Clostridium novyi-NT
Cancer Therapeutic

Chordoma Foundation
March 22nd 2013

Chetan Bettegowda MD PhD
Saurabh Saha MD PhD
BioMed Valley Discoveries

BVD-CNv (Saurabh Saha MD PhD)
- Preclinical

BVD-CNv (Chetan Bettegowda MD PhD)
- Companion dogs
- Human
BioMed Valley Discoveries (1/2)

Background

• Headquartered in Kansas City, MO with a Boston office, BioMed Valley Discoveries was incorporated in 2007 as a for-profit entity of the Stowers Group of Companies with over $120M in evergreen funding and access to a $2B endowment established by billionaire philanthropist Jim Stowers

• Perform bench-to-bedside translational research with a focus on addressing unmet medical needs instead of on achieving commercial returns, advancing science by tackling projects that may be considered too early or too unconventional for traditional biotech or pharmaceutical companies

• Pursue projects across different therapeutic and diagnostic areas, including cancer, inflammation, and infectious disease. Goal is to ensure that innovative treatments, backed by strong scientific evidence, will reach patients across the world

• Our investment strategy is to take long-term perspective, work with our network of partners to advance projects from ‘proof-of-concept’ to the marketplace.
BioMed Valley Discoveries engages in research and development projects that have the potential to address unmet clinical needs. BioMed will consider opportunities at any stage of development.

**Research and Development Pipeline**

- **In Vivo Diagnostic for Imaging Infections**
  - Learn more or go to clinical trial
  - BVD-INF / PJH
  - BVD-INF / DFI
  - BVD-CN1 / IV
  - BVD-CN1 / IT

- **Novel Cancer Biologic Therapy**
  - Learn more or go to clinical trial
  - BVD-ERK
  - BVD-MOR
  - BVD-PHX
  - BVD-EXF
  - BVD-AB1
Contents

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Case Study – Bacterial Tumor Infection (1/3)
Liver Metastases - Month 0
Case Study – Bacterial Tumor Infection (2/3)
3 Months Later, Post 5-FU
Case Study – Bacterial Tumor Infection (3/3)

1 Month Later, Post C. septicum
THE PRACTITIONER.

NOVEMBER, 1902.


By WILLIAM B. COLEY, M.D.

The subject of the treatment of sarcoma with the mixed toxins of erysipelas and bacillus prodigiosus is one upon which I have been working constantly for the last seventeen years, and one which has grown more interesting to me with each succeeding year.

While the results have not been as satisfactory as one who is seeking perfection could wish, they have been sufficiently real and tangible, I think, to be entitled to more careful consideration than they have yet received. Furthermore, they may have an important bearing upon the whole cancer problem, since, if by the administration of certain bacterial toxins we can cause the degeneration, death, and absorption of living tumour cells of one variety of cancer, sarcoma, it is not unreasonable to suppose that by the use of some other forms of bacterial toxins, we may succeed in destroying or inhibiting the growth of the other and more common variety, carcinoma.

- William B. Coley, MD
Heterogeneous Oxygenation
Typical human liver metastasis
Why Anaerobic Bacteria?

- Hypoxia present in all solid tumors
- Hypoxia associated with tumor progression and metastasis
- Hypoxia a determinant of radio- and chemoresistance

However

Hypoxic/necrotic tissue in solid tumors is a perfect “breeding ground” for anaerobic bacteria
## Bacterial Strains Tested

<table>
<thead>
<tr>
<th>Bifidobacteria</th>
<th>ATCC Number</th>
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<tbody>
<tr>
<td>B. adolescentis</td>
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<td>B. pseudolongum</td>
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<td>C. bifermentans</td>
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<td>ATCC 19401</td>
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<td>ATCC 19402</td>
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<td>C. Sordelli</td>
<td>ATCC 9714</td>
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<td>C. Perfringens</td>
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**C. novyi**

ATCC 19402
Effects of *C. novyi* *in vivo*

Before *C. novyi* → 12 hours → Tumor lysis → 6 hours → Secreted α-Toxin
Discovery of Non-toxic Strain of *C. novyi*

*C. novyi*

Eliminate Lethal Toxin Gene on Phage Episome

*C. novyi -NT*
C. novyi-NT Product Development

C. novyi-NT

Spore form

Non-proliferative
• Biologically Inert
• Resistant to temp, pH, chemical insults
• With higher density

Vegetative form

Proliferative
• Highly motile
• Secreting lytic factors
• Eliciting host immune responses
• With lower density

Hypoxia
Use live anaerobic bacteria to colonize, replicate within and destroy solid tumors
Spores Alone in Nude Mice Do Not Cure

Day 0

Day 30

*C. novyi-NT*
C. novyi-NT + Chemotherapy

HCT116 xenografts 300 million spores/animal, i.v.

<table>
<thead>
<tr>
<th></th>
<th>HT1-286</th>
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<tr>
<td></td>
<td>C. novyi-NT</td>
<td>+ C. novyi-NT</td>
<td>C. novyi-NT</td>
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<td>Day 0</td>
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</table>
C. novyi-NT + External Beam Radiation

Xenograft, 300 million spores/animal, IV 2 Gy/day x 5 days, Cs-137

HCT116

Radiation Alone  Radiation + C. novyi-NT

Day 0

Day 5

Day 10

HuCCT1

Radiation Alone  Radiation + C. novyi-NT
Spores Alone Cure Tumors in Immune Competent Mice

DAY 0  DAY 3  DAY 6  DAY 12  DAY 24
Rabbit Studies

**MODEL:** New Zealand White Rabbits

**TUMOR:** VX2 NZW rabbit liver carcinoma

**DOSE:** Single dose of *C. novyi-NT* spores
Rabbit Studies with C. novyi-NT
PET/CT Images

<table>
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<tr>
<th>Day</th>
<th>No Treatment</th>
<th>Post- Rx C. novyi-NT</th>
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<tr>
<td>71</td>
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<td>440</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
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</table>
Rabbit Studies with C. novyi-NT

Overall Survival

Kaplan Meyer Survival Curve:
Rabbit VX2 Liver Tumor

C. novyi-NT treated (n = 23)
Untreated (n = 7)

Untreated (n = 7)
Long-Term Immune Response Against Tumor

- Cured mice and rabbits were resistant to *re-challenge* with original tumor
- Subsequent acquired immunity was found to be CD8⁺-dependent
Small Animal Data Excitement

“Germ Warfare of Sorts Shows Promise Against Cancer”
A New Class of Cancer Therapeutic
C. novyi-NT Advantage

- Selective ⇒ target only hypoxic tumors
- Amplification ⇒ bacteria replicate in tumors
- Tumor dissemination ⇒ motile, spreading throughout tumor
- Versatility ⇒ kills quiescent and dividing cells
- Safety ⇒ neutralized by antibiotics
- Gene Therapy Vehicle ⇒ transform bacteria with payload
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C. novyi-NT Studies in Companion Dogs

Objectives

• Learn about the toxicity, management of infection, and evaluable responses of C. novyi-NT administered at various doses in companion animals with spontaneous tumors (previous preclinical studies were performed in animals with experimental tumors)

• Clinical observations from canine studies will inform human Ph1 study

• Pursue mono- and combination studies, as well as IV repeat dosing and intratumoral dosing with C. novyi-NT in animals with spontaneous tumors

• Potentially seek registration of C. novyi-NT (as a mono- or combo- therapy) in animal health for appropriate cancer indication(s)
C. novyi-NT Ongoing Canine Studies

More Translational Studies for Efficacy and Toxicity Management

- Local intra-tumoral administration
- Repeated IV dosing
- Imaging study to assess germination, immune response and tumor response
- Combination with radiation therapy
C. novyi-NT Intra-tumoral Dog Studies

1 to 4 cycles of intratumoral delivery of C. novyi-NT spores into a target tumor lesion successfully achieved:

- Biological response in 14/16 dogs treated (tumor inflammation, edema, discharge, erythema)
- Complete response in 3/8 dogs evaluable to-date; partial response in 1/8 and stable disease in 2/8
- Therapy well tolerated with mostly Grade 1-2 AEs
Intratumoral *C. novyi-NT* in Companion Dogs

**11-R01 Andy**

As of Mar 06, 2013

**Baseline**
- 29 mm PNST
- Prior therapy: Surgery

**Therapy Course**
- Day 2: Mild signs of infection (swelling and erythema)
- Day 3: Tumor lanced and drained
- Day 14: Wound healed
- Day 70: Thicken skin (suspected scar tissue) remaining at the tumor site

**Response Analysis:**
Grossly tumor-free at D120, suspected scar tissue remaining
Intratumoral *C. novyi*-NT in Companion Dogs

04-R03 Baxter *complete*  

As of Mar 06, 2013

**Baseline**
- 55 mm PNST
- Prior therapy: None

**Therapy Course**
- Day 15: Signs of infection following 3rd cycle
  - Grade I lameness, swelling, bleeding, fever, anorexia
  - Grade II lethargy and pain
- Day 16: Tumor lanced and debrided
- Day 19: Adverse events resolved
- Days 16-60: Wound managed with bandage changes
- Prior tumor site is healed and remains grossly tumor-free.

**Response Analysis:**
Grossly tumor-free at D94
Belle – Complete Response without Abscess
Single intratumoral injection x 4 cycles

- Mast cell tumor on paw
- No observable tumor 16 days after last cycle of intratumoral therapy
- Currently grossly tumor free at day 120+
Intratumoral *C.novyi-NT* in Companion Dogs
11-501 Hope

As of Mar 06, 2013

Baseline
- 99 mm PNST
- Prior therapy: None

Therapy Course
- D1-3: Signs of infection following 1st cycle
  - Grade I tumor warmth
  - Grade II fever and tumor abscess
    - Max fever 104.5
    - Lanced and debrided
    - “Scooped the tumor out”
- D4: Sent home, daily bandage changes
- D14: Closed the open wound by primary intent

Response Analysis:
Grossly tumor free at D28
New protocol designed to minimize patient risks and maximize therapeutic benefit based on the following considerations

- SOFA scoring system to guide initiation of antibiotics
- Requirement for 7-day hospitalization; patient to reside within 45 min. from an ER and have a caregiver for 28 days after dosing
- Antibiotics, once started, to be given indefinitely (low dose doxycycline)
Human Phase I Clinical Trial Study Overview
BVD Sponsored Protocol & Commercial IND

Current ongoing phase I clinical study (www.clinicaltrials.gov | NCT01118819)

- Design: Open-label, multi-center, non-randomized, single dose escalation
- Patients with treatment-refractory solid tumors and good performance status
- Standard 3+3 dose escalation with pre-defined doses for each of 5 cohorts

Study objectives

- To determine the safety profile, dose limiting toxicities (DLT), and maximum tolerated dose (MTD)
- To document preliminary evidence of anti-tumor activity
- To study the disposition of C. novyi-NT spores in circulation
- To assess the host immune and inflammatory response
Human Phase I Clinical Trial Inclusion/Exclusion
BVD Sponsored Protocol & Commercial IND

Patient eligibility (inclusion/exclusion)

- Age $\geq 18$ with histologically documented cancer refractory to standard therapy or at least one line of therapy in those for whom no standard treatment exists
- Measureable disease, ECOG performance status of 2 or less, adequate renal, hepatic and bone marrow function
- No brain metastases
- Adequate oxygen saturation, blood pressure and Glasgow Coma Score
- Absence of large effusions or ascites
- No concomitant immunosuppressive agents
- An intact spleen
- No allergy to antibiotics used to treat Clostridia infections; not have been treated with antibiotic(s) within 2 weeks of dosing
- 7-day hospitalization; reside within 45 min of an ER and have a caregiver for 28 days after dosing
Dosing Schedule Design

- Patients to be observed for 4 weeks prior to escalating to a new cohort; 1st patient in a cohort to be observed for a minimum of 2 weeks prior to enrollment of subsequent patients;

- Doses increased in successive cohorts until the MTD is reached or until complete germination and tumor regression occurs in all target lesions, making higher doses unnecessary.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of Patients</th>
<th>Dose $(x\ 10^5$ spores/kg)</th>
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<tr>
<td>1</td>
<td>3-6</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3-6</td>
<td>3</td>
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<tr>
<td>3</td>
<td>3-6</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>3-6</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>3-6</td>
<td>100</td>
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</table>
SOFA Score: Guidance of Initiation of Antibiotics

Sequential Organ Failure Assessment (SOFA) score will be calculated by adding the individual scores from each system based on the table below. (assessed predose, 8, 16, 24 hrs post-dose and daily through day 7)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Modified SOFA Score</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂ (torr)</td>
<td>&gt;400</td>
</tr>
<tr>
<td>SpO₂/FiO₂ (torr)</td>
<td>≥512</td>
</tr>
<tr>
<td>Coagulationa</td>
<td></td>
</tr>
<tr>
<td>Platelets (x10³/mm³)</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Liver a</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL) (μmol/L)</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td></td>
<td>&lt;20</td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
</tr>
<tr>
<td>Central Nervous System (Glasgow coma score scale)</td>
<td>15</td>
</tr>
<tr>
<td>Renal a</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL) (μmol/L)</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>or urine output</td>
<td>&lt;110</td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

Respiratory + Coagulation + Liver + Cardiovascular + CNS + Renal = SOFA Score
Guided by SOFA Score

- A total SOFA score of 5 or greater; OR
- An individual organ system SOFA score of 2 or greater within the respiratory, cardiac, coagulation, or central nervous systems; OR
- An individual organ system SOFA score or 3 or greater within the liver or renal systems.
- Antibiotics can be initiated any time based on Investigator discretion

Antibiotics will be administered by the following schedule:

- Parenteral piperacillin/tazobactam (Zosyn) and metronidazole (flagyl) until the patient is afebrile and clinically stable for 48 hours, then
- Six weeks of oral or parenteral metronidazole.
- Indefinite oral doxycycline (100mg po bid)
Status of Phase 1 Study (IV administration)

- Study start: April 2011
- Study sites: 4 sites activated, 2 sites to be initiated
  - Johns Hopkins – PI: Charlie Rudin, M.D.
  - Albert Einstein – PI: Sanjay Goel, M.D.
  - Univ. Michigan – PI: Scott Schuetze, M.D.
  - Washington Univ. (Siteman) – PI: Andrea Wang-Gillam, M.D.
- Four patients enrolled and treated on cohort #1 at a dose of $1 \times 10^5$ spores/kg
  - Tumor types include colorectal, fibrolamellar liver, ovarian and chordoma
  - 1 patient not evaluable due to need for antibiotic treatment on day #3 for an unrelated *Klebsiella* bacteremia incurred prior to dosing of the drug
  - Only Grade 1 and 2 drug-related adverse events observed
  - SOFA score for antibiotic initiation not reached in any patient
  - 1 patient started on antibiotics on Day 8 based on clinical judgment
  - 2 patients discharged without need for antibiotics; both remained afebrile
- One patient treated on cohort #2 at a dose of $3 \times 10^5$ spores/kg on Feb 7th. No AEs have been reported as of the end of Week 3 post-treatment.
Second Human Phase I Clinical Trial Underway
C. novyi-NT Intratumoral (IT) Administration Protocol

A new protocol with a new local route of administration
- Protocol submitted to the FDA for review
- FDA agrees with the IT route of treatment for the targeted patient population
- Further discussion with FDA regarding dose design underway
- Expect to open in the Summer of 2013

Key features of the new IT protocol
- Similar study design and patient population as the open Phase I IV study, except the target tumor should be measurable, palpable and amendable to intratumoral injection.
- Hospitalization required for 5 days (instead of 7 days for the phase I IV study)