New Drug Candidates and Innovation for HAT: From Discovery to Promising Candidates, Illustrated by Oxaboroles Development

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Neglected Diseases and Innovation

- Innovation in Neglected Diseases cannot be created with only “old” compounds
  - Combinations, new formulations, repurposing…
  - Toxicity, resistance, drug-drug interference, compliance…

- New drugs have to be discovered
  - New modes of action (resistance)
  - Safe (toxicity)
  - Easy-to-use (compliance)
  - Cheap (COGs)

- DNDi: created HAT Lead Optimization Consortium in 2007
  - SCYNEXIS: center piece
SCYNEXIS
An Integrated Parasitology Research Group

- Expertise in early discovery, lead optimization and pre-clinical development
  - Integrated medicinal chemistry, biochemistry, biology and ADMET-DMPK teams
  - Currently have 3 infectious disease compounds in clinical development

- Core business built on partnerships with PPP’s, Biotech, Pharma, Animal Health companies
  - Screening paradigms targeting key NTD therapeutic areas
  - Internal expertise built through multi-year research programs for animal health and neglected disease discovery
  - Finding value for partners via the integrated parasitology expertise
SCYNEXIS Integrated Parasitology Discovery Platform

**Human Health**
- Filarial Disease
- Schistosomiasis
- Soil Transmitted Helminthiasis
- Trypanosomiasis
- Leishmaniasis
- Malaria
- Dengue
- Chagas

**Vector Control**
- Mosquitoes
- Sandflies
- Ticks
- Bedbug
- Lice

**Animal Health**
- Trypanosomiasis
- Gastrointestinal Nematodes
- Biting Flies
- Cattle Tick
- Flea/Tick
- Heartworm
What It Takes: People, Time and Money

- People fully dedicated to HAT project: 19
  - DNDI: 2 Project management
  - SCYNEXIS: 15
    - 7 Chemists
    - 4 Drug Metabolism and Pharmacokinetics
    - 3 Biologists
    - 1 Project Leaders
  - Haskins Laboratories, Pace University: 2 Biologists

- Timeline:
  - 18 months - Lead Optimization
  - 20 months - Preclinical

  Among the best in industry

- Money
  - $15 Million over 3 years
What It Takes: Partners

- **SCYNEXIS**: *In vitro* *T. b. brucei*, cytotoxicity, ADME assays; time-kill assays, bioanalysis
- **Haskins Laboratories, Pace Univ.**: *In vivo* *T. b. brucei* assays (Stage 1 and Stage 2)
- **Swiss Tropical and Public Health Institute**: *In vitro* *T. b. rhodesiense*, *T. b. gambiense* assays; *In vivo* *T. brucei* spp. assays (Stage 1 and Stage 2); Microcalorimetry studies
- **Advinus**: *In vivo* toxicology and safety pharmacology studies in rat and dog; GLP genotoxicity studies;
  - **Anacor**: Profiling in antibacterial, antifungal and antiinflammatory assays
  - **Drugabilis**: Physicochemical characterization (solubility, polymorphism)
  - **Vivisource**: *In vivo* PK evaluation in mouse
  - **Sinclair Research Laboratories**: *In vivo* PK evaluation in rat, dog
  - **SNBL**: *In vivo* PK evaluation in cynomolgus monkey
  - **Aptuit**: Synthesis of [14C]-SCYX-7158
  - **BioReliance**: Non-GLP genotoxicity studies of SCYX-7158 and potential impurities
  - **Cellular Dynamics**: Non-GLP hERG electrophysiology study
  - **MDS Pharma Services**: Receptor, enzyme and ion channel profiling
  - **Penn Pharma**: Formulation of drug product for Ph 1 clinical trial
  - **Prof. S. Benkovic, Penn State Univ.**: pKa Determination
  - **Prof. M. Ferguson, Univ. of Dundee**: MOA studies in *T. b. brucei*
  - **Prof. M. Barrett, Glasgow Univ.**: Metabolomics studies in *T. b. brucei*
Benzoxaborole Series Progression

- C(6) Carboxamides - Anacor
  - Provide high potency
  - Overcome limitations of sulfoxide (AN2920)
    - Stereochemistry
    - Metabolism to sulfone

- C(2') Substitution
  - Enhances potency, PK and brain disposition
  - Trifluoromethyl, chloro preferred

- C(4') Substitution
  - Blocks oxidative metabolism of benzamide
  - Enhances bioavailability
  - Increases brain disposition
  - Fluoro preferred

- C(3) Substitution
  - Enhances PK, brain disposition
  - Monosubstitution compromised by cytotoxicity
  - Potency decreased by more sterically demanding substituents
SCYX-7158: Profile of an Orally-Active Stage 1 & 2 HAT Drug Candidate*


- In vitro activity vs. Trypanosoma brucei:
  - IC$_{50}$ = 0.2 – 1.1 µM (including T.b. gambiense, T. b. rhodesiense)
- Physicochemical properties:
  - logD = 3.51; aq. solubility = 25 µM
- In vitro ADME properties:
  - Mouse, rat, human S9 t$_{1/2}$ > 350 min
  - MDCK-MDR1 P$_{app}$ = 415 nm/Sec; AQ = 0.03

Curative of Stage 1 Murine HAT model @ 2.5 mg/kg, po, once-daily x 4 days
Curative of Stage 2 Murine HAT model @ 25 mg/kg, po, once-daily x 7 days
Excellent PK in mouse, rat, dog and cynomolgus monkey;
Excellent safety profile in rat and dog (28 day NOAEL = 15 mg/kg)
Non-genotoxic, no hERG effects, clean safety pharmacology profile
No evidence of irreversible binding to tissues, good tissue distribution ($^{14}$C)
Synthesized in 6 steps, no chromatography, crystalline API and intermediates
Building A HAT Pipeline

- **Discovery**
  - HAT LO Consortium

- **Preclinical**
  - Oxaborole
  - DDD85646 (Stage 1)

- **Clinical**
  - Fexinidazole
  - CPD-0801 (Stage 2)

**HCV**

- Proteases: 12
- Non-nucleotides: 14
- Nucleotides: 8
- Others: 6
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