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The first journal to highlight chemistry and its role in the multidisciplinary and collaborative field of infectious disease research.

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Vincent Rotello
University of Massachusetts at Amherst

Moderator TBA

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Creating New Models to Combat Neglected Disease
Through, Industry, Government, and Public-Private Partnerships

Michael Pollastri
Professor and Chair of Chemistry and Chemical Biology
Northeastern University

Félix Calderón
Drug Discovery Manager
GlaxoSmithKline

Slides available now and an invitation to view the recording will be sent when available.

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This ACS Webinar was co-produced by ACS Infectious Diseases
CREATING NEW MODELS TO COMBAT NEGLECTED DISEASE THROUGH INDUSTRY, GOVERNMENT, AND PUBLIC-PRIVATE PARTNERSHIPS

Northeastern University

Understanding the audience: Which of the following best describes you?

- Academic scientist (faculty, student, postdoc, etc)
- Biotech or pharma scientist
- Industrial scientist in transition to academics
- Working at a non-profit working on rare or neglected diseases (in industry or academia)
- Other
A DRUG DISCOVERY PRIMER

Northeastern University

The early stages of drug discovery

A multidisciplinary process

10-20 years!

Idea ———— Drug

- Target ID
- Validation
- Screen
- Hit Optimiz
- Lead Optimiz
- Candidate Optimiz
- Clinical Trials

Biology: Mechanistic hypotheses, assays, & disease models

Medicinal chemistry
Molecular modeling
Formulations
Drug metabolism & pharmacokinetics
Informatics – Database systems

Northeastern University
What makes a molecule a “drug”? 

Hit or Lead Compound  →  Drug 

What makes a molecule a “drug”? 

Hit or Lead Compound  →  Medicinal Chemistry  →  Drug 

- Potency 
- Selectivity 
- Oral bioavailable 
- Non-toxic 
- Intellectual property 
- Solubility 
- Efficacy 
- Exposure
Medicinal chemistry
An iterative process

- **Design**
  - Propose compound to test hypothesis

- **Synthesis**
  - Prepare, purify & analyze analog structure

- **Screening**
  - Potency/selectivity
  - Physical property/ADME

- **Analysis**
  - Form versus function
  - Inform next design step

NEGLECTED TROPICAL DISEASES

Northeastern University
Neglected tropical diseases
A significant disease burden

20 NTDs listed by WHO
- Buruli ulcer
- Chagas disease
- Dengue & Chikungunya viruses
- Dracunculiasis
- Echinococcosis
- Foodborne trematodiases
- African sleeping sickness
- Leishmaniasis
- Leprosy (Hansen’s disease)
- Lymphatic filariasis
- Mycetoma & deep mycoses
- Onchocerciasis (river blindness)
- Rabies
- Scabies and other ectoparasites
- Schistosomiasis
- Soil-transmitted helminthiases
- Snakebite envenoming
- Taeniasis/Cysticercosis
- Trachoma
- Yaws

Focus of the London Declaration? 2017 additions to the list of NTDs

www.who.int/neglected_diseases/diseases/en/
www.unitingtocombatntds.org

2009-2010 Data

• 2.3 billion at risk
• 1.1 billion are infected

NTDs represent a serious healthcare disparity

• Total spend in 2011 for 31 tropical diseases was $3.05 billion
  – 67% for HIV, TB, malaria, leaving ~$1 bn for 28 NTDs!
• New therapeutic outputs are grim:
  – 1975-1999: 13 out of 1,398 new drugs for NTDs (1%)
  – 2000-2011: 37 out of 850 (4%); 4 new chemical entities (1%)

The primary reason behind this disparity is the level of poverty of patients who suffer from these diseases
An example of an NTD

*Human African trypanosomiasis* ("sleeping sickness")

- Caused by protozoan parasites *Trypanosoma brucei gambiense* (W. African) and *T. b. rhodesiense* (E. African)
- Transmitted by bite of infected tsetse fly
- ~3,000 people affected annually
- Clinical course:
  - Stage I – infection of blood and lymph
    - Mild symptoms include headache, fever, muscle pain etc.
  - Stage II – parasite crosses blood-brain barrier
    - Sleep & behavioral disruption, coma, death
- 100% fatal unless treated
- Neurological damage common

### Limitations of current drugs

* African sleeping sickness

<table>
<thead>
<tr>
<th>Drug</th>
<th>First used</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suramin</td>
<td>1920</td>
<td>Anaphlaxis, renal failure, neuro effects</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>1940</td>
<td>Hypotension, hyper-or hypo-glycemia</td>
</tr>
<tr>
<td>Melarsoprol</td>
<td>1949</td>
<td>Death (5%), reactive encephalopathy</td>
</tr>
<tr>
<td>Eflornithine</td>
<td>1981</td>
<td>Bone marrow toxicity, seizures,</td>
</tr>
</tbody>
</table>

### In clinical use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melarsoprol</td>
<td>2-3.6 mg/kg/day iv x 3 days. Every other week x 3 weeks</td>
</tr>
<tr>
<td>Eflornithine</td>
<td>400 mg/kg/day iv infusions x 14 d (28g/day. Almost 400g for full treatment)</td>
</tr>
<tr>
<td>NECT</td>
<td>Nifurtimox: 15 mg/kg/day po for 10 days plus eflornithine 400 mg/kg/day for 7 d</td>
</tr>
</tbody>
</table>

---

*Photo credit: Tulane University*
Targeted product profiles are defined

<table>
<thead>
<tr>
<th>Properties</th>
<th>Targeted lead properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. brucei pEC₅₀</td>
<td>&gt;7.5 (12 h), cidal</td>
</tr>
<tr>
<td>HepG2 TC₅₀</td>
<td>&gt;100x tryp IC₅₀</td>
</tr>
<tr>
<td>HLM clearance</td>
<td>Clᵣ &lt;8.6 uL/min/mg</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>&lt;95%</td>
</tr>
<tr>
<td>PAMPA</td>
<td>&gt;200 nm/sec</td>
</tr>
<tr>
<td>Solubility (pH=7)</td>
<td>&gt;10 uM</td>
</tr>
<tr>
<td>Key kinase selectivity</td>
<td>&gt;25x tryp EC₅₀</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>&gt;10 x IC₅₀ for &gt;4 h</td>
</tr>
<tr>
<td>CNS exposure</td>
<td>&gt;3 x IC₅₀ &gt;4 h</td>
</tr>
<tr>
<td>BS mouse efficacy</td>
<td>&lt;50 mg/kg po x 5 days; &gt;90% cure</td>
</tr>
<tr>
<td>CNS mouse efficacy</td>
<td>&lt;100 mg/kg po x 10 days; &gt;90% cure</td>
</tr>
<tr>
<td>CYP450 pIC₅₀</td>
<td>Profiled</td>
</tr>
<tr>
<td>CYP450 induction</td>
<td>Profiled</td>
</tr>
<tr>
<td>hERG inhibition</td>
<td>Profiled</td>
</tr>
</tbody>
</table>

Definition:
A Lead Compound will be a potent, non-toxic, fast-acting trypanocide that shows in vivo efficacy in mouse models of Stage I and Stage 2 HAT following oral dosing.

Properties devised for compounds to meet the TDR “Lead Activity Criteria” for HAT

Our laboratory’s goal is to discover high quality lead compounds that can launch partnered preclinical studies for tropical disease therapeutics.
## Challenges

### Academic (or non-profit) drug discovery

<table>
<thead>
<tr>
<th>Industry</th>
<th>Expertise</th>
<th>Infrastructure</th>
<th>Resource</th>
</tr>
</thead>
</table>
|          | • Broad and deep diversity of expertise  
          | • Singly focused on drug discovery  
          | • Co-located  
          | • Defined processes and workflows  
          | • Speak the same scientific “language”  | • Fit-for-purpose  
          | • Sample logistics and workflow  
          | • Harmonized assays, data analyses, and reporting  
          | • Robust data systems  | • (Roughly) commensurate with needs  
          | • Often inventing cost-effective (cheap) solutions  
          | • Ad hoc logistics, workflow, assays, analyses and reporting, on a project-by-project basis  
          | • Data often shared via email spreadsheet or other low-cost solutions  | • Appropriate staffing and infrastructure support  
          | • Seldom sufficient funds to cross all t’s and dot all i’s  
          | • Often need to seek in-kind support for key experiments  
          | • Effort diverted to obtain publications and external visibility  
          | • Significant effort diverted toward fundraising (grants, crowdfunding)  |
| Academic | • Siloed and deep expertise in areas  
          | • Mission is research, teaching/training  
          | • Diffuse collaborative teams  
          | • Differing understanding of drug discovery, targeted properties, etc.  |
**Audience Challenge Question**

**ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT**

**Place your bets! Into which of the following would you invest time or funding first?**

- Finding collaborators
- Constructing research infrastructure
- Seeking funding

---

### Issues to address, up-front

#### Project Niche
- Identify potential collaborators at targeted conferences
- Compare research areas with funding opportunities
- Minimize redundancies
- Seek a consistent theme

#### Resource & Expertise
- Focus on what I know (medicinal chemistry)
- Collaborate with others on aspects I don’t know (most everything else)
- Seek out in-kind collaborations

#### Data Sharing
- Excel spreadsheets are untenable for data management
- Shared data system for registration, chemical and biological data needed
- No desire to maintain a database.

#### Funding
- University startup, NIH R01 award (year 1)
Finding biology collaborators
My first conference in the field - 2009

2009 Molecular Parasitology Meeting
Nearly every one of our collaborations over the last decade were spawned at this or similar meetings!

Our collaborators

AstraZeneca
Peter Webborn
Mark Timms
Jeff Andrews

GlaxoSmithKline
Pepe Fiandor
Pili Manzano
Silvia Gonzalez
Julio Martin
Manuela Berlanga
David Drewry
Bill Zuercher

University of Georgia
Kojo Mensa-Wilmot
Paul Guyett
Ranjan Behera

New York U
Ana Rodriguez
Cristina Galen
Rodriguez

WRAIR
Rick Sciotti
Norma Roncal

Southern Methodist University
Larry Ruben
Vidya Pandarinath

Marine Biological Lab
Bob Campbell
Nick Bland

CSIC – Granada, Spain
Miguel Navarro
Rosario Diaz-Gonzalez

U of Glasgow
Harry de Koning

UC San Diego
Jim McKerrow
Jair Siqueira-Neto
Conor Caffrey

Seattle Biomed
Ken Stuart
Igor Cestari
Chris Merritt

Washington U., St. Louis
Stephen Beverly
Matt Kuhlmann

Vanderbilt University
Galena Lepesheva

Northeastern University
https://college.uchicago.edu/
Specific expertise needs for our work

A flexible data system was needed

*(Excel is not a data system)*

**Desired criteria**
- Chemist-proof
- Low maintenance
- Ability to import/export data easily
- Low cost

**Capabilities**
- Compound registration
- Biological data import
- Computed properties
- Selective data sharing with public and collaborators outside NEU
Collaborative Drug Discovery

A cloud-based solution

Specific expertise needs for our work

We set off knowing we had biology collaborators and a database. ADME/PK would just need to wait until funding came through!

Northeastern University
Target repurposing
Finding opportunities among kinases

Trypanosomatid Kinases
- 176 T. brucei
- 190 T. cruzi
- 199 L. major
- No protein or receptor tyrosine kinase
- Few species-unique genes

Observation: Nonspecific tyrosine kinase inhibitors block transferrin uptake in *T. brucei* and impact parasite growth

Rapid SAR development

44 analogs, 3 cycles
ChemAxon (free acad license)

NEU617 as a lead compound

NEU617 treatment provides 4 day life extension over controls

Project screening funnel, v1.0

Northeastern University
Other parasite labs were interested

*Screening funnel v1.2*

---

**Parasite hopping**

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>T. brucei: 1.5 μM&lt;br&gt;HepG2: 5.2 μM (NIH AID: 461255)</td>
</tr>
<tr>
<td>NEU28</td>
<td>T. brucei: 0.81 μM&lt;br&gt;L. major (amaSTAG): 2.05 μM&lt;br&gt;P. falciparum: 0.65 μM&lt;br&gt;HepG2: 1.9 μM</td>
</tr>
<tr>
<td>NEU27</td>
<td>T. brucei: 0.53 μM&lt;br&gt;T. cruzi: 10%&lt;br&gt;L. major (amaSTAG): 1.67 μM&lt;br&gt;P. falciparum: 0.03 μM&lt;br&gt;HepG2: &gt;25 μM</td>
</tr>
<tr>
<td>NEU54</td>
<td>T. brucei: 0.65 μM&lt;br&gt;T. cruzi: 10%&lt;br&gt;L. major (amaSTAG): 0.5 μM&lt;br&gt;P. falciparum: 0.47 μM&lt;br&gt;HepG2: &gt;25 μM</td>
</tr>
</tbody>
</table>

---

**University of Georgia**
- Kojo Mensa-Wilmot

**New York U**
- Ana Rodriguez

**WRAIR**
- Rick Sciotti

---

Northeastern University
WIPO RE:Search and BVGH

*Patent pool for NTDs*

- Participating organizations “deposit” intellectual property that would be made available for NTDs (no cost, royalty-free)
- Managed by BioVentures for Global Health
  - Introduces participating organizations to each other, to identify collaboration opportunities

*We were introduced to AstraZeneca, who were willing to support our work with excess Tier 1 ADME capacity.*

**Added Tier 1 ADME**

*Screening funnel v1.3*

---

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- Kojo Mensa-Wilmot

**New York U**
- Ana Rodriguez

**WRAIR**
- Rick Sciotti

**AstraZeneca**
- Peter Webborn
- Mark Timms
- Jeff Andrews
Contract organizations filled the gaps

*Screening funnel v2.0*

Funds liberated by in-kind ADME redirected to later stage experiments

**Northeastern University**

All looks promising, except...

Time for a shift in focus from potency to properties

**Northeastern University**

Color: compound core
Improving properties

The headgroup is largest and most lipophilic region and has the flattest SAR.

**OpenEye (free acad license)**

Properties-based design

**Quinazoline scaffold**

First generation library (109 quinazolines)

NEU617-similar, CNS MPO compliant VL (26 compounds)

NEU961

Polar heterocyclic replacements

**Head**

Properties filter

Properties compliant virtual library

3D shape & electrostatics comparison

NEU-617 ▲

Tbb EC_{50}: 0.042 µM
Tbb pEC_{50}: 7.37
LogP: 7.31
LLE: 0.06
Aqueous sol: <1 µM

Northeastern University
Properties-based design

*Quinazoline scaffold*

First generation library

(109 quinazolines)

NEU617-similar, CNS MPO compliant VL

(26 compounds)

**Solubility isn’t driven by lipophilicity**

*“Greaseball” versus “Brick dust”*
Solubility isn’t driven by lipophilicity

“Greaseball” versus “Brick dust”

Northeastern University
Current status

*Best T. brucei lead to date*

**NEU-4438**
- *T. brucei* EC$_{50}$ = 13 nM
- *L. major* EC$_{50}$ = 2.3 µM
- *L. donovani* EC$_{50}$ = 20 nM
- TC$_{50}$ = >35 µM
- cLog P: 2.37
- Log D: 0.9
- LLE: 5.52
- Aq sol: 882 µM
- HLM: 21.8 µL/min/mg
- PPB: 15%
- CNS MPO: 5.4

Current status

*Other good leads to date*

**NEU-4643**
- *Pfal (D6)* EC$_{50}$: 0.08 µM
- TC$_{50}$ = 25 µM
- cLog P: 2.5
- Log D: 0.7
- LLE: 4.60
- Aq sol: 864 µM
- HLM: 22.4 µL/min/mg
- PPB: 40%

**NEU-4837**
- *T. brucei* EC$_{50}$ = 0.31 µM (4.23)
- *T. cruzi* EC$_{50}$ = 3.7 µM (3.1)
- TC$_{50}$ = >35 µM
- cLog P: 2.28
- Log D: 2.3
- Aq sol: 828 µM
- HLM: 79.4 µL/min/mg
- PPB: 58%

**NEU-4781**
- *Lmj* EC$_{50}$: 1.53 µM
- TC$_{50}$ = >35 µM
- cLog P: 3.25
- Log D: 1.2
- LLE: 2.56
- Aq sol: 891 µM
- HLM Clint: 51 µL/min/mg
- PPB: 41%
Summary

• Academic drug discovery, especially in NTDs, requires creative solutions to access all the data needed for good decisions
• Tempting to get everything in place before starting....
  – But don’t let “perfect” get in the way of the “good”!
• Understand what industry and government can (and can’t) do.
  – In-kind work and advising, versus cash infusions
• Lining up good collaborators requires clearly stated alignment of goals and priorities, which isn’t always easy.
• Look beyond the NIH for funding schemes

Northeastern University

Research Faculty
Dr. Lori Ferrins
Research Scientist
Dr. Baljinder Singh
Postdoctoral Associates
Dr. Melissa Buskes
Dr. Hitesh Jalani
PhD students
Kelly Bachovchin
Dana Klug
Westley Tear
Andrew Spaulding
Undergraduates
Jack Fisher
Jeremy Armand
Brady Greene
Mitch Rivers
Raeann Dalton
Erin Burchfield
Max Staab
Kate Schneider
Alex Hughes

Funding & In-Kind Support
R01 AI114685
R01AI124046
R21AI127594
R01AI12611
R56 AI099476
R01 AI082577
OpenLab Foundation
BMGF/Struct Genomics Consort
GlaxoSmithKline
AstraZeneca
OpenEye Scientific Software
ChemAxon
CDD

Group Alumni
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Dr. Pooma Mahalingam
Dr. Daljit Matharu
Dr. Seema Bag
Dr. Takashi Satoh
Dr. Emanuele Amata
Dr. Trent Ashton
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Angela Tanner, MS
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Cristin Juda
Michael Russo
Katherine Spring
Matthew Stevenson
Craig Talman
Anthony Varca
Travis DeLano
Vivian Hibborne
Melanie Frithsche
Laura Tchegg
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CDk2  PDE4  PI3K  EGFR  GSK3β

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Through, Industry, Government, and Public-Private Partnerships

- Michael Pollastri
  Professor and Chair of Chemistry and Chemical Biology
  Northeastern University

- Félix Calderón
  Drug Discovery Manager
  GlaxoSmithKline

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