Overview of the SBIR/STTR Program

IUPUI

Presented by
Kris Parmelee, President
kris@parmeleeconsulting.com

Parmelee Consulting Group, Inc.
Indianapolis, IN 46256

317.491.5051
www.parmeleeconsulting.com
Overview of the Program

What Does SBIR and STTR Really Mean?
Ground Rules for the Presentation

- Remember each agency has different rules, expectations and outcomes

- There is an exception to almost every situation I will present today; it’s a government program

- SBIR=STTR
SBIR
Small Business Innovation Research
- Promotes technological innovation and commercialization by small businesses
STTR

Small Business Technology Transfer

- Promotes cooperative research and development between small business and U.S. research institutions
SBIR/STTR Program

- Small Business Innovation Development Act of 1982
  - Stimulates technological innovation
  - Small businesses meet federal R&D needs
  - In FY 2012, estimated 5,656 awards made for a total of more than $2.2 billion
- SBIR/STTR=Growth in U.S. economy and market presence
SBIR vs. STTR

**SBIR**
- Permits research institution as a partner
- Primary employment (at least 51%) of PI must be with small business
- Responsible for at least 66% of the work

**STTR**
- Requires research institution as a partner
- PI employment not stipulated
- Responsible for at least 40% of the work

Copyright Parmelee Consulting Group, Inc. 2015
SBIR vs. STTR

- Small Business
- Subcontract

- Small Business
- Research Institution
- Other
Why SBIR?

- Allows businesses to:
  - Maintain control of operations
  - Retain all intellectual property
  - Safely “test” new ideas

- Recognizes—REQUIRES—an inherent sense of RISK in exploring new ideas—there will be failures

- Success rate is greater than other sources; other sources attracted to SBIR success
SBIR/STTR Reauthorization

- Reauthorized in 2011 (6 years) after several CRs
- Set aside gradually increase from 2.6% to 3.2% by 2017 (SBIR) and to .45% by 2016 (STTR)
- Increased use of funds for technical assistance
- Cross Program Awards
- Streamline Award Process
- Increased reporting requirements for agencies
- New measures to guard against Fraud, Waste and Abuse
- Increased support for Commercialization
SBIR/STTR Reauthorization

- Pilot program for Administrative Funding
- Direct to Phase II Pilot
- Increase in Award floors
  - $150,000 Phase I
  - $1 million Phase II
- Allowing firms that are majority-owned by multiple venture capital operating companies (VCOCs), hedge funds and/or private equity firms to receive SBIR/STTR awards
Three-Step Program

- Phase I
  - Feasibility
  - $150K (up to $225,000)
  - 6 to 9 months (STTR 1 year)

- Phase II
  - Prototype
  - $1 million (up to $1.5 million)
  - Usually 2 years

- Phase III
  - Commercialization
  - No SBIR funds
  - Sole-source procurement

A variety of other funding mechanisms—depending on agency and success
Other Funding Mechanisms

FastTrack

- FastTrack is a Phase I and Phase II proposal submitted together
- Not recommended for new companies
- Phase II funding remains contingent on performance and results of Phase I work
- Not all agencies offer a FastTrack program (CDC and FDA do not; NIH does)

Direct to Phase II

- Pilot program within NIH ONLY
- for innovations that have already surpassed the feasibility stage but require additional development in preparation for commercialization

Copyright Parmelee Consulting Group, Inc. 2015
Who is Eligible for SBIR?

- 500 or fewer employees, including affiliates
- For profit business
- Located and primarily operated in the United States
- PI’s primary employment must be with the small business at the time of the award
Who is Eligible for SBIR?

- At least 51% owned and controlled by U.S. Citizens or Permanent Resident Aliens
  
  or

- Owned and controlled by a (one) for-profit small business that is 51% owned and controlled by U.S. Citizens or Permanent Resident Aliens in the United States

- ...and now, VCs can play too...
Eligibility Points for Both SBIR/STTR

- Eligibility for both is determined at the time of the award
- “If come” basis allowed/expected
- PI is not required to have advanced degrees
- PI is expected to have knowledge and experience needed to successfully implement and oversee the project scientifically and technically
Eligibility Points for Both SBIR/STTR

- Applications may be submitted to multiple agencies for similar work
- Applications for different work may be submitted to same agency
- Must disclose all and can only accept one award for each project

*Fast Track is not an option for most new companies*
SBIR/STTR Awards

Copyright Parmelee Consulting Group, Inc. 2015
# SBIR/STTR Awards (2010-2014)

<table>
<thead>
<tr>
<th>Agency</th>
<th>Awards</th>
<th>Agency</th>
<th>Awards</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHS</td>
<td>170</td>
<td>DOC</td>
<td>89</td>
</tr>
<tr>
<td>DoD</td>
<td>8773</td>
<td>DOE</td>
<td>1149</td>
</tr>
<tr>
<td>DOT</td>
<td>78</td>
<td>DoEd</td>
<td>112</td>
</tr>
<tr>
<td>EPA</td>
<td>104</td>
<td>HHS</td>
<td>2398</td>
</tr>
<tr>
<td>NASA</td>
<td>1520</td>
<td>NSF</td>
<td>979</td>
</tr>
<tr>
<td>USDA</td>
<td>181</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SBIR/STTR Awards by State (2010-2014)

<table>
<thead>
<tr>
<th>State</th>
<th>Awards</th>
<th>State</th>
<th>Awards</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>3196</td>
<td>Alaska</td>
<td>6</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>1896</td>
<td>North Dakota</td>
<td>13</td>
</tr>
<tr>
<td>Virginia</td>
<td>1050</td>
<td>Washington D.C.</td>
<td>13</td>
</tr>
<tr>
<td>Colorado</td>
<td>694</td>
<td>South Dakota</td>
<td>14</td>
</tr>
<tr>
<td>New York</td>
<td>689</td>
<td>Wyoming</td>
<td>17</td>
</tr>
<tr>
<td>Ohio</td>
<td>6223</td>
<td>West Virginia</td>
<td>24</td>
</tr>
<tr>
<td>Indiana</td>
<td>135</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Who Wins in SBIR?

- About 33% of Phase I winners each year have never won before
- 41% of companies have between 2 and 9 employees
- For some agencies, odds are 1 in 10
## SBIR/STTR Success Rates (2010)

<table>
<thead>
<tr>
<th>Agency</th>
<th>Phase I (%)</th>
<th>Phase II (%)</th>
<th>Agency</th>
<th>Phase I (%)</th>
<th>Phase II (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USDA</td>
<td>17</td>
<td>63</td>
<td>DOC</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>DoD</td>
<td>16</td>
<td>73</td>
<td>DoEd</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>DOE</td>
<td>14</td>
<td>33</td>
<td>HHS</td>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>DHS</td>
<td>16</td>
<td>67</td>
<td>EPA</td>
<td>7</td>
<td>61</td>
</tr>
<tr>
<td>DOT</td>
<td>9</td>
<td>1.29</td>
<td>NASA</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>NSF</td>
<td>17</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall Phase I Rate: 16  
Overall Phase II Rate: 55
Overview of Agencies

....What is the difference?
Overview of Structure

Congress Enacts Legislation

SBA Administers Program

DoD

- Army
- Air Force
- Navy
- Other Components

HHS

- NIH
- CDC
- FDA

USDA

NSF

DOC

- NIST
- NOAA

Other Agencies
What Agencies Participate?

- Based on an agency’s extramural research budget
- Once it reaches a predetermined threshold of $100 million, must play
- Reaches second threshold, must play in STTR too (much smaller program)
- Agencies can be in or out
Agencies

- Some agencies are **granting** agencies—a problem to solve, but not the end customer (topics repeat)

- Some agencies are **contracting** agencies—a problem to solve, and you will be their (sole source) supplier

- Some are one, but act like the other!

- Some agencies are both (NIH)
## What’s Different?

<table>
<thead>
<tr>
<th></th>
<th>Grants</th>
<th>Contracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Due Dates</td>
<td>Apply</td>
<td>Do not apply</td>
</tr>
<tr>
<td>Topics</td>
<td>Broad in scope and interests</td>
<td>Specific</td>
</tr>
<tr>
<td>Contact with Program Managers</td>
<td>Encouraged any time</td>
<td>Not permitted once contract solicitation is officially released</td>
</tr>
<tr>
<td>Budget</td>
<td>Room for larger budgets</td>
<td>Firm fixed price contracts</td>
</tr>
<tr>
<td>Submission</td>
<td>Grants.gov</td>
<td>Direct to the IC</td>
</tr>
<tr>
<td>Review Process</td>
<td>Uses Center for Scientific Review Process (study sections)</td>
<td>Internal review panel</td>
</tr>
<tr>
<td>Unfunded Proposals</td>
<td>Can be resubmitted one time within 2 years</td>
<td>No resubmissions permitted</td>
</tr>
</tbody>
</table>
What is Different from Agency to Agency?

Some examples include:

- Solicitation calendar
- Submission method
- Topic areas (broad vs. focused)
- Topic interests
- Investigator-initiated topics
- Dollar amount of awards
- Proposal preparation instructions

- Financial details and available options
- Due dates/times
- Proposal review process
- Success rates
- Resubmit process
- Phase II process
- And much, much more...

Make very few assumptions in SBIR!
DoD

- Department of Defense
  - SBIR and STTR, some components—Contracting
    - Army
    - Navy*
    - Air Force
    - SOCOM*
      - Special Operations Command
    - DARPA
      - Defense Advanced Research Projects Agency
    - MDA
      - Missile Defense Agency
    - Smaller Divisions

*SBIR Only
HHS

- Department of Health & Human Services
- Public Health Services
  - SBIR and STTR—contract and granting agency
    - CDC*
      - Centers for Disease Control and Prevention
    - NIH
      - National Institutes of Health (23 funding components—Institutes and Centers)
    - FDA*
      - Food and Drug Administration

*SBIR Only
USDA
- US Department of Agriculture (AG)
  - NIFA—National Institute of Food and Agriculture
  - SBIR only and a granting agency

NSF
- National Science Foundation
  - SBIR and STTR and a granting agency

DoEd
- DoEd—Department of Education
  - SBIR only, both contracting and granting
    - Moving one division within DoEd to DHHS
DOE

- **DOE**—Department of Energy
  - SBIR and STTR and a granting agency

DHS

- **DHS**—Department of Homeland Security
- **HSARPA**—Homeland Security Advanced Research Projects Agency
  - SBIR only and a contracting agency

NASA

- **NASA**—National Aeronautics & Space Administration
  - SBIR and STTR and a contracting agency
DOC

- DOC—Department of Commerce
  - NISTA—National Institute for Standards and Technology Administration
  - NOAA—National Oceanic and Atmospheric Administration
  - SBIR only and contracting

EPA

- EPA—Environmental Protection Agency
  - SBIR only and a contracting agency

DOT

- DOT—Department of Transportation
  - SBIR only and a contracting agency
Preparing Your Phase I Proposal
Pre-Proposal

• Identify a solicitation—READ the solicitation!

• Contact agency, if allowed

• Complete required registrations

• Establish the team

• Outline the project for Phase I, II and III
Identifying a Solicitation

- Use online resources
  - Zyn.com

- Use agency websites

- **Read** solicitations
  - Make no assumptions about what agency may be interested in your technology
  - Think outside of the box
  - Make sure project aligns with company mission
Contacting the Agency

- Focus the discussions around solving the agencies problem, not more research in a lab (BIG Issue!)
- Gain a clear understanding of the review process
- Listen, don’t talk!
- Establish credibility and demonstrate knowledge of the solicitation and agency
- Ask open-ended questions
Registrations

**Step 1:** Get an EIN from the IRS
- Available online
- Instant (no delay in processing)

**Step 2:** Acquire a DUNS number (must have TIN/EIN)
- Available online
- Instant (no delay in processing)
- Must match your EIN registration
Registrations

*Step 3: SAM.gov (replaced CCR)*

- A 48 hour delay after DUNS activated
- Can take up to 14 days
- Do not use Incubator address
- Requires a bank account (work-around ideas!)
- Involves IRS validation
- Requires CAGE Code assignment by DLA

Start EARLY and ask for help if delays are experienced!
Registrations

**Step 4: Grants.gov**

- Can take up to 48 hours after SAM clears
- Need MPIN you created during SAM registration
- Need DUNS number

**Step 5: SBA Registration**

- Required of all small businesses competing
- Must download certificate and attach to grant
Registrations

**Step 6: Agency-Specific Registrations**

- eRA Commons (HHS)
- FastLane (NSF)
- DoD’s website

- Start registration process early!
  - Registration delays and problems are common:
    - Multiple DUNS numbers
    - Tax verification
    - Lost passwords
    - Inactive
    - Browser Issues (Firefox is preferred browser of SAM.gov)
Establish The Team

- Who is the appropriate PI?

SBIR: The PI must be 51% employed by the small business at the time of award.

STTR: The PI can be employed by the small business or the Research Institution.

- What are their qualifications?
- Do they have publications (NIH)?
- Residency restrictions?
The Team

- What expertise is needed on the team that is missing?
- Who will support the project:
  - Consultants
  - Advisors
  - Subcontractors/Subawardees
  - Fee for service
- End user input and support?
- Commercialization experience
  - Specific to your industry
  - Concept to market
Outline Phase I, II and III

- Make Sure the project fits the SBIR framework:
  - Time
  - End result
  - Required resources
  - Commercial potential
  - Element of risk
  - A NEED exists in the marketplace
Four Most Common Mistakes:

- Not enough detail
- Too much unrelated information
- Not following agency’s guidelines
- Research study—not development of technology for commercialization
Consider the Following:

- This workshop or any other doesn’t make you an expert
- Be wary of people who will “write” the proposal for you
- Even with the help of a grant writer, SBIR proposals require an extensive amount of work (50-80 hours) and are full of unexpected surprises, technology challenges, delays and wrong turns
- **BE WISE**: Use resources available (What are those? Ask around!)
The Indiana SBIR/STTR Program

Aiding Hoosier Small Businesses & Entrepreneurs Pursuing Federal R&D funding

Dr. Lisa R. Sproul Hoverman
State of Indiana

Indiana Procurement Technical Assistance Center (PTAC)
Office of Small Business and Entrepreneurship (OSBE)

April 24, 2015
Session Overview

• Introduction
• Goal of the Indiana SBIR/STTR Program
• Indiana SBIR/STTR Program Services
• Indiana Matching Funding for SBIR/STTR Awards
• Review
• Q & A
Introduction

• Who we are:
• **Indiana Procurement Technical Assistance Center**
  – part of the Indiana Office of Small Business and Entrepreneurship (OSBE), a state agency existing under the management of the Lieutenant Governor’s office
  – Our purpose is to generate employment and improve the general economic condition of the state by assisting Indiana companies including those eligible for preferential consideration in obtaining and performing under local, state and federal government contracts
    • *SBIRs/STTRs are federal government grants and contracts that fall under this purpose*
Why state support for SBIR/STTR?

• “I just need help getting started. A little seed money.”

• SBIR/STTR Funding is $1-3M over 2-3 years, this spans 3 Phases.
Ideal Source of Funding for Commercialization

• **Non-Dilutive vs.**
  - Debt
  - Equity
Review of the Introduction

• SBIR/STTR enables small businesses (SBs) to explore new technologies by providing the incentive of profit from commercialization
  – Including Hoosier small businesses in the Nation’s R&D arena, stimulates high-tech innovation in Indiana’s economy
  – Indiana gains entrepreneurial spirit as it meets specific Federal R&D needs
Session Overview

• Introduction
• Goal of the Indiana SBIR/STTR Program
• Indiana SBIR/STTR Program Services
• Indiana Matching Funding for SBIR/STTR Awardees
• Review
• Q & A
Indiana SBIR/STTR Services

- The Indiana SBIR/STTR Program aids Hoosier (or Boiler!) Small Businesses in:
  - Vetting project(s) for SBIR/STTR
  - Solicitation Research & Matching
  - Registration Requirements Aid
  - Meeting with Federal Program Managers and Technical Points of Contacts (TPOCs)
  - Writing Assistance*
  - Tech Transfer
  - Other, various
Vetting the Project

• Apply for OSBE PTAC SBIR/STTR Program Assistance
  – Must be IN based (75% Asset in IN, and/or 50% employees based in IN)
• Meet with SBIR/STTR Program Specialist
• Review technology/innovation
• Initiate solicitation research*
• Review selected solicitation
• Discussion with PM/TPOC about idea and application, if possible
Solicitation Research & Matching

• IN SBIR/STTR Specialists match Hoosier SB technology with open SBIR/STTR solicitations for SB to pursue across the 11 agencies
  – On-going, until SB disengage with OSBE
  – Monthly touch points
  – Aid with outreach to PMs and TPOCs
Registration Requirements Aid

• Once a solicitation is chosen for pursuit, the PTAC can aid SBs in fulfilling all registration requirements (vary per agency)

• Examples include:
  – SAM ([www.sam.gov](http://www.sam.gov))
  – SBA ([www.sba.gov](http://www.sba.gov))
  – ERA Commons (NIH) ([www.public.era.nih.gov](http://www.public.era.nih.gov))
Meeting with the PMs/TPOCs

• SBIR/STTR Specialists can send an introductory email regarding your SB’s pending response

• SBIR/STTR Specialists can arrange phone calls and aid in communication of technology

• SBIR/STTR Specialists can aid in submission issues
Writing Assistance*

- MUST BE SCHEDULED at a minimum, 2 weeks in advance.
- Verify correct forms
- Verify format
- Reviews & setting milestones for drafts
  - Draft 1 (Rough Draft)
  - Draft 2 (Polished Draft)
  - Final (Ready for Submission)
- Providing editorial and content feedback at each milestone review
- Review for compliance
- *We do not write the response/grant*
- *We do not submit the grant*
Tech Transfer

• Connect Hoosier SBs with IP/technologies developed at universities, military installations, large corporations
  – Crane, Purdue, IU, and more to come!
• SBs can license this IP/technology and develop it further for commercialization and profit
Session Overview

• Introduction
• Introduction to Federal SBIR/STTR Program
• Indiana SBIR/STTR Program Services
• Indiana Matching Funding for SBIR/STTR Awardees
• Review
• Q & A
Indiana Matching SBIR/STTR Funding

• OSBE PTAC partnership with the Indiana Economic Development Corporation (IEDC) and Elevate Ventures

• Hoosier companies awarded Phase I SBIR/STTR funding can access matching awards up to an additional 50 cents for every federal dollar, up to $50,000 per award.
  – More non-dilutive funding!

• Additional co-investment opportunities for select Phase II recipients and those moving to commercialization (Phase III) may also be available.
Review

• SBIR/STTR funding for SB Innovation is available

• Indiana offers SBIR/STTR application aid through PTAC SBIR/STTR Program Specialists

• Matching Funding ($50 K/award*) is available for Phase I awardees (*max of 3 matched awards/lifetime of company as of 2014 relaunch)
Review – Useful Links

• Open and Closed SBIR/STTR Topics:

• Indiana SBIR/STTR Help:
  – www.indianaptac.com/sbirsttr/

• Indiana SBIR/STTR Phase I Matching Funding:

• Indiana Database for University Research Expertise (INDURE)
  – https://www.indure.org

• Purdue TAP
  – http://tap.purdue.edu
Thank You for Attending!

Dr. Lisa R. Sproul Hoverman
Indiana PTAC, a part of OSBE
lhoverman@osbe.in.gov
Upcoming IN SBIR/STTR Events

• Responding to a DOD SBIR/STTR Solicitation Webinar – May 12, 2:00pm - [https://global.gotomeeting.com/join/879488669](https://global.gotomeeting.com/join/879488669)

• Responding to an NIH SBIR/STTR - Omnibus and Targeted Solicitations Webinar – June 4, 2:00pm - [https://global.gotomeeting.com/join/723575141](https://global.gotomeeting.com/join/723575141)

• OSBE Entrepreneurship-Week: Tech Transfer 101 – June 18, 9:00 AM – Noon, Fifth Third Bank, The Precedent, 3515 E. 96th Street, Indianapolis, IN 46240

• IN PTAC hosts the SBA SBIR/STTR Bus Tour – July 13, 8:00 AM – 3:00 PM, Government Building South, Indianapolis, IN 46204
The Indiana Ecosystem for Lifescience Entrepreneurism

Jay McGill, Senior Director, LRL Operations Science and Technology Partnerships

April 24, 2015
Disclaimer

The following content is intended to share general information about Eli Lilly and Company in support of business development activities. This information is not intended, and may not be used, to promote any Lilly product(s). There are significant risks and uncertainties in Pharmaceutical research and development. Scientific and regulatory hurdles may cause pipeline molecules to be discontinued, or delayed, or fail to reach the market. There can be no guarantee that pipeline molecules will receive regulatory approval, or that they will prove to be commercially successful.

For presentation purposes only; no further distribution.
Lilly Fundamentals

Our Mission
We make medicines that help people live longer, healthier, more active lives.

Our Vision
To make a significant contribution to humanity by improving global health in the 21st century.

Our Values
Integrity, excellence, respect for people.
Lilly Fast Facts

- A heritage more than 135 years strong, founded on May 10, 1876
- Headquarters located in Indianapolis, Indiana, U.S.A.
- Approximately 39,000 employees worldwide*
- Products marketed in 125 countries

* Headcount as of September 2014
Lilly R&D Fast Facts

- R&D expenditures in 2014 between $4.6 to 4.8 billion*
  - Approx. US $18 million spent per workday globally*

- Clinical research conducted in more than 55 countries

- Research and development facilities located in 8 countries

- More than 8,000 employees engaged in research and development or 21% of total workforce**

* Financial figures based on 2014 Guidance issued with Q3 earnings on 23-Oct-2014
** Headcount as of September 2014
Openness to Collaborate with Academia

We are open for innovation, our laboratory is the world.

- 79 funded LRAP/LIFA Collaborations
- 50 institutions in 7 countries
- Over 110 Active Engagements (Academia, PPPs, Small Biotech, NIH)
  - >400 Universities and Small Biotechs
  - 600 Active Investigators
LRL Innovation Facilitation Team (LIFT) - LIFT was created with the mandate to enable sustainable and unhindered innovation. The team seeks to drive organizational change and foster innovation in three dimensions: technology, people and environment.

LIFT PROGRAMS

Lilly Research Award Program (LRAP) - Established to support and fund innovative, precompetitive research and technology collaborations between LRL scientists and external experts.

Lilly Innovation Fellowship Award (LIFA) - Created to identify and foster exceptional post-doctoral scientists pursuing ground breaking research projects. The LIFA program pairs a post-doctoral scientist with their academic mentor and a Lilly scientist, who serves as an industry mentor.

Lilly Graduate Research Advanced Degrees (LGRAD) - The LGRAD program provides a flexible framework for Lilly employee’s to pursue an advanced scientific degree while fully satisfying the requirements for graduate study at the School of Medicine, School of Public Health, or School of Science.
Academic “Connect” Initiative

The goal of this initiative is to strengthen LRL’s connections with local institutions and provide a mechanism to allow scientists to connect/collaborate on non IP-generating projects.

The New Program will:

• Connect scientists to enable novel collaborations
• Provide a cash-free mechanism to connect university researchers to LRL scientists
• Limit to non-IP generating research
  • Development of technologies
  • As with other LIFT initiatives, not linked directly to the portfolio of tomorrow, but focused on enabling our scientists to connect
Rationale For Lilly Connect Program

“For scientists, by scientists”

Exchange of ideas: initial research is non-IP generating and not related to Lilly portfolio of molecules

• Provide help to projects/ideas to nurture them along
• No expectation of immediate benefit for Lilly
• No expectation or rights to background technologies

Exchange of non-proprietary materials
Facility, equipment, etc.
Others...
Addressing scientific gaps through PPPs

AMP
Accelerating Medicines Partnership
NIH
Lilly
ANTIN
Alzheimer's Research UK
Defeating Dementia
Eisai
Lilly
MRC
Medical Research Council
SPARC
Lilly
Takeda
INDIANA CTSI
Clinical and Translational Sciences Institute
NIH
National Center for Advancing Translational Sciences
MWPC
UNIVERSITY OF CINCINNATI
Lilly
NIH
National Center for Advancing Translational Sciences

Target Chem
Preclin
Tox
Translate
Differentiate
Clin dev
Regulatory
Outcome

strategic, synergistic, and sensible
Governed through a universal MTA and affiliation process

The Lilly TB Drug Discovery Initiative
Mission:
• Support early stage drug discovery across CTSI partner universities,
• Act as a clearinghouse for regional drug discovery and development resources, and
• Facilitate compound library sharing and collaborative translational research between drug discovery chemical and biological researchers.

Established service agreements with drug development service companies, Covance and Quintiles to provide services to Indiana CTSI partners.

• Covance, for standard in vivo studies for early drug discovery assessment.

• Quintiles (Indiana Operations), to provide standard in vitro ADME characterization services for early drug discovery programs.

For more information on MTP program check the website:
https://www.indianactsi.org/mtp
BioCrossroads

• BioCrossroads is Indiana’s initiative to build on Indiana’s life sciences strengths

WE INVEST:
By launching and investing in new life sciences enterprises

Indiana SEED Fund II
New Ventures Competition

WE EDUCATE:
By expanding science and math education in grades K-12 and higher learning institutions

WE CONNECT:
By partnering with Indiana’s life sciences research institutions, corporations, philanthropic organizations and state government to build new opportunities

WE SPREAD THE WORD:
By marketing Indiana’s life sciences industry

BioCrossroads® LINX
Connections to Drug Development Resources

Framework®
An Idea Exchange for Indiana Life Sciences

BioCrossroads®
Lilly Academic Hubs - VC Funded

Multi-faceted collaborations – Connected – Disease excellence

Integrate academia and industry to prosecute novel targets and technologies across key priorities

Lilly scientists to shape targets and molecules in partnership with academics

Position Lilly to share in ‘New Co’ as the science progresses

Academic Institutions
Early Innovation

Lilly
Capabilities

EPI DAREX
CAPITAL

accelerator

Strategic collaborations

Copyright © 2016 Eli Lilly and Company
Questions or Contact Us…
Click “External Innovation Partnering” on Lilly.com
Yvonne Lai, Ph.D.
Co-Founder, Anagin
Senior Scientist, Dept of Psychological and Brain Sciences, IUB
Indiana CTSI, navigator, IUB campus
April 24, 2015
JCEB Annual Innovation Workshop
Introduction

- Anagin utilizes a novel therapeutic approach to inhibit excessive glutamate receptor signaling in the central nervous system
- Novel compounds developed using this platform have the capability to address unmet medical needs in several diseases including post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), depression and chronic pain
Overview

**Vision:** Anagin is the industry leader with a novel therapeutic platform to inhibit excessive glutamate receptor signaling in the CNS with a focus on several diseases with unmet medical needs

**Location:** Indianapolis, IN

**Technology:** Novel PSD95-nNOS; Novel nNOS-NOS1AP Modulators

**IP Estate:** IURTC filed patent

**Founders:** Anantha Shekhar, M.D., Ph.D.
Yvonne Lai, Ph.D.

IURTC
Anantha Shekhar, M.D., Ph.D.; Founder
• Director of Indiana CTSI
• Professor of Psychiatry
• Associate Dean of Translational Research

Yvonne Lai, Ph.D; Co-founder, Director of R&D
• Senior Scientist, ICOS Corporation
• Senior Scientist, MDS Pharma Services

Joe Trebley, PhD; Business Manager
• Head of IURTC start up
IU Academic Collaborators

Andrea Hohmann, Ph.D.
Professor, Linda and Jack Gill Chair of Neuroscience
Expert in preclinical models of pain, addiction and memory

Xiao-Ming Xu, Ph.D.
IUSM; Scientific Director, Spinal Cord and Brain Injury Research Group; Stark Neurosciences Institute;
Professor and Mari Hulman George Chair of Neurological Surgery; Expert in preclinical models of traumatic brain injury.
What is the technology?
Disruption of Glutamate Signaling Complex
What are the clinical opportunities?

A novel technology platform that addresses multiple indications

Global Market

![Bar chart showing market size for PTSD, Chronic pain, Depression, and Stroke. PTSD has the smallest market size, Stroke has a moderate market size, Depression has the largest market size, and Chronic pain falls in between.]
Small molecule development Roadmap

2011-present; IUB-Hohmann, Pain models
IUSM-Shekhar, PTSD; Xu-TBI

Target ID/Target Validation
2000-2006
ICOS HTS
Cell based validation
Preclinical validation

Preclinical validation
2013
Started Anagin
With help from IURTC

Chemistry optimization

Clinical Trials
Submitting SBIR-Science

How much data do we have when we apply for SBIR phase I?
• Found small molecule hit from HTS (ICOS)
• Demonstrated efficacy in primary neurons (ICOS, IUB)
• Demonstrated preclinical efficacy in animal models of pain (ICOS; Hohmann, IUB), PTSD (Shekhar, IUSM)
• Chemistry exploration steps designed by Thakur (NEU) and proposed in SBIR phase I
• Goal of SBIR is to use medicinal chemistry to evolve/improve existing lead; future Phase II will focus on identifying drug development candidate
Discussion with Program Officer

Phone conference with NIMH SBIR program officer:

1. Suggested special two year SBIR phase I funding mechanism (expired in 2013)
2. Confirmed scope of research is within limit of SBIR phase I and guided us through research aims
Starting a company with IU

IU Spinup provided support in:

• Registration of a new company; certification as small business
• File patents; patent search and guidance from IURTC
• SBIR/STTR grant preparation (content, letters of support; budget (and university subcontract/budget), grant submission (through IU spin up) and follow up; External consultant available through IURTC
• Once company has started, provide business guidance, hire CRO accountant/HR; suggest incubator space; access to equipment/resources
Forming a Team

Business: Joe Trebley, Ph.D., Polina Feldman, Ph.D., M.B.A.

Yvonne Lai, Ph.D.; Melissa Haulcomb, Ph.D.
Chemists (academic and CRO)
Andrea Hohmann, Ph.D. (preclinical; IUB subcontract)
Pharmacology and Project Management Consultants
Anantha Shekhar, Ph.D., M.D.
How to get funded

Red: External grants; Blue: IU internal grants; Green: pending/submitted

R21/NIDA; R21/NIMH -> 2 year SBIR-I/NIMH; State: $50k matching

Target ID/ Target Validation

Preclinical validation

Chemistry optimization

Clinical Trials

CTSI core grant

IURCG

Small HTS

CTSI core grant

FORCES

IURTC; filed use patent

Submitted, April 2015

STTR/SBIR
Next Steps

Build management team (hire CEO), raise non-NIH money to accelerate drug discovery; continue to use NIH grants to fund mechanism of action studies and build novel disease models.

2015
- Hire CEO
- With guidance from Trebley
- Raise early Seed money
- Add back-up chemical series

2016
- Continue chemistry
- Identify lead structure
- Submit Phase II SBIR
SBIR application

Research plan:
• Specific Aims; Research strategy and References

Budget:
• Company budget (calculating indirect; add 7% SBIR fee; know the restrictions for academic subcontracts); subcontracts (academic; CRO)
• Access to CTSI discounted rates at Covance and Quintiles; Letters of support:
• IU Spin up; collaborators; Consultants Facilities/Equipment:
• Access to resources from IU Spin up (Indianapolis)
• Methodist Hospital (Indianapolis) research center
SBIR application continued

Consortium agreement/Gantt chart
- To clarify who is doing what and when
- To clarify who is responsible for each milestone
- To describe the business plan of the company
- To show you have the necessary resources to not only complete goals of Phase I SBIR, but to move on to SBIR Phase II and beyond.
Angel Investors

Who Are They
What Do They Do
How can They Help You
How Can They Help You

• Angels provide help to early companies in many ways including:
  – ProvidingAdvice: in an advisory capacity or as a member of the corporate board
  – Making key introductions to useful contacts
  – Providing capital
Who Are They

• Angels come in all age groups, genders, and ethnicities
• They can invest individually or collectively in small amounts or very large sums
• Commonly they invest as groups or in syndicates
• They all share one common qualification of being accredited investors
Accredited Investors

• Category presently under review for possible revision and created to insure that investors have the resources to invest in this the most risky of asset classes
• Requires liquid assets (excluding home) in excess of 1 million dollars or
• An annual income in excess of 250 thousand dollars
What Do They Do

• They are involved in helping nurture early stage companies (start ups)
• This involvement often includes much expert council when appropriate and often participation in corporate governance
They Also Invest Money

- Angels also invest their money in companies often at very early stages of development
- In a recent year they invested $22.5 billion dollars in 66,230 entities
- They differ from Venture Capital in that they invest their own money and usually at much earlier stages in the development of the company
What of These Dollars

- Studies from 1980 to 2005 and subsequently confirmed by others show that ALL net job growth in the US economy came from companies existing five years or less
- Net job growth is directly related to startups
- Angels provide over 90% of the equity funding for these early companies
Angel Investments
the asset class

• High risk high reward
• Even under best practices investors will loose all of part of their money in half of their investments
• Significant investment returns resulting in profitability of the portfolio come from only a small percentage of holdings (10% to 20%)
• Best practices including prior knowledge and research of the company and investment space help but don’t insure successful outcomes
• Money can be tied up for several years
Why Do They Do It

• This is a labor that is motivated by many factors including shared experiences and interests, a desire to be involved in creating new solutions and often a sense of giving back to others.

• Regardless of the causes for this involvement it is helpful for entrepreneurs to understand these factors to take better advantage of their involvement with angels.
Should You Talk to an Angel

• Consider doing so only if you are willing to share a percentage of your company through the issuance of equity or convertible debt.
• Understand outside equity often comes with conditions which might relate to governance and management of the company including the possibility of ultimately replacing the founders under certain circumstances.
If So When

• When your product is developed or near completion
• You have existing customers or others committed to purchasing your product
• You are exhausting existing funds
• You have a solid business plan and can demonstrate that your company will likely grow rapidly reaching revenues of $10 million dollars in three to seven years
How to Talk to an Angel

• Be able to demonstrate a strong and experienced management team with proven skills
• Have a unique product with strong competitive advantages and patent protection when indicated that addresses a large potential market
• Provide a clear understanding of the potential market and a realistic plan for market penetration
• Provide an accurate accounting of past expenses and income and a realistic estimate of future costs and revenues
How to Find an Angel

• Local and institutional resources
• The Angel Capital Association Member directory at angelcapitalassociation.org
• Social networks
• Remember angels get their name because they are supportive, therefore don’t be afraid to reach out for help even if you may not be ready to apply for funding.
Antibody-based Prevention and Therapy for Infectious Diseases: Safety, Efficacy and Industrialization

Kevin J Whaley, PhD
CEO, Mapp Biopharmaceutical, Inc.
San Diego, CA
April 24, 2015
Critical Path

(FDA, 2004)
FDA Approved Monoclonal Antibodies

[Bar chart showing the number of FDA approved monoclonal antibodies for different categories: Autoimmune Disorders, Oncology, Infectious Disease, Others.]
Mapp: Developing Antibody Drugs for Global Health and Biodefense

• Founded in 2003 to develop antibody drugs for the prevention and treatment of infectious diseases
• Focusing on unmet needs in global health and biodefense
• 19 employees
  • ½ R&D
  • ½ CMC, Regulatory, Clinical
<table>
<thead>
<tr>
<th>Target</th>
<th>Proof of concept efficacy</th>
<th>Disease Expert Collaborator (Institution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's</td>
<td>rodent</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>C. difficile toxins A and B</td>
<td>rodent</td>
<td>Iowa State University</td>
</tr>
<tr>
<td>Contraceptive, topical (anti-sperm)</td>
<td>rabbit</td>
<td>Boston University, Johns Hopkins</td>
</tr>
<tr>
<td>Cholera</td>
<td>being evaluated in rodents</td>
<td>Wadsworth Institute</td>
</tr>
<tr>
<td><strong>Ebola virus (ZMap™)</strong></td>
<td>NHPs; compassionate use human data</td>
<td>PHAC, USAMRIID, Scripps</td>
</tr>
<tr>
<td>Junin virus</td>
<td>rodent</td>
<td>University of Texas Medical Branch</td>
</tr>
<tr>
<td>Marburg virus</td>
<td>rodent</td>
<td>PHAC, UTMB, Vanderbilt</td>
</tr>
<tr>
<td>MB66 HIV/HSV vaginal film</td>
<td>NHPs; Phase 1 human study Q4 2015</td>
<td>Boston U., Brown U., Emory U., UNC, Johns Hopkins</td>
</tr>
<tr>
<td>MERS</td>
<td>NHP</td>
<td>Harvard University</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>rodent</td>
<td>Aridis Pharmaceutical</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>rodent</td>
<td>CSIR</td>
</tr>
<tr>
<td><strong>Ricin</strong></td>
<td>rodent</td>
<td>Wadsworth Institute, Tulane University</td>
</tr>
<tr>
<td>RSV (extended half-life)</td>
<td>rodent</td>
<td>University of Texas</td>
</tr>
<tr>
<td>SEB</td>
<td>NHP</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Sudan virus</td>
<td>rodent</td>
<td>PHAC, USAMRIID</td>
</tr>
<tr>
<td>Venezuela equine encephalitis</td>
<td>rodent</td>
<td>USAMIIID, DRDC, Dstl</td>
</tr>
</tbody>
</table>
1890: Emil von Behring and Shibasaburo Kitasato

- From anti-toxin to the serotherapy of diphtheria, tetanus
- Nobel prize for von Behring in 1901
The Birth of Monoclonal antibodies

1975 Cesar Milstein and Georges Köhler develop technique for making monoclonal antibodies

Nobel prize: 1982
The pros and cons of monoclonal antibodies for infectious diseases

- Rapid development pathway
- Safety theoretically easy to predict (but not always…)
- Functions rapidly (unlike vaccines)

- Cost (not always)
- Route of administration
- Escape mutants
- …
The Opportunities

- Emerging infections
- Pandemics
- Where vaccines not used
- Where vaccines fail – e.g., conserved subdominant epitopes
- Antimicrobial resistance
- Immuno-senesced and Immuno-suppressed
- Bio-defense
Some of the Challenges

- **Regulatory**:
  - Gathering adequate data for rare or emerging diseases
  - Trial design for highly lethal diseases
  - Switching from approved polyclonal to new monoclonal

- **Economic viability**
  - An antibody only works against a single disease target. If this disease is rare, or episodic is there a business model to support the continued production?

- **Pathogen escape**
  - Polyclonal serum targeted multiple sites – will pathogens develop escape mutants to monoclonal products?
Ebola Virus

- Transmitted by direct contact with body fluids
- Associated mortality rates as high as 90%
- Causes viral hemorrhagic fever
  - Massive destruction of organs, vascular damage and hemorrhage
- Identified as a bioweapon threat since it has the potential for aerosol dissemination
- Currently there are no licensed vaccine or treatment

Sporadic EBOV outbreaks in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Dead</th>
<th>Total</th>
<th>CFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>Democratic Republic of the Congo</td>
<td>280</td>
<td>318</td>
<td>88.0503</td>
</tr>
<tr>
<td>1977</td>
<td>Democratic Republic of the Congo</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>1994</td>
<td>Gabon</td>
<td>31</td>
<td>52</td>
<td>59.6154</td>
</tr>
<tr>
<td>1995</td>
<td>Democratic Republic of the Congo</td>
<td>250</td>
<td>315</td>
<td>79.3651</td>
</tr>
<tr>
<td>1996</td>
<td>Gabon</td>
<td>21</td>
<td>37</td>
<td>56.7568</td>
</tr>
<tr>
<td>1996-97</td>
<td>Gabon</td>
<td>45</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>1996</td>
<td>South Africa*</td>
<td>1</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>2001-02</td>
<td>Gabon, Republic of the Congo</td>
<td>96</td>
<td>122</td>
<td>78.6885</td>
</tr>
<tr>
<td>2002-03</td>
<td>Republic of the Congo</td>
<td>128</td>
<td>143</td>
<td>89.5105</td>
</tr>
<tr>
<td>2003</td>
<td>Republic of the Congo</td>
<td>29</td>
<td>35</td>
<td>82.8571</td>
</tr>
<tr>
<td>2005</td>
<td>Republic of the Congo</td>
<td>9</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>2007</td>
<td>Democratic Republic of the Congo</td>
<td>187</td>
<td>264</td>
<td>70.8333</td>
</tr>
<tr>
<td>2008-09</td>
<td>Democratic Republic of the Congo</td>
<td>15</td>
<td>32</td>
<td>46.875</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1093</strong></td>
<td><strong>1393</strong></td>
<td><strong>78.4637</strong></td>
</tr>
</tbody>
</table>

*Exported cases from the second 1996 Gabon outbreak

- Fruit bats are suspected to be one of the reservoirs of EBOV, but there has been no direct evidence so far

http://www.who.int/csr/disease/ebola/Global_EbolaOutbreakRisk_20090510.png
Figure 2: Geographical distribution of new and total confirmed cases
As the Ebola epidemic slows, efforts turn to accelerating clinical trials of investigational therapies.

Figure 1: Confirmed, probable, and suspected EVD cases worldwide (data up to 5 April 2015)

- **Guinea**: 3515 Cases, 9862 Deaths
- **Liberia**: 2333 Cases, 12 138 Deaths
- **Sierra Leone**: 4408 Cases, 3831 Deaths
- **Mali**, **Nigeria**, **Senegal**, **Spain**, **United Kingdom**, **United States of America**

**Total**
- Cases: 10 587
- Deaths: 25 550

Source: Centers for Disease Control and Prevention.
Ebola virus (EBOV)

- Taxonomy:
EBOV virology

- Baltimore class V: (-)ssRNA virus
- Genome is 18-19kb in size
  - Encodes for 7 genes (9 viral proteins)
- Virion is filamentous in shape, 970 nm long, 80nm in diameter on average

Qui 2014, PHAC
Glycoprotein (GP)

- is sole protein on the surface;
- is believed to be the most important protein involved in pathogenesis;
- is responsible for receptor binding, viral entry, cytotoxicity and vascular permeability and cellular tropism;
- is the key target for developing neutralizing antibodies.

Qui 2014, PHAC
Potential Treatments

- **Recombinant Human Activated Protein C (rhAPC)**
  - 18% protection (Rhesus macaques)

- **rNAPc2**
  - 33% protection (Rhesus macaques)

- **PMOplus** (phosphorodiamidate morpholino oligomers)
  - 62.5% protection
  - 30–60 min after infection

- **VSV-based vaccine**
  - 50% protection (Rhesus macaques)
  - 30 min post-infection

- **Small Interfering RNAs (siRNA)**
  - 100% protection
  - 7 post-exposure treatments 30-60 min post-infection

 Qui 2014, PHAC
Antibody Therapy in Filovirus Disease

[The isolation of hyperimmune horse serum to the Ebola virus].
[Article in Russian]
Kraainikhi VE, Mirzalev VV, Bonachev IV, Gradochov VN, Evseev AA, Pshenichnov VA.

Passive immunization of Ebola virus-infected cynomolgus monkeys with immunoglobulin from hyperimmune horses.
Laudenbo FB, Geisbert TJ, Scheurer ST, Jern GP, Lewis T, Haagensen JK, Schmidt M, LaGru JF, Peters CJ.
United States Army Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21702-6071, USA.

Neutralizing Antibody Fails to Impact the Course of Ebola Virus Infection in Monkeys

Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease
John M. Dye, Andrew S. Herbert, Ana I. Kuehne, James F. Barth, Majidat A. Muhammad, Samartha E. Zak, Ramon A. Ortiz, Laura I. Prugar, and William D. Pratt.

Protective Efficacy of Neutralizing Monoclonal Antibodies in a Nonhuman Primate Model of Ebola Hemorrhagic Fever
Animal Models for Filoviruses

- Mouse, Guinea Pig, Nonhuman Primate (NHP)

• Critical link that may be difficult to achieve with animal data

Qui 2014, PHAC
## Efficacy of mAb cocktails in the Ebola NHP model

<table>
<thead>
<tr>
<th>mAb cocktail</th>
<th>Species</th>
<th>Days treatment initiated post-infection</th>
<th>Dosing every 3 days (# doses)</th>
<th>% Survival (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB-003</td>
<td>Rhesus</td>
<td>1</td>
<td>50 mg/kg (4)</td>
<td>67% (3)</td>
</tr>
<tr>
<td>MB-003</td>
<td>Rhesus</td>
<td>2</td>
<td>50 mg/kg (4)</td>
<td>67% (3)</td>
</tr>
<tr>
<td>MB-003</td>
<td>Rhesus</td>
<td>4-5</td>
<td>50 mg/kg (3)</td>
<td>43% (7)</td>
</tr>
<tr>
<td>ZMAb</td>
<td>Cyno</td>
<td>1</td>
<td>25 mg/kg (3)</td>
<td>100 (4)</td>
</tr>
<tr>
<td>ZMAb</td>
<td>Cyno</td>
<td>2</td>
<td>25 mg/kg (3)</td>
<td>50 (4)</td>
</tr>
</tbody>
</table>

MB-003 = c13C6 + c6D8 + h13F6  
ZMAb = 4G7 + 2G4 + 1H3

# Efficacy evaluation of plant-derived chimerized mAbs in Guinea Pigs

<table>
<thead>
<tr>
<th>Treatment Groups/time</th>
<th>Dose (mg)</th>
<th># Survivors / # Total</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS/ 3dpi</td>
<td>N/A</td>
<td>0/4</td>
<td>0</td>
</tr>
<tr>
<td>ZMAb /3dpi</td>
<td>5</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>MB-003 /3dpi</td>
<td>5</td>
<td>0/6</td>
<td>0</td>
</tr>
<tr>
<td>13C6+2G4+4G7/ 3dpi</td>
<td>5</td>
<td>4/6</td>
<td>67</td>
</tr>
<tr>
<td>13C6+1H3+2G4/ 3dpi</td>
<td>5</td>
<td>3/6</td>
<td>50</td>
</tr>
<tr>
<td>13C6+1H3+4G7/ 3dpi</td>
<td>5</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>13C6 /1dpi</td>
<td>5</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>13F63 /1dpi</td>
<td>5</td>
<td>1/6</td>
<td>17</td>
</tr>
<tr>
<td>6D8 /1dpi</td>
<td>5</td>
<td>0/6</td>
<td>0</td>
</tr>
</tbody>
</table>
ZMapp™ treatment initiated 3, 4, or 5 dpi

D = Dosing days 3, 6, 9
E = Dosing days 4, 7, 10
F = Dosing days 5, 8, 11

c13C6 + c2G4 + c4G7
Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp

Group A = c13C6 + c2G4 + c4G7 (n=6)
Group B = c13C6 + 1H3 + c2G4 (n=6)
Group C = PBS or control IgG (n=2)
Since August 2014, twenty-nine doses of ZMapptm have been administered to nine patients under expanded access/compassionate use provisions.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Outcome of hospitalization</th>
<th>doi</th>
<th>Criteria for discharge and sequelae / Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alive at discharge</td>
<td>30</td>
<td>Asymptomatic and PCR-negative for two consecutive days. No significant sequelae.</td>
</tr>
<tr>
<td>2</td>
<td>Alive at discharge</td>
<td>29</td>
<td>Asymptomatic and PCR-negative for two consecutive days. Sequelae restricted to a mild peripheral sensory neuropathy without motor involvement.</td>
</tr>
<tr>
<td>3</td>
<td>Death</td>
<td>12</td>
<td>Multiple organ failure with respiratory distress and severe shock attributed to progression of EVD</td>
</tr>
<tr>
<td>4</td>
<td>Alive at discharge</td>
<td>19</td>
<td>PCR negative and asymptomatic for 24 hours. No significant sequelae.</td>
</tr>
<tr>
<td>5</td>
<td>Alive at discharge</td>
<td>25</td>
<td>PCR negative and asymptomatic for 24 hours. No significant sequelae.</td>
</tr>
<tr>
<td>6</td>
<td>Death</td>
<td>26</td>
<td>Progressive neurological and cognitive impairments including disorientation, depression and rapid onset of stupor attributed to progression of EVD</td>
</tr>
<tr>
<td>7</td>
<td>Alive at discharge</td>
<td>15</td>
<td>Asymptomatic and blood PCR-negative for six consecutive days. No significant sequelae.</td>
</tr>
<tr>
<td>8</td>
<td>Alive at discharge</td>
<td>14</td>
<td>Asymptomatic and PCR-negative. No known sequelae.</td>
</tr>
<tr>
<td>9</td>
<td>Death</td>
<td>~13</td>
<td>TBD</td>
</tr>
</tbody>
</table>
Investigational New Drug (IND) Application

- Rolling submission to the pre-IND
- IND submitted February 3, 2015
- OK to proceed received February 5, 2015
- OK to proceed received by NIAID February 6, 2015 for their Phase 1/2 RCT Master Protocol
Phase 1/2 Study

Principal Investigator:

Richard Davey, M.D. (NIAID)

ClinicalTrials.gov Identifier: NCT02363322

- “A Multicenter Randomized Safety and Efficacy Study of Putative Investigational Therapeutics in the Treatment of Patients with Known Ebola Infection”
  - Designed to establish the safety and efficacy multiple therapeutics
    - ZMapp™ is the first to be evaluated
  - Randomized and controlled to a current optimized standard-of-care (oSOC)
  - Adaptive trial design with frequent interim monitoring to facilitate the following:
    - dropping of poorly performing arms
    - introduction of new candidate therapies
    - modification of current oSOC
- Sponsored by the National Institute of Allergy and Infectious Diseases
- Sites in the U.S. and Liberia (initially), Sierra Leone/Guinea (recently)
- Primary Outcome Measure: Mortality at Day 28
- Secondary Outcome Measures:
  - Clinical and virology effects of treatment
  - Adverse events
  - Plasma viral load
Continued plans for development

- NHP dose reduction study at USAMRIID: in-life completed (DTRA)
- Allometric scaling and PK modeling (Gates Foundation)
- Continuing manufacture (BARDA)
- BLA enabling activities (BARDA)
- Additional manufacturing systems being explored (BARDA)
Mucosal Antibodies for Multipurpose Prevention: MB66 (HSV/HIV Abs)

- HSV8-N, VRC01-N (cell-free virus)
- IgG1, IgG2, IgG3, IgG4, IgA, S-IgA, IgM
- GnGn, Aglycosylated, GnGn+galactose, GnGnNaNa
- 2\textsuperscript{nd} Generation Ab-based MPT: VRC01-N, PGT121-N, HSV8-N, HC4 (sperm and cell-associated HIV)
Formulating Antibody-based MPTs

- **Ab Film**: HSV/HIV/sperm Abs for use without or with a cervical barrier
- **Ab Ring**: a non-hormonal ring consisting of HSV/HIV/sperm Abs (LNG could be used in conjunction with sperm Ab to enhance contraceptive efficacy)
- **Ab Injectable**: co-administration of HSV/HIV Abs with 1 or 3 month injectable contraceptives
- **Ab Vaccine**: FcRn-mediated mucosal vaccines; fusion proteins gD-Fc and Gag-Fc
Antibody-based Film: On Demand
Ab Ring: Non-Coital

Replaceable Pod Design

- PVA-coated mAb core
- Silicone shell with two delivery channels (release rate controlling)
- IVR release window (not rate controlling)
- Delivery channel
- Silicone shell
- PVA coated mAb core
Potential Antibody Targets
to Block Cell-associated HIV transmission

<table>
<thead>
<tr>
<th>Target Class</th>
<th>Specific targets (antibodies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV specific antigens</td>
<td>CD4 binding site (NIH45-46, 3BNC60, VRC01)</td>
</tr>
<tr>
<td></td>
<td>glycan/V3 loop (10-1074, PGT121)</td>
</tr>
<tr>
<td></td>
<td>gp41 (10E8, 4E10)</td>
</tr>
<tr>
<td>HIV binding sites on CD4+ cells</td>
<td>CD4 (Ibalizumab)</td>
</tr>
<tr>
<td></td>
<td>CCR5 (PRO140)</td>
</tr>
<tr>
<td>CD4-negative cell-bound virus</td>
<td>CD18</td>
</tr>
<tr>
<td>Host derived antigens on both free virus and cells</td>
<td>CD36</td>
</tr>
<tr>
<td></td>
<td>LFA-1/CD11a (MEM30)</td>
</tr>
<tr>
<td></td>
<td>TSG101 (CB8-2)</td>
</tr>
<tr>
<td></td>
<td>GM3 (DH2)</td>
</tr>
<tr>
<td></td>
<td>ICAM-1</td>
</tr>
<tr>
<td>Uninfected dendritic cells</td>
<td>CD169</td>
</tr>
<tr>
<td>Reproductive tract coating antigens</td>
<td>SAGA-1, male tract specific glycoform of CD52 (H6-3C4, S19)</td>
</tr>
</tbody>
</table>
Cocktail of Ricin, SEB, ETX Antibodies: Protection in Mice
RSV-N Antibodies (5mg/kg) in Mice

1. Half-live extension technology may enable Abs to be circulating systemically for 3-6 months resulting in seasonal protection for diseases like RSV and influenza.

2. Reduced costs and increased scale may enable larger markets (prevention in infants and elderly; global).
Critical Path

(FDA, 2004)
Costs and Scale of Antibody Manufacturing (DS)

• Mammalian:
  • Costs: Currently $100-$200/g; near term target $10/g
  • Scale: 3-(30?)g/L; 20,000L fermenters (three story high) coupled to three story high protein A columns; several week cycle?

• Fungi
  • Costs: $10/g?
  • Scale: 1-3 g/L; 300,000L fermenters; 7 day cycle

• Plants
  • Costs: $10/g?
  • Scale: 0.1-1g/kg; 3,000 kg/acre; 7 day cycle

• VIP/IGT
  • Costs: low?
  • Scale: not a significant issue?
Large scale manufacturing in *Nicotiana* at KBP

More than 1 acre of indoor controlled growth space
Productivity of existing KBP facility

- ~ 50,000 doses/yr of a typical single mAb drug (e.g. 1 mg/kg)
- ~ 10,000,000 doses/yr of a typical vaccine antigen
- ZMapp™ challenges:
  - 3 mAbs must be manufactured individually
  - Current dosing is large (~ 12g /course of treatment; ~3.5 g/dose; 1:1:1)
  - Expression optimization
  - Infrastructure for manufacturing in Nicotiana very limited compared to mammalian cell culture
## Release Assays

### Drug Substance

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visible Appearance</strong></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Osmolality</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Protein Concentration</strong></td>
<td>UV Absorbance</td>
</tr>
<tr>
<td><strong>Identity</strong></td>
<td>IEX-HPLC</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>GP-binding ELISA</td>
</tr>
<tr>
<td><strong>Purity</strong></td>
<td>Size Exclusion HPLC</td>
</tr>
<tr>
<td><strong>SDS-PAGE</strong></td>
<td>(non-reduced)</td>
</tr>
<tr>
<td><strong>SDS-PAGE</strong></td>
<td>(reduced)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Endotoxin</td>
</tr>
<tr>
<td><strong>Bioburden</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Impurities</strong></td>
<td>Residual Host Cell DNA</td>
</tr>
<tr>
<td><strong>Residual Protein A</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Residual Host Cell Protein</strong></td>
<td></td>
</tr>
<tr>
<td><strong>GC for Nicotine Content</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Heavy Metal Content</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Drug Product

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visible Appearance</strong></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Osmolality</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Protein Concentration</strong></td>
<td>UV Absorbance</td>
</tr>
<tr>
<td><strong>Other Tests</strong></td>
<td>Uniformity</td>
</tr>
<tr>
<td><strong>MFI/FLOWCam</strong></td>
<td>Particulate Matter</td>
</tr>
<tr>
<td><strong>Identity</strong></td>
<td>IEX-HPLC</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>GP-binding ELISA</td>
</tr>
<tr>
<td><strong>Purity</strong></td>
<td>Size Exclusion HPLC</td>
</tr>
<tr>
<td><strong>SDS-PAGE</strong></td>
<td>(non-reduced)</td>
</tr>
<tr>
<td><strong>SDS-PAGE</strong></td>
<td>(reduced)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Endotoxin</td>
</tr>
<tr>
<td><strong>Sterility</strong></td>
<td></td>
</tr>
</tbody>
</table>
Accelerating Clinical mAb Production via Plants

**mAbs from *N. benthamiana* to produce GMP Bulk DS**

- DNA to Released GMP Bulk DS in 7-8 months
- IND-enabling Tox material in 3-4 months (using untested MCB)
- Upstream comments:
  - Minimal to zero USP development required
  - Plants can be growing consistently for any mAb program
  - No inter-campaign time lost due to product changeover

**mAbs from CHO to produce GMP Bulk DS**

- Cell Line Generation DOEs (~10-12 months to single clone selection)
- Transfection pool DS
- Platform Methods
- USP/DSP Process Development DOEs
- Analytical Method Development
- Analytical Method Qualification
- Formulation Dev.
- Adventitious testing/viral clearance
- Eng. campaign
- GMP campaign

DNA T=9 months

MCB bank and test (3 months)

DSP Dev. and DS

Platform Methods

Analytical Method Dev/Qualification

Formulation Dev.

GMP campaign

Release and test
Distribution of N-Linked Glycans: \( \text{IgG}_1 \) (Mol %)

<table>
<thead>
<tr>
<th>Glycan Type</th>
<th>Synagis</th>
<th>Rituxan</th>
<th>HSV8-N</th>
<th>VRC01-N</th>
</tr>
</thead>
<tbody>
<tr>
<td>M5</td>
<td>15</td>
<td>53</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>GnM</td>
<td>12</td>
<td>35</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>GnMF</td>
<td>7</td>
<td></td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>G1M</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G0</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnGn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- GlcNAc
- Mannose
- Fucose
- Galactose
The other end of the antibody

Alter, 2015
Mammalian Cell Manufacturing

• Over two decades expression of recombinant proteins has increased from 100mg/L to 10g/L
• Current drivers: maintaining product quality while reducing time to market, cost effectiveness, and manufacturing flexibility
• Since antibody therapies may require large doses over a long period of time, manufacturing capacity becomes an issue because the drug substance must be produced in large quantities with cost and time efficiency to meet clinical requirements and pave the way toward commercialization.
• Many companies have built large scale manufacturing plants containing multiple 10,000L (some 20,000L) cell culture bioreactors.
Glycoengineered Fungi

- Ease of genetic manipulation (including glycosylation)
- Stable expression
- Rapid cell growth (batch every 7 days)
- Good yield of secreted antibody (1-3g/L)
- Low-cost scalable fermentation processes (300,000L fermenters in multiple manufacturing plants located around the world)
- No risk of human pathogenic virus contamination
Table 4. Breakdown of Costs for Various Process Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>cell culture</th>
<th>purification</th>
<th>fill-finish</th>
<th>depreciation and labor</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>base case (10 tons)</td>
<td>2</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>low titer (0.5 g/L) (1 ton)</td>
<td>20</td>
<td>4</td>
<td>10</td>
<td>100</td>
<td>134</td>
</tr>
<tr>
<td>3-column purif (10 tons)</td>
<td>2</td>
<td>23</td>
<td>10</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>combined low titer and 3 column (1 ton)</td>
<td>20</td>
<td>23</td>
<td>10</td>
<td>100</td>
<td>153</td>
</tr>
</tbody>
</table>

Kelley B, Biotechnol. Prog. 2007;23:995-1008
Cost of goods breakdown by unit operation.

Kelley B, Biotechnol. Prog. 2007;23:995-1008
Figure 1. Process flow diagram for the 10-ton mAb purification process.
Strategies to Further Lower Cost

- Improve expression
- Simpler Purification: e.g. flocculation, disposable Protein A
- Extend systemic half-life (2-6 months): YTE, Xtnd Fc mutations
- Local manufacturing of Drug Substance
  - Mammalian: single use bioreactors (SUB)
  - Fungi: large fermenters currently available
  - Plants: transgenic, focus on purification
  - VIP/IGT: ?
Vectored Immunoprophylaxis

- 200-1000 ug/ml of Ab in systemic circulation of mice
- Protection against HIV, influenza A, and malaria sporozoite infection in mice
- A Phase 1 dose-escalation trial of a VIP vector encoding a broadly-neutralizing anti-HIV Ab (PG9) is currently recruiting healthy HIV-uninfected volunteers (NCT01937455; www.clinicaltrials.com)

Immunoprophylaxis by Gene Transfer

Zmapp IGT studies being conducted at several institutions
Some of the Challenges

● Regulatory:
  - Gathering adequate data for rare or emerging diseases
  - Trial design for highly lethal diseases
  - Switching from approved polyclonal to new monoclonal

● Economic viability
  - An antibody only works against a single disease target. If this disease is rare, or episodic is there a business model to support the continued production?

● Pathogen escape
  - Polyclonal serum targeted multiple sites – will pathogens develop escape mutants to monoclonal products?
The Opportunities

- Emerging infections
- Pandemics
- Where vaccines not used
- Where vaccines fail – eg conserved subdominant epitopes
- Antimicrobial resistance
- Immuno-senesced and Immuno-suppressed
- Bio-defense
Mapp Funding Overview: Target Diseases

Target diseases for which Mapp is developing monoclonal antibody-based preventive and/or therapeutic products:

- Ebola (NIH/DOD/OTHER: U01, SBIR, BAAs, Gates)
- HSV/HIV microbicide (NIH: U19)
- EEV (DOD: DTRA BAA)
- C. difficile (NIH: Phase 1 SBIR)
- Marburg virus (NIH: Phase 2 SBIR)
- Junin virus (NIH: U01)
- Ricin (DOD: Phase 1 SBIR)
- RSV (NIH: Phase 1 SBIR)
- SEB (NIH: RO1, Phase 1 SBIR)
Reflections on Innovation and Entrepreneurship in Biotechnology

- SBIR program (esp. SBIR-AT-NIAID) has been instrumental for funding, initiating and sustaining collaborations
- Maintain long term, productive collaborations with appropriate funding mechanisms (e.g. U19)
- Utilize existing infrastructure (academic, preclinical, clinical, manufacturing, regulatory) when feasible; minimize burn rate
- Understand market failures and unmet need
- Develop a diverse pipeline of products based on a robust (likely to be safe, effective, and industrializable) platform technology
Acknowledgements

AI58345, AI72915, AI109762

AI58345, AI72915, AI109762

HDTRA1-13-C-0018

HHSO100201400009C