Discovery and Lead optimisation programs: a future generation of drugs for neglected diseases

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Scynexis

SCYNEXIS Proprietary and Confidential Information
SCYNEXIS is a premier drug discovery and development company

- Located in Research Triangle Park, North Carolina
  - 130 employees, 100,000 square feet of laboratories
- Proprietary Cyclophilin Inhibitor technology
  - Lead compound, SCY-635, Phase 2a HCV
  - Other indications include: CNS, Oncology, Ophthalmology and CV
- Fully-integrated drug discovery & development outsourcing and consultancy
  - Eleven pre-clinical drug candidates delivered in last five years
Drug Discovery & Development
Outsourcing & Consultancy

- Pharmacological Optimization
  - Integrated medicinal chemistry, biochemistry and ADMET-DMPK teams
  - Screening platforms
  - Mode of Action(s)
  - Process chemistry & development, cGMP synthesis
  - Data management, HEOS®

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Neglected Disease Program

• SCYNEXIS Global Health Alliance.
  – A comprehensive expertise in Neglected Disease
  – Protozoan, Helminth and Vector Screening Platform
  – Unique collections of Antiparasitic and Insecticidal compounds

• Drugs for Neglected Diseases initiative (DNDi) for
  sleeping sickness (HAT).
  – Collaboration signed in 2007 with DNDi, SCYNEXIS, Anacor
    and Pace University
  – Support by Bill & Melinda Gates Foundation

• Neglected Disease Collaborative Discovery
  Software - HEOS®.
  – SaaS platform for drug discovery collaborations
  – More than 60 research organizations connected
  – MMV, DNDi, WHO/TDR ...
Current HAT Chemotherapy

Stage 1 HAT - Hemo-lymphatic

- Suramin (1916)
- Pentamidine (1937)

Stage 2 HAT - Meningo-encephalitic

- Merlasoprol (1946)
- DFMO (1977)

Recent Clinical Candidates

- Bis-amidines
  - Withdrawn 2009
- Fexinidazole
  - Phase I 2009

Issues

- Toxicity
- Unknown MOA
- Narrow spectrum
- Drug resistance
- Expensive
- Long IV/IM regimens
HAT Drug Discovery Galaxy

- SCYNEXIS™
- ANACOR PHARMACEUTICALS
- PACE UNIVERSITY
- DNDi
- HELVETICUM INSTITUTUM TROPICUM
- CPDD

Drugs for Neglected Diseases initiative
HEOS® has, over the past seven years, supported many discovery programs from early discovery to the pre-clinical stage. It is heavily used by users around the world including large pharmaceutical companies and biotechnology companies.
HAT HTS Summary

Primary HTS
108,745 compounds

>75% inhib. @ 2 μg/mL

Actives

n = 3942

IC₅₀ < 1 μg/mL

Hits

n = 551

Low cytotoxicity, evidence of SAR

n ≈ 200

Chemotypes progressed to Hit-to-Lead

Ext1 Ext2

External HTS

Collaborators
External Lead: Benzoxaboroles

- Benzoxaboroles synthesized by Anacor and identified as effective against *T. b. brucei*
  - Initial screening at Sandler Center (J. McKerrow); active @ 1 mM
  - “Best” compound, AN2920, evaluated in an *in vivo* model @ Sandler – active @ 50 mg/kg, ip, bid.

![AN2920](image)

- DND/i was granted a license to develop this series in the field of HAT, Leishmania and Chagas disease.
- DND/i initiated ANACOR-SCYNEXIS interaction in March, 2008
- Characterization for efficacy on HAT, ADME, physicochemical properties identified three chemotypes for focused Lead Optimization
- Pharmacological optimization parameters
  - Stage 1 and 2, orally available
Pre-Clinical Candidate: SCYX-7158

Key Properties

- Orally active in Stage 1 and Stage 2 HAT models
  - Cures Stage 1 HAT at 2.5 mg/kg/day x 4 days
  - Cures Stage 2 HAT at 25 mg/kg/day x 7 days

- Excellent PK profile
  - Low *in vivo* clearance
  - Bioavailability ~ 50% (mouse, rat, monkey)
  - Sustained brain exposure above MIC for ~ 24h
  - T1/2 > 20 h in rat and monkey

- Attractive Pre-clinical Safety Profile
  - Minimal interaction with over 100 mammalian receptors, enzymes and ion channels
  - Not genotoxic (AMES)
HAT Disease Program Timeline

- High Throughput Screening: April 2006 – April 2007
  - Screening vs Trypanosoma brucei brucei
  - SCYNEXIS contributed:
    - 50,000 compounds from about twenty chemotypes
    - Laboratory space and equipment
    - Data management support (HEOS®)
    - Potent hits identified, initial Structure-Activity Relationships (SAR) developed

  - Refinement of SAR and potency vs. T.b. brucei
  - Evaluation of drug like properties
  - Selection of compounds for in vivo evaluation

- Pharmacological Optimization: May 2008 – present
  - Two distinct and diverse chemotypes
  - Robust in vivo activity observed in lead series

- Pre-clinical Candidate Nomination: December 2009
Information Sharing and Publications

• Protection of Intellectual Property
  – Filed seven PCT patent applications assigned to Anacor, rights for use to DNDi
  – Two additional applications in preparation

• Scientific conferences
  – Multiple poster presentations at ASTMH, ACS, Keystone, GRC conferences since 2008

• Publication of results in Refereed Journals
  – Antimicrobial Agents and Chemotherapy (2010)
  – PLoS NTD (pending, 2011)
  – Journal of Medicinal Chemistry (submitted)
Conclusion

- The HAT program illustrates the Best Science for the Most Neglected
  - SCYX-7158: Orally active in Stage 1 and Stage 2
- DNDi at the center of the Innovative Partnerships
  - Access to premier global health experts worldwide while maintaining confidentiality and ownership
- SCYNEXIS Global Health Platform at the center of the Innovation
  - Fully-integrated drug discovery & development
  - Unique Pharmacological Optimization platform
  - Project managed virtually through HEOS®
- From Concept to Preclinical compound in three years
  - 18 months from Lead to Preclinical compound
Thank You