungal, anti-inflammatory and anti-infective applications

- **Drugs for Neglected Diseases initiative (Geneva, Switzerland)**
  - Founded in 2003; ~ 100 staff; origins with MSF; non-profit, virtual R&D organization focused on neglected diseases

- **SCYNEXIS (RTP, North Carolina)**
  - Founded in 2000; ~ 100 employees; contract drug discovery/development focus
  - Responsible for medicinal chemistry, *in vitro* biology and DMPK

- **Haskins Laboratories, Pace University (New York, NY)**
  - Established 1977; interdisciplinary research in kinetoplastids and related parasites; discovered eflornithine (DFMO) for stage 2 HAT
  - Responsible for in vivo evaluation of compounds in HAT models

- **Swiss Tropical and Public Health Institute (Basel, Switzerland)**
  - Founded in 1943; ~ 500 staff; world-leading expertise in HAT research and clinical applications of HAT drugs
**Benzoxaboroles: Project Progression**

1. **AN2920**
   - Initial screening hit identified at UCSF Sandler Center (J. McKerrow)

2. **AN4169**
   - Initial “lead” identified from further screening and early SAR development at SCYNEXIS

3. **AN5568**
   - Optimized lead which was progressed to pre-clinical and clinical evaluation

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2. Nare, B., et al., Antimicrobial Agents Chemotherapy 2010, 54, 4379
• The geometric mean value for half-life across the 20 – 160 mg treatment groups is 325 hr/ 13.5 days (range, 259 – 402 hr/ 10.8 – 16.8 days).
• The prolonged half-life is consistent with a single dose treatment, which is desirable to mitigate against potential treatment failures from poor compliance.

Trypanosoma cruzi and Chagas Disease

- 25-100 million at risk, mostly in Latin America\(^1,2\)
- At least 7.6 million people infected\(^2\)
- Transmitted by triatomine insects, blood transfusion, organ transplantation, congenitally, or orally\(^3\)
- Largest parasitic cause of death in western hemisphere and leading infectious cause of cardiomyopathy\(^3\)
- Usually controlled by immune response, but not eliminated
- Majority of patients undiagnosed until decades into the infection
- Up to 30% of chronically infected people develop cardiac alterations, and up to 10% develop digestive, neurological or mixed alterations\(^3\)
- Estimated that <1% of infected people get treatment
- Zoonotic infection – will not be eradicated
- Solution for control – reduce transmission, survey for infected, treat those infected

Like benznidazole, AN4169 Exhibits Attractive \textit{in vitro} Activity and Speed of Kill\textsuperscript{1}

Like benznidazole, AN4169 is highly active against \textit{T. cruzi} strains from DTUs I-VI.

\textsuperscript{1} Moreas, C.B., et al. (2014) \textit{Nature Scientific Reports} 4, 4703. doi: 10.1038/srep04703
Rapid and “cure” assays suggest comparable results for Nifurtimox and AN4169

Rapid assay¹

2e05 T. cruzi
tdTomato strain
foot pad infection

untreated

BZ 50mg/kg, 2 doses, oral
Ef: -16.4
Toxicity: 1 out of 5
carrier: water
Treatment: 1/day (2dpi, 3dpi)

AN4169 50mg/kg, 2 doses, oral
Ef: -3.6
Toxicity: 0 out of 5
carrier: carboxymethylcellulose
Treatment: 1/day (2dpi, 3dpi)

Cure assay²

1000 T. cruzi
Brazil strain

~2 weeks after immunosuppression

Parasites/ml of blood

NFX (100 mg/kg/day)
AN4169 (20 mg/kg/day)

Benzoxaboroles have been a rich source of leads for development of new drugs to address the significant unmet medical need in kinetoplastid diseases.\(^1\)

The most advanced benzoxaborole designed to treat a kinetoplastid disease is AN5568 (SCYX-7158), which has recently completed Phase 1 clinical trials for HAT, with Phase 2 clinical trials anticipated to begin in 2015.\(^2\)

Screening of the benzoxaboroles against *T. cruzi* and *Leishmania spp* has provided good leads for treatment of diseases caused by these parasites as well.

The lead compound AN4169 has demonstrated good activity across a phylogenetically diverse panel of *T. cruzi* parasites,\(^3\) and has shown activity in both rapid screening and chronic cure models in mice.\(^4,5\)

\(^3\) Moreas, C.B., etal. (2014) *Nature Scientific Reports*, 4, 4703. doi: 10.1038/srep04703
\(^5\) Bustamante, J etal, (2014) *J Infect Dis*, 209, 150
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