Drug Discovery Pipeline

Bench.............to.............Bedside

Some facts:

- 10% of the compounds make it to preclinical development
- 70% of these compounds make it to Phase 1
- 20% of Phase 1 compounds make it to market
- Odds are < 10% of making it to market
- 30% of new drugs return cost of development
- 6 yrs from idea to First In Human (FIH)
- 8 yrs from FIH to market approval
  - Total of ~ 12-15 yrs to get to market
- $802 MM cost of drug to market

-AlzForum.org ~2007
A Few Steps to Clinical Trials

- Intellectual Property
- Potency
- Selectivity
- Metabolic stability in mice and human
- Hepatocyte stability in mice and human
- Solubility
- Pharmacokinetic profiling
- CNS penetration
- Formulation
- In vivo toxicity (MTD)
- In vivo efficacy
- Clinical Trial
- Clinical
- Trial
- A Few Steps to Clinical Trials
- Lead identification
Steps to go from ‘Hit to Lead’

1. **Identification of Hits/Lead Compounds**
   a. High Throughput Screens (HTS)
   b. Structure-based computer design
   c. Medicinal chemistry of known literature compounds

2. **Good Chemical Matter**
   a. Does the compound/chemical series have drug-like properties?
   b. Can modifications be made to the compound/chemical series to make it drug-like?
   c. Is the compound or chemical series a dead-end?
Compound Libraries at Southern Research

One million small molecules

- Chembridge, Enamine, Tripos
- Kinase library
  - 26,734 compounds theoretically designed to inhibit kinases
- Approved drugs and biological actives library
  - 2,500 FDA approved drugs
  - 460 unapproved drugs
- Fragment libraries

- Southern Research Proprietary library (14K)
  - Compounds from SR Research Programs
Examples of ADDA Programs with Hits / Chemical Series from HTS

1. LRRK2 – Parkinson’s Disease

184K Compound HTS: Novel autophosphorylation assay

2566 Hits → Hit Rate: 1.4%
Several diverse hit series identified

Hit-to-Lead: Modeling & multi-parameter optimization

Compounds with IC$_{50}$ < 100 nM from 4 hit series identified

Focus on most drug-like series:
Pyridopyrroldines
Examples of ADDA Programs with Hits / Chemical Series from HTS

2. **14-3-3-theta – Parkinson’s Disease**

   2 Pilot screens done (5K each)

   - Primary 115K screen assay using conditions optimized and adapted to high throughput
   - Positive controls: compound from the 10K & a known compound called Rosiglitazone

   Secondary Confirmation Assay established

   Evaluation of hits/chemicals series underway
Examples of ADDA Programs with Hits / Chemical Series from HTS

3. Tau-Fyn – Alzheimer’s Disease

Primary screen (10µM) 108,000 compounds

Hit Cutoff: >=64%

Compounds for dose response: 1853

Dose response in 4 assays; Main assay, off-target & 2 counter screens

64 compounds met criteria
HIV Programs with Hits / Chemical Series from HTS

731,616
> 25% Inhibition in Primary Screen

3,196
IC$_{50}$ in Dose Response

1,750
Three Counter Screens

805
Three “Rules of 10”

91
Selectivity in MDMs

24
Bind Nef

6

selected 2 leads

SAR studies

Med. Chem. Analogs Generation
Steps to go from ‘Hit to Lead’

1. Identification of Hits/Lead Compounds
   a. High Throughput Screens (HTS)
   b. Structure-based computer design
   c. Medicinal chemistry of known literature compounds

2. Good Chemical Matter
   a. Does the compound/chemical series have drug-like properties?
   b. Can modifications be made to the compound/chemical series to make it drug-like?
   c. Is the compound or chemical series a dead-end?
**Physicochemical Properties**

**MW = Molecular Weight**
- Mass of one molecule of that substance

**PSA = Polar Surface Area**
- Surface sum over all polar atoms (oxygen and nitrogen), including hydrogens; Used for optimization of cell permeability

**Solubility**
- In PBS (Phosphate buffered saline) at pH 7.4 ($\mu$M)

**Log D**
- Distribution (D) coefficient
  - Ratio of sum of concentrations of ionized + un-ionized form of the compound in water and a hydrophobic solvent

**Log P**
- Partition (P) coefficient
  - Ratio of concentrations of un-ionized compound between the two solvents

**Lipinski’s Rule of 5**
- Molecular weight $< 500$
- cLog P $< 5$ (lipophilicity)
- $< 5$ hydrogen bond donors
- $< 10$ hydrogen bond acceptors
Pharmacokinetic Properties

MLM, RLM and HLM = Mouse, Rat or Human Liver Microsomes

% Compound Remaining @ 60 min (1h) or t ½

Liver microsomes
- contain drug-metabolizing enzymes, e.g., CYP isoenzymes, such as CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4
- widely used as an *in vitro* model system to investigate metabolic fate of the compound

HEP= Hepatocytes (mouse, rat or human)

% Compound Remaining @ 120 min (2h) or t ½

Hepatocytes
- liver cells
- contain phase II enzymes, e.g. sulfatases, glutathione S-transferases, and UDP-glucuronosyltransferase
- Hepatoctye metabolism profiles usually yield more metabolites and information about the metabolic fate of the test compound
Guidelines to Drug-Like Properties

STEP 1 / Early Stage
- Rule of 5
- Structural ‘alerts’
- Ease of synthesis
- Solubility (>10 µg/mL)
- Log D (2-4)
- Mouse (Rat) Micr/Hep (>20%)
- Human Micr/Hep (>20%)
- IC₅₀ (< 1 µM)

CNS DRUGS
Brain Penetration
- Smaller is Better (MW = 300)
- Log D (2-4)
- Polar Surface Area < 70
- ≤ 5 Total H-Donors or Acceptors
- ≤ 4 Total Rings, Rotatable Bonds
- ≤ 3 Three Aromatic Rings

STEP 2 / Optimization
- % Bioavailability (30)
- t ½ (> 2h, i.e., BID)
- Clearance
- Nontarget selectivity profile
- Plasma protein binding
- hERG testing
- P450 interactions (>3 µM)
- Pgp
- Mini-Ames
- Minimum effective dose
- Brain / Plasma (0.5 – 1)

STEP 3 / Pre-Clinical Development
- Genetic toxicology
- In vivo studies / dose response
- Side-effect profiling
- Biomarker
- Defined mechanism of action
- Differentiation vs. known drugs

POC = Proof of Concept
Structural Alerts

- Structural alerts have the potential for:
  - Intrinsic reactivity
  - DNA intercalation
  - Metal coordination or metabolic activation (e.g., to a species capable of covalent binding)
  - This binding could then lead to:
    - Mutagenicity
    - CYP inhibition
    - Direct toxicity
    - Carcinogenicity
    - Idiosyncratic toxicity

- A structural alert alone is not predictive of an adverse outcome.

Other factors to consider:

- Clinical dose
- Route of drug clearance
- Presence of metabolic routes (e.g., that divert metabolism away from the structural alert)
And.....

Some molecules with a structural alert may never generate an adverse toxicological or CYP inhibition outcome.

• There are examples of safe marketed drugs with a structural alert.

(There are examples of attrition of compounds due to an adverse outcome without a recognized structural alert.)
Examples of Structural Alerts

Potential DNA Damaging Agents

- Amino triazoles
- Furocoumarins/tricyclics

Potential Metal Chelators

- Imidazoles and Triazoles
- Pyridine derivatives

Undergo Metabolic Activation........or not........

- Furan
- Thiophene
- Pyrrole
- Thioamides
- Aldehyde
- Michael Acceptor
- Thiocarbamates
- Thioureas
- Thiols and Disulfides
Metabolism...How to improve?

• Avoid structural alert moieties in a molecule

• Find replacements (bioisosteres) of particular groups/rings

• Block potential sites of metabolism on aryl rings

• Use calculations such as CSL (StarDrop) to prioritize analogs with predicted better metabolic stability
  • CSL (Composite Site Liability) is a measure of the efficiency of metabolism of a molecule by e.g., CYP3A4, one of the CYP isoenzymes.
  • CSL varies between 0 and 1 (lower values indicate greater metabolic stability)
Towards Stable Analogs via CSL Calculation (StarDrop)

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<tr>
<th>Target Values</th>
<th>Data</th>
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<th>36430</th>
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<td>CSL (Composite Site Liability)</td>
<td>0.762</td>
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<td>0.58</td>
<td>0.38</td>
<td>0.32</td>
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<td>&gt; 50 % Inh. at [12.5] (µM)</td>
<td>52</td>
<td>54</td>
<td>54</td>
<td>30</td>
<td>53</td>
<td>57</td>
<td></td>
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<tr>
<td>≥ 10 µM)</td>
<td>Sol (µM))</td>
<td>73</td>
<td>85.3</td>
<td>&gt; 100</td>
<td>80</td>
<td>60</td>
<td>62</td>
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<td>t_{1/2} &gt; 60 min</td>
<td>MLM</td>
<td>18</td>
<td>51.4</td>
<td>105.6</td>
<td>226</td>
<td>46</td>
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<td>Mouse In Vivo PK</td>
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<td>NA</td>
<td>t_{1/2} IV = 12 min</td>
<td>t_{1/2} IV = 12 min</td>
<td>t_{1/2} IV = 96 min</td>
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<tr>
<td>▪ PO 5 mpk</td>
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</tbody>
</table>

Original hit | In vivo studies | Back-up candidate

- | Within target value | Borderline target value | Outside target value

4/12/2017

Southern Research Drug Discovery
Potency, Solubility...how to improve?

• Add polar or solubilizing groups
  • OH, N, OR, COOH

• Include cycloalkyls containing heteroatoms

• Insert heterocycles

• Interrupt intramolecular hydrogen bonding

• Insert groups that will allow rings to rotate within a molecule....disrupting planarity
Example of Potency, Stability and Selectivity

1st Generation

\[
\text{Cl} - \text{SO}_2nis \quad \text{CF}_3
\]

*\[\text{A}_{40} \text{IC}_{50} = 120 \text{ nM}\]*

2nd Generation

\[
\text{Br} - \text{SO}_2nis \quad \text{CF}_3
\]

*\[\text{A}_{40} \text{IC}_{50} = 3400 \text{ nM}\]*

Resolution

\[
\text{Br} - \text{SO}_2nis \quad \text{(S)} \quad \text{NH}_2
\]

*\[\text{A}_{40} \text{IC}_{50} = 13 \text{ nM}\]*

Racemate

\[
\text{Br} - \text{SO}_2nis \quad \text{NH}_2
\]

*\[\text{A}_{40} \text{IC}_{50} = 113 \text{ nM}\]*

Potency

BMS-708163 (Avagacestat)

*\[\text{A}_{40} \text{IC}_{50} = 0.3 \text{ nM}\]*

*\[\text{Notch IC}_{50} = 58 \text{ nM (190x)}\]*

Selectivity

Stability

*\[\text{B/P} = 0.01 \text{ (low BBB penetration)}\]*

*\[\text{RLM (19%), HLM (44%) @10 min incub}\]
Example of Potency and Stability

\[ \text{A}\beta_{40} \text{ IC}_{50} = 5549 \text{ nM} \]
Selectivity: 3.7-fold

\[ \text{A}\beta_{40} \text{ IC}_{50} = 25 \text{ nM} \]
Selectivity: 10-fold

\[ \text{A}\beta_{40} \text{ IC}_{50} = 15 \text{ nM} \]
Selectivity: 14-fold

\[ \text{A}\beta_{40} \text{ IC}_{50} = 16 \text{ nM} \]
Selectivity: 15-fold

\[ \text{A}\beta_{40} \text{ IC}_{50} = 294 \text{ nM} \]
Selectivity: 10-fold

**Potency and Stability**

**Hit** \[ \text{GSI-953} \]

**Lead**

- Potency:
  - \[ \text{A}\beta_{40} \text{ IC}_{50} = 25 \text{ nM} \]
  - Selectivity: 10-fold

- Oxidation
  - >90 min (human)

- Glucuronidation
  - >90 min (human)

- Stability:
  - \[ \text{A}\beta_{40} \text{ IC}_{50} = 15 \text{ nM} \]
  - Selectivity: 14-fold
  - 48 min (mice)
  - >90 min (human)

  - \[ \text{A}\beta_{40} \text{ IC}_{50} = 16 \text{ nM} \]
  - Selectivity: 15-fold
  - 24 min (mice)
  - 8 min (human)

  - \[ \text{A}\beta_{40} \text{ IC}_{50} = 25 \text{ nM} \]
  - Selectivity: 10-fold
  - 1 min (mice)
  - 8 min (human)
**Example of Metabolic Stability**

<table>
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<th>Data</th>
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<th>1112</th>
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<td><img src="image2" alt="Molecule 2" /></td>
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<table>
<thead>
<tr>
<th></th>
<th>1231</th>
<th>1112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ42 Elisa&lt;sub&gt;cells&lt;/sub&gt; IC&lt;sub&gt;50&lt;/sub&gt; nM</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td>Notch Luc&lt;sub&gt;cells&lt;/sub&gt; IC&lt;sub&gt;50&lt;/sub&gt; nM</td>
<td>28,600</td>
<td>4588</td>
</tr>
<tr>
<td>Not Luc&lt;sub&gt;cells&lt;/sub&gt;/Aβ42 Elisa&lt;sub&gt;cells&lt;/sub&gt;</td>
<td>421</td>
<td>574</td>
</tr>
<tr>
<td>Not Elisa&lt;sub&gt;cells&lt;/sub&gt;/Aβ42 Elisa&lt;sub&gt;cells&lt;/sub&gt;</td>
<td>6995</td>
<td>350</td>
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<tr>
<td>Molecular Weight</td>
<td>426</td>
<td>422</td>
</tr>
<tr>
<td>Polar Surface Area</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Solubility (µM)</td>
<td>303</td>
<td>305</td>
</tr>
<tr>
<td>Log D</td>
<td>1.6</td>
<td>2</td>
</tr>
<tr>
<td>Microsome Stability: Mouse</td>
<td>71</td>
<td>18</td>
</tr>
<tr>
<td>Microsome Stability: Human</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>Hepatocyte Stability: Mouse</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Hepatocyte Stability: Human</td>
<td>52</td>
<td>26</td>
</tr>
</tbody>
</table>

44% reduction Aβ in hippocampus

12% reduction Aβ in hippocampus

---

**4/12/2017**
Comparison of Properties: (+) and (-)

**Benzoic Acid Analogs**

*AD749*  
1. Orally Active in Mice  
2. Metabolically Stable  
3. Very soluble

*AD1231*  
1. Modest Potency  
2. < Avagacestat Selectivity

**Amide Side Chain Analogs**

*AD1138*  
1. More Selective than Avagacestat  
2. Subnanomolar APP activity

**Substituted-Phenyl Analogs**

*AD802*  
1. Insoluble  
2. Metabolically Unstable  
3. Inactive in Mice
Utility of Metabolite Identification

- Proposed metabolic pathway

**AD1138**

Dealkylation of cyclo ring

- M1 = 4.4%

Oxidation

- M2 = 3%

- M3-M5, M7, M8, M11, M12

Di-Oxidation of cyclo ring + Me grp

- M6 = 3.2%

- M4 = 21%

- M5 = 15%

Total = 47%

Parent = 38%

Fragments = 15%

(*mouse hepatocytes)
Evolution of Chemical Matter

Gleevec

Inhibitor 2

Tocris Library (50 cpds)

Rational Design

Structure Modification

Pyridopyrimidines

Aryl Amides

γ-Amino Alcohols

Structural Alerts

WJ Netzer, P Greengard, et. al.
PNAS, 100 (2003) 12444

PC Fraering, et. al.
JBC, 280 (2005) 41987

1366
IC₅₀ = 60 µM

1367
IC₅₀ = 20 µM
Sulfonamide Chemical Matter

Conversion of: Aryl Amides to Aryl Sulfonamides

1. Common replacement for amide
2. Sulfonamide conformation may offer more binding orientations
3. Naphthyl to aryl and alkylbenzyl amine to more diversified amines

Results
• Increased *in vitro* and cellular potency
• Improved selectivity
## Lead Quality Attribute Checklist

<table>
<thead>
<tr>
<th><strong>Chemical Series (Sulfonamide) Attributes</strong></th>
<th><strong>Met</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Potency:</strong> <em>In vitro</em> potency &lt; 100 nM</td>
<td>yes</td>
</tr>
<tr>
<td><strong>2 SAR:</strong> Evidence of SAR with ≥ 10X change in potency</td>
<td>yes</td>
</tr>
<tr>
<td><strong>3 Cellular activity / toxicity:</strong> Active / no toxicity</td>
<td>yes</td>
</tr>
<tr>
<td><strong>4 Selectivity:</strong> Versus Notch receptor</td>
<td>yes</td>
</tr>
<tr>
<td><strong>5 Safety:</strong> No toxicophores or reactive moieties</td>
<td>yes</td>
</tr>
<tr>
<td><strong>6 Physicochemistry:</strong> <em>In vitro</em> ADME studies of similar framework show solubility and absorption</td>
<td>yes</td>
</tr>
<tr>
<td><strong>7 Synthesis:</strong> Synthetic chemistry flexibility is high; amenable to rapid, highly productive analog synthesis</td>
<td>yes</td>
</tr>
<tr>
<td><strong>8 Intellectual property:</strong> Proprietary</td>
<td>yes</td>
</tr>
<tr>
<td><strong>9 Synthesis:</strong> Amenable to parallel synthesis</td>
<td>yes</td>
</tr>
</tbody>
</table>
## Compound Profile

### Physicochemical and Pharmacokinetic Properties

<table>
<thead>
<tr>
<th>DATA</th>
<th>TARGETED VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(\beta)<em>{42}\text{cells } IC</em>{50} (nM)</td>
<td>&lt; 100 nM</td>
</tr>
<tr>
<td>Selectivity (Notch Elisa\text{cells} / A(\beta)42 Elisa\text{cells})</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>&lt; 500</td>
</tr>
<tr>
<td>Polar Surface Area</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Solubility ((\mu)M) (In PBS at pH 7.4 ((\mu)M))</td>
<td>&gt; 10 (\mu)M</td>
</tr>
<tr>
<td>Experimental Log D</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Microsome Stability: Mouse (% remaining @ 60 min)</td>
<td>&gt; 20% (or t (\frac{1}{2}) = 1h)</td>
</tr>
<tr>
<td>Intrinsic Clearance(^1)</td>
<td>&lt;15 Low Risk; &gt;40 High Risk</td>
</tr>
<tr>
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<td>Intrinsic Clearance(^1)</td>
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</tr>
<tr>
<td>Hepatocyte Stability: Mouse (% remaining @ 120 min)</td>
<td>&gt; 20% (or t (\frac{1}{2}) = 1h)</td>
</tr>
<tr>
<td>Intrinsic Clearance(^1)</td>
<td>&lt;15 Low Risk; &gt;40 High Risk</td>
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<td>Intrinsic Clearance(^1)</td>
<td>&lt;15 Low Risk; &gt;40 High Risk</td>
</tr>
</tbody>
</table>

\(^1\) (mL/min/mg/protein)
Screening Tree – Compound Selection

- Solubility
- Mouse + Human liver microsome stability
- Mouse + Human hepatocyte stability
- Log D

- New Lead Series
- Purified γ-Secretase Enzyme Assay
  Aβ40 ELISA + Notch Flag WB

- IC₅₀’s: Aβ42 + Notch Cellular Assays
  + Cellular Toxicity (MTS)
  - Active & Interesting Compounds
  - In vivo Candidates

- Mouse Studies
- Proof of Principle
- Efficacious cpds

- Microdialysis Studies
- Neuronal Culture Assay

- In-house
- Outsourced

- P450 enzymes
- Selectivity panel
- Toxicity

- PK studies
- Brain penetration

- SAR & Lead Development
- Lead Optimization

- Total compounds >1400

4/12/2017 Southern Research Drug Discovery
Medicinal Chemistry Strategy

Synthesis of Analogs

Test Potency and Selectivity  ➔  PK Parameters on Leads

< 100 nM  ➔  IC₅₀ <10 µM; <1 µM
2- to 3-fold > Avagacestat (known drug)  ➔  (Notch) Selective  ➔  Good PK

IC₅₀ >10 µM  ➔  Nonselective  ➔  Poor PK

Test In Vivo  ➔  Terminate Series
**Assay Selection**

*Notch Luciferase Reporter Assay*
- Measures effect of compound on Notch processing (NICD) using a Notch-Luciferase reporter assay
- Indirect reflection of Notch proteolysis
- Cell Line: Human osteosarcoma (U2OS)

*Notch ELISA Assay*
- Measures effect of compound on Cleaved Notch by ELISA
- Direct measure of selectivity
- Cell Line: Human T-cell lymphoma (SUP-T1)

*Notch proteolysis ELISA is comparable to the Aβ ELISA*
- Both assays quantify the actual cleavage products of APP and Notch processing
- Same type of results are compared
Additional Tools to prioritize targets...

**Modeling**
Explore key ligand-receptor interactions(s) and apply computer-aided drug design to guide the identification of more potent inhibitors.

**Structural Biology**
Purification and crystallization of protein with and without inhibitors
The Right Balance……

- Solubility
- Molecular weight
- Metabolic stability

- Potency
- Selectivity
- Toxicity

- Brain penetration
- Bioavailability
- Half-life

‘BALANCED’ OPTIMIZED Candidates

In vivo Efficacy in Animal Models

POC
Southern Research Chemistry Department

Capabilities for Medicinal Chemistry and Drug Discovery

- In Vitro Pharmacokinetics
  - In Vivo Pharmacokinetics
  - Toxicity Studies
  - Animal Efficacy Studies

- Structural Biology
  - Protein Crystallography

- Computational Chemistry

- Informatics
  - Electronic Notebooks
  - Dotmatics

- Iterative Medicinal Chemistry

- Mass Directed Purification

- Parallel Synthesis

- Intellectual Property

- US Patent x,xxx,xxx

- Nuclear Magnetic Resonance
  - Exact Mass

- Proof of Concept Animal Model
  - “Making Drugs that Matter!”

- Lead Development & Optimization

- Southern Research Drug Discovery

Compartes that meet Activity/Efficacy Criteria

4/12/2017
# Southern Research Medicinal Chemistry Research Projects

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<thead>
<tr>
<th>Disease</th>
<th>Grant Type</th>
<th>Project</th>
<th>Status</th>
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<td>U19</td>
<td>Flu, Flavi-, Corona-, and Alpha-viruses</td>
<td>HTS/Lead Opt</td>
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<td>NIAID</td>
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<td>Vif-Vif / HIV</td>
<td>Lead Opt</td>
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<td></td>
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THANK YOU…

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