ANACOR® PHARMACEUTICALS

Discovery and Development of Novel Benzoxaboroles to Treat Kinetoplastid Diseases

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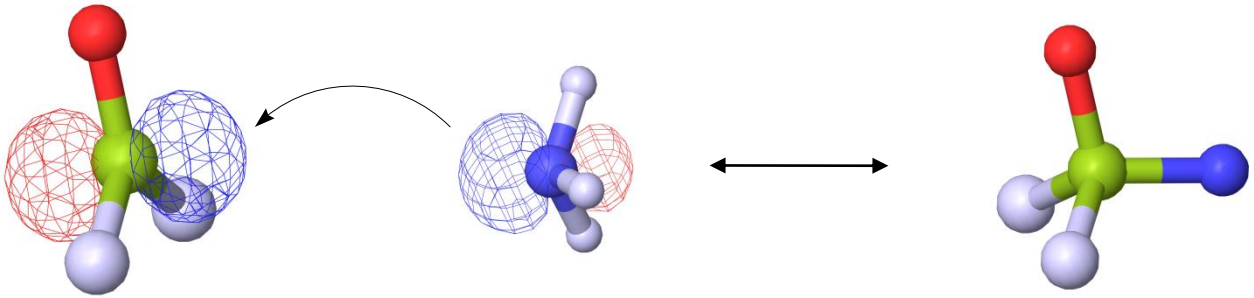
Vice President, Chemistry
November 13, 2014

Boron has a Unique Bonding Orbital Configuration: An Empty P-Orbital[1]



Trigonal Planar

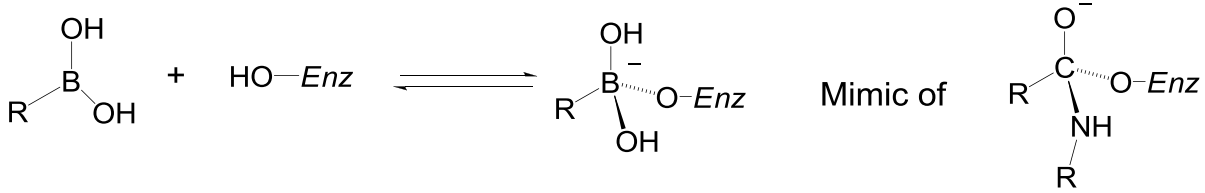
Tetrahedral

- 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

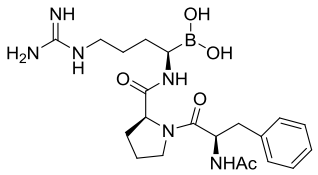
1 Baker *et al.* (2009) Future Medicinal Chemistry, 1(7), 1275-1288

History and Overview of Boronic Acid Drug Discovery Efforts[1]

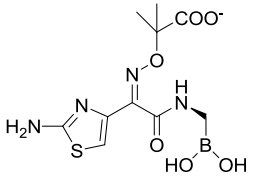
- Design of boronic acid enzyme inhibitors initiated in 1970s



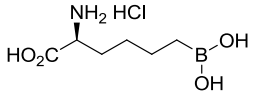
- Multiple disease targets have been pursued



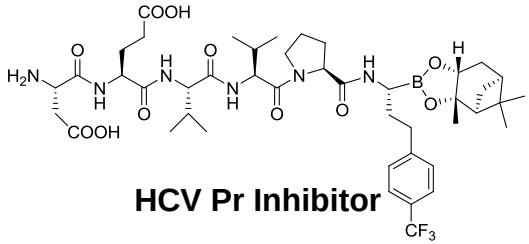
Thrombin
Dup 714



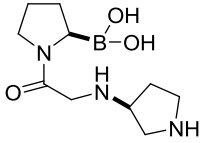
β-Lactamase Inhibitor



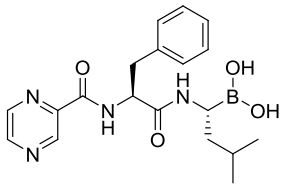
Arginase Inhibitor



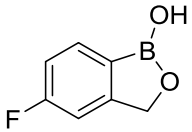
HCV Pr Inhibitor



DPP4 Inhibitor – PHX-1149



bortezomib



tavaborole

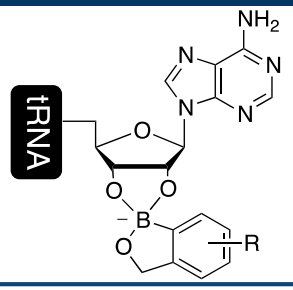
- Velcade® (bortezomib) was approved by FDA in 2008 for use in multiple myeloma[2]
- KERYDIN™ (tavaborole) topical solution, 5% was approved by FDA in 2014 for topical treatment of onychomycosis[3]

1 Baker *et al.* (2009) Future Medicinal Chemistry, 1(7), 1275-1288.
2 US Dept of Health and Human Services, www.fda.gov, June 23, 2008
3 KERYDIN™ (Tavaborole) Topical Soltuion, 5%, Package Insert. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; 2014

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

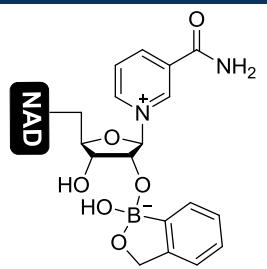
All shown by X-Ray Crystallography

Covalent Boron Interaction with Activated Cis-diol



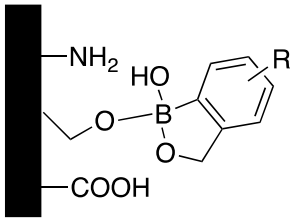
LeuRS Inhibitor[1]

Covalent Boron Interaction with NAD+ OH



Oxidoreductases[2]

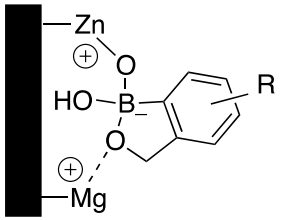
Covalent Boron Interaction with Activated OH of Serine



Serine Protease[3]

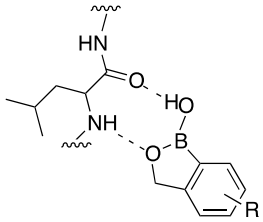
Novel chemistry
Broad target applicability
High selectivity

Oxaborole Metal Chelating Interaction



PDE4[4]

Conventional Hydrogen Bonding Interaction



Kinase Inhibitor[5]

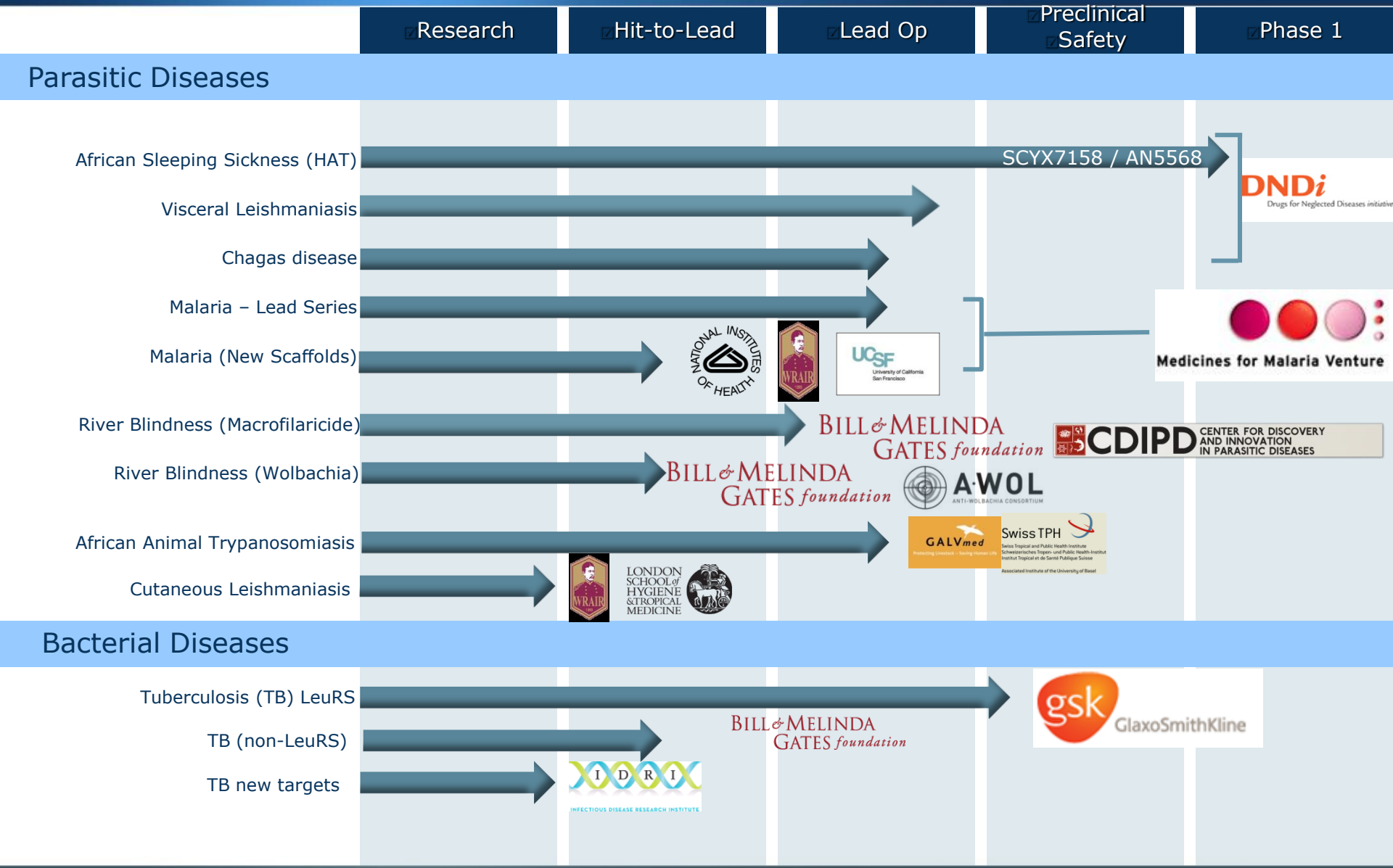
Covalent Bonding

Metal Interaction

Hydrogen bonding

1. Rock, F etal (2007) *Science*, **316**, 1759-1761.
2. Anacor Pharmaceuticals, X-ray data on file, March 2011.
3. Li, X etal (2010*) Bioorg. Med. Chem. Lett.*, **20**, 5695-5700.
4. Freund, Y etal (2012) *FEBS Lett.*, **586**, 3410-3414.
5. Akama, T etal (2013) *J. Pharm. Exp. Ther.*, **347**, 615-625.

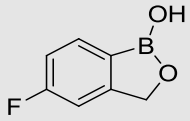
Anacor's Boron Chemistry Pipeline for Neglected Diseases



Anacor's Boron Chemistry Technology Has Delivered 8 Drug Candidates

Clinical Candidates

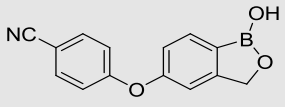
Antifungal



KERYDIN™

FDA Approved

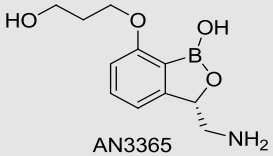
Anti-inflammatory



AN2728

Phase 3

Antibacterial



AN3365

Phase 2

Antitrypanosome

SCYX-7158
(AN5568)

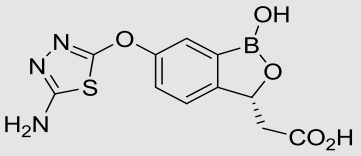
Phase 1 completed

Boron Chemistry Technology

Preclinical Candidates

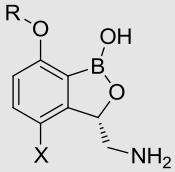
Antibacterial

Preclinical Candidate



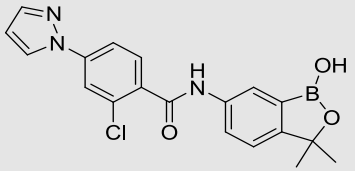
Antitubercular

Preclinical Candidate



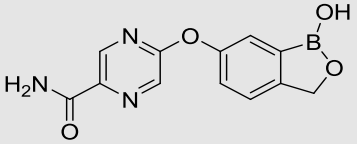
Antitrypanosome

Preclinical Candidate



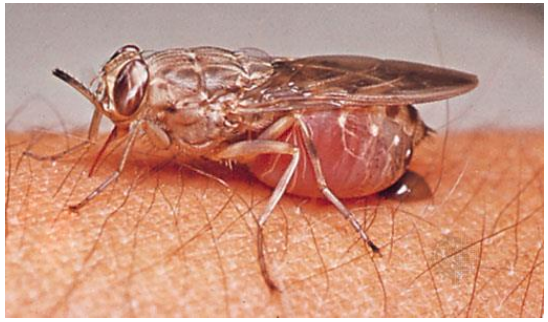
Antimalarial

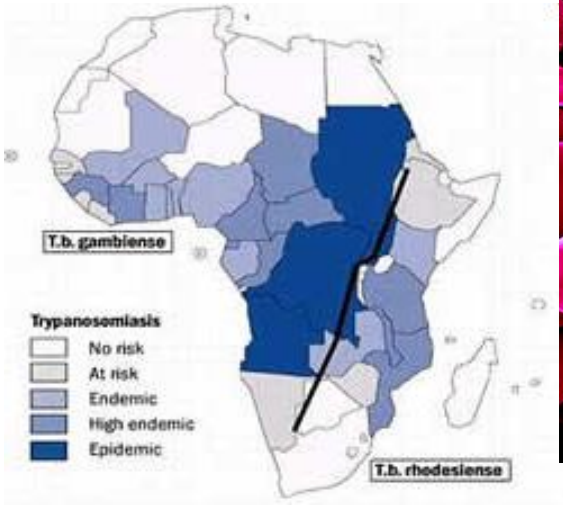
Advanced Lead



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]



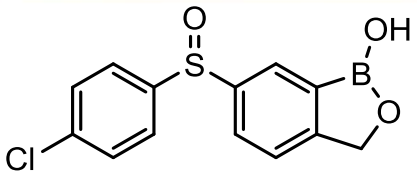


[1] WHO. Human African trypanosomiasis (sleeping sickness): epidemiological update. Wkly Epidemiol. Rec. 81 (8), 71-80 (2006)
[2] Grab, DJ, etal. J. Neuroviral. 14(5), 344 -351 (2008)

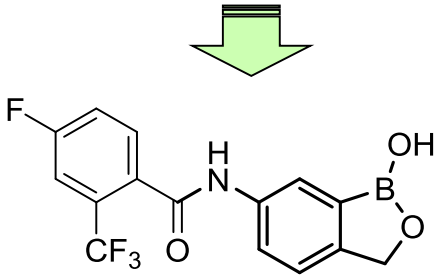
HAT Collaboration: Partners

- 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

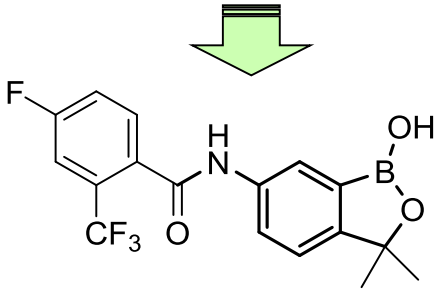
Benzoxaboroles: Project Progression[1,2]



AN2920



AN4169

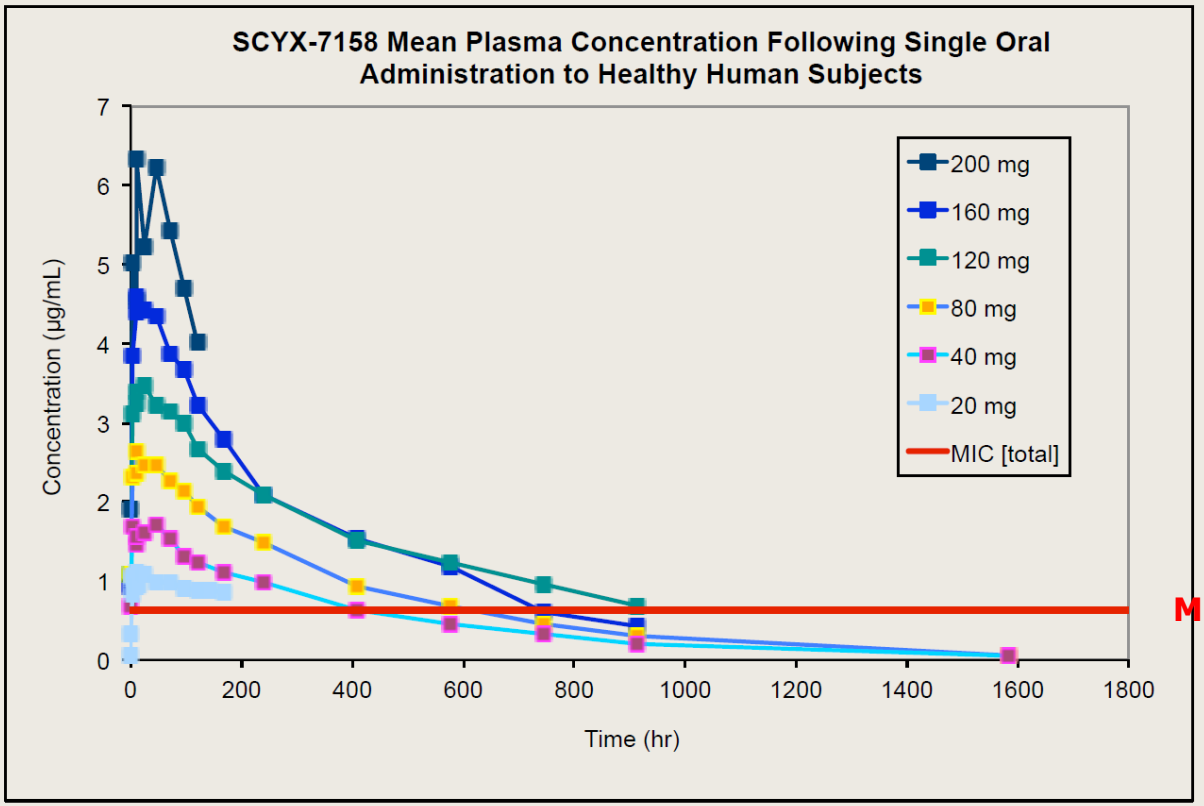


AN5568

- Initial screening hit identified at UCSF Sandler Center (J. McKerrow)
- Initial "lead" identified from further screening and early SAR development at SCYNEXIS
- Optimized lead which was progressed to pre-clinical and clinical evaluation[3]

[1]Jacobs, R.T., etal, Future Med Chem **2011**, 3, 1259
[2]Nare, B., etal, Antimicrobial Agents Chemotherapy **2010**, 54, 4379
[3]Jacobs, R.T., etal, PLoS Negl Trop Dis **2011**, 5, e1151

AN5568 (SCYX-7158): Interim Pharmacokinetics in Healthy Human Subjects[1]



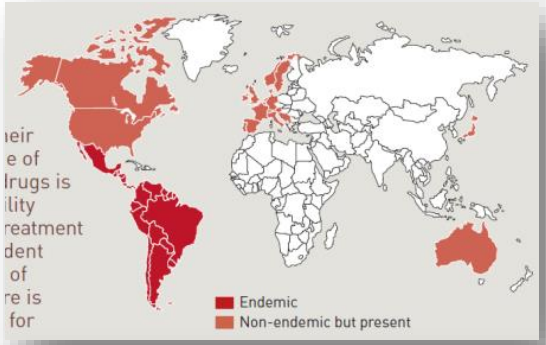
MIC = 0.6 µg/mL

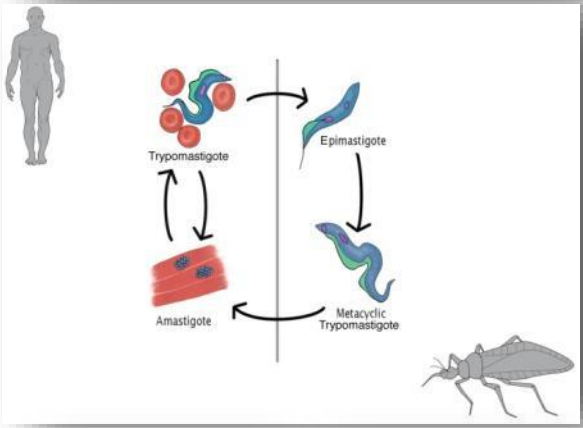
- The geometric mean value for half-life across the 20 – 160 mg treatment groups is 325 hr/ 13.5 days (range, 259 – 402 hr/ 10.8 – 16.8 days).
- The prolonged half-life is consistent with a single dose treatment, which is desirable to mitigate against potential treatment failures from poor compliance.

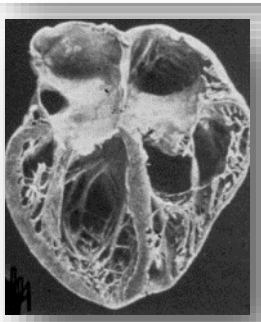
1 Wring, S, etal, 62nd ASTMH Meeting, November 2013, Poster LB-2117. Available at www.dndi.org/media-center.

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

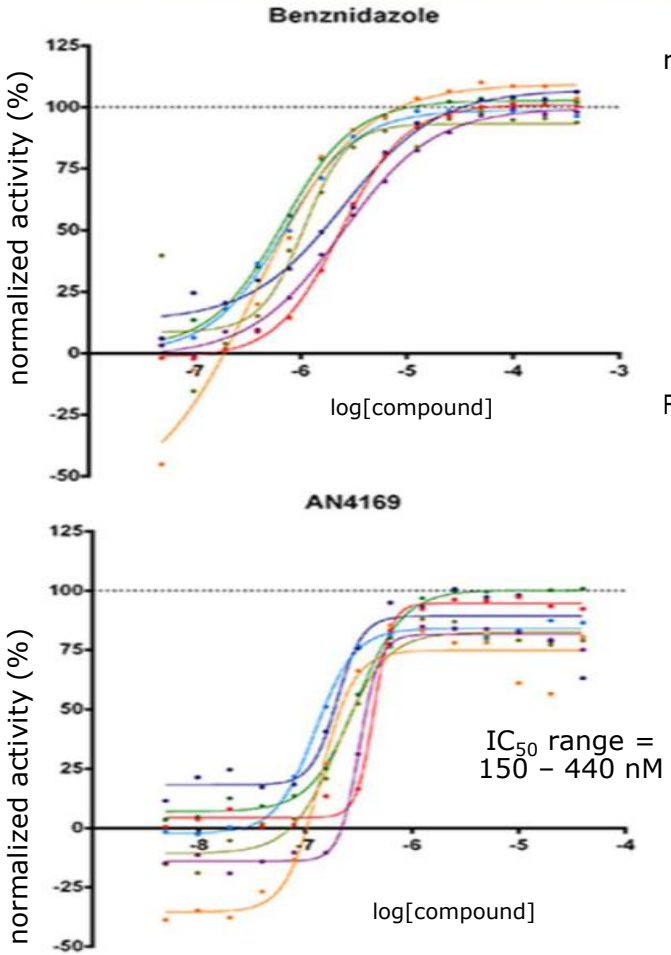




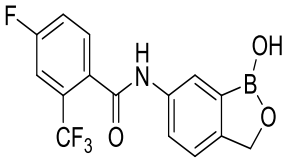


[1] Hotez, P etal (2007) *New Engl J Med*, **357**, 1018-27.
[2] WHO Technical Report 975 (2012) http://www.who.int/tdr/publications.
[3] Coura, J etal (2002) *Mem Inst Oswaldo Cruz*, **97**, 3-24.

Like Benznidazole, AN4169 Exhibits Attractive *in vitro* Activity and Speed of Kill[1]

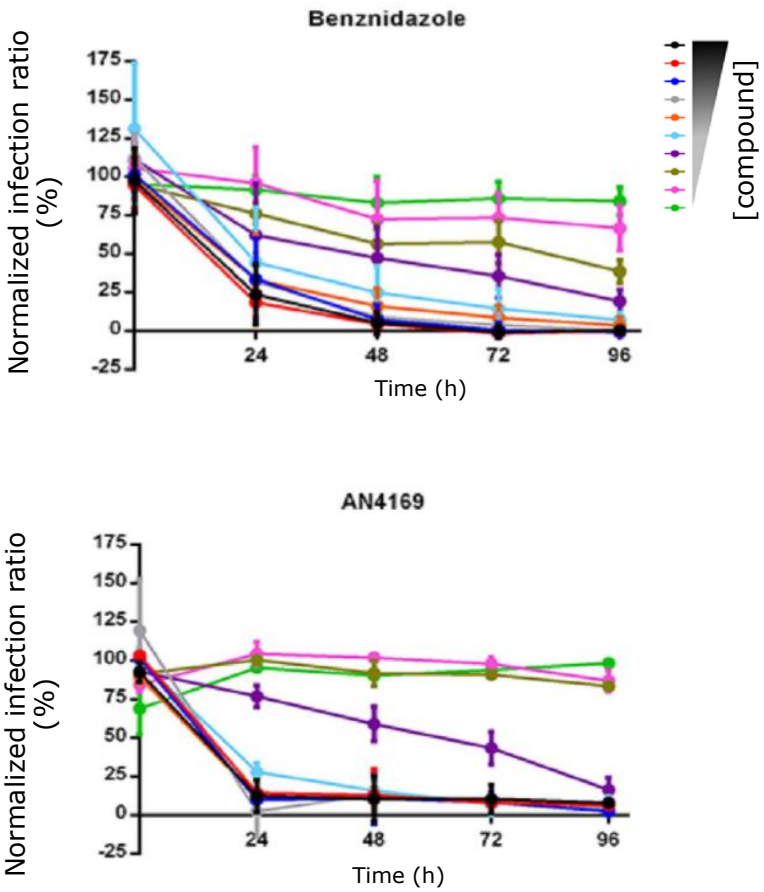


Each curve represents a strain of *T. cruzi*



AN4169

Like benznidazole, AN4169 is highly active against *T. cruzi* strains from DTUs I-VI.



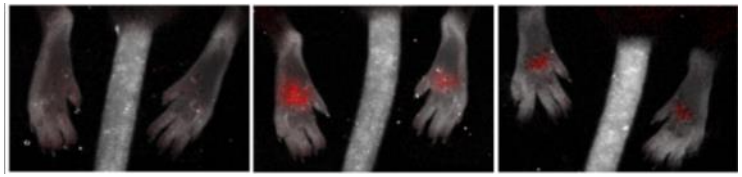
Like benznidazole, AN4169 exhibits fast trypanocidal activity and can significantly reduce intracellular *T. cruzi* with 24-48 h exposure

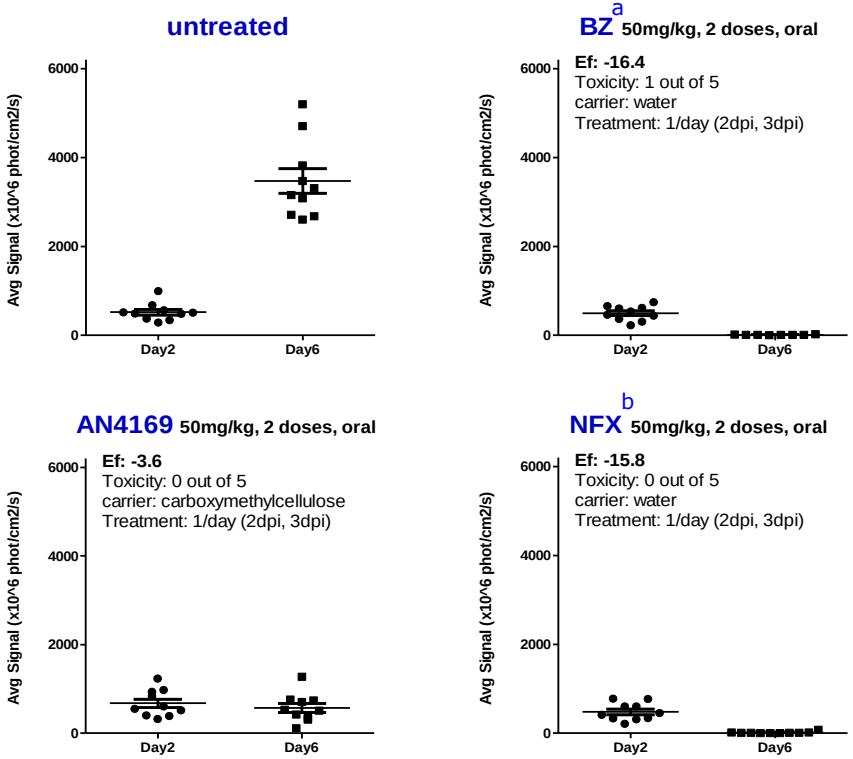
[1] Moreas, C.B., etal. (2014) *Nature Scientific Reports* 4, 4703. doi: 10.1038/srep04703

Rapid and "cure" assays suggest comparable results for Nifurtimox and AN4169

Rapid assay[1]

2e05 *T. cruzi* tdTomato strain foot pad infection

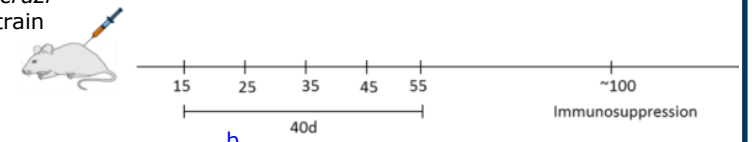




[a]Benznidazole; [b]Nifurtimox

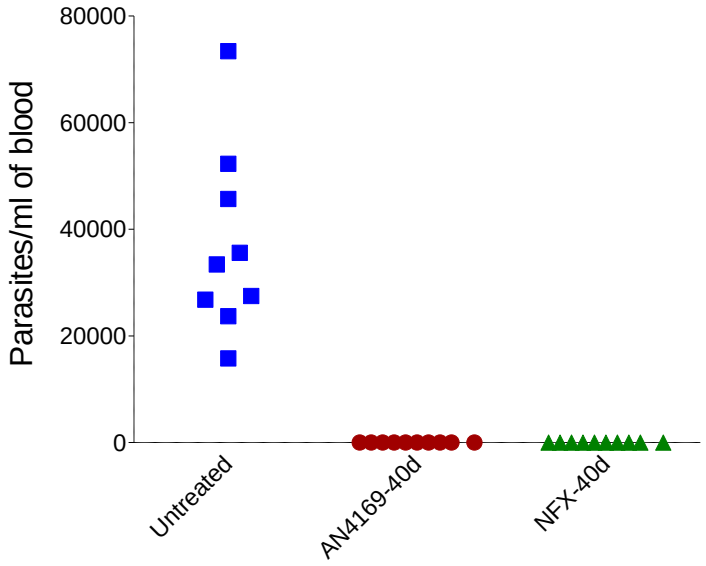
Cure assay[2]

1000 *T. cruzi* Brazil strain



NFX[b] (100 mg/kg/day)
AN4169 (20 mg/kg/day)

~2 weeks after immunosuppression



[1] Canavaci, AM, etal (2010) *PLoS Negl Trop Dis* e740
[2] Bustamante, J etal, (2014) *J. Infect. Dis.*, *209*, 150

Summary

- 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]

[1] Jacobs, R.T. etal, (2011) *Curr Opin Infect Dis*, *24*, 586-592.
[2] Jacobs, R.T., etal, (2011) *PLoS Negl Trop Dis*, *5*, e1151
[3] Moreas, C.B., etal. (2014) *Nature Scientific Reports,* 4, 4703. doi: 10.1038/srep04703
[4] Canavaci, AM, etal (2010) *PLoS Negl Trop Dis* e740
[5] Bustamante, J etal, (2014) *J Infect Dis*, *209*, 150

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  - Delphine Launay
  - Charles Mowbray
  - Denis Martin
- Pace University
  - Cy Bacchi
  - Nigel Yarlett
- SCYNEXIS
  - Daitao Chen
  - Bakela Nare
  - Matt Orr
  - Jessica Sligar
  - Steve Wring
- University of Georgia
  - Rick Tarleton
  - Juan Bustamante

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