WP1122:
Novel Therapy for CNS Malignancies

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Treatment Paradigm

- Inhibition of glycolysis for the treatment of primary and metastatic brain tumors
- Novel agent: Orally bioavailable small molecule inhibitor of glycolysis with high CNS uptake and retention with demonstrated in vivo activity in orthotopic glioma model
- Our discovery overcomes limitations of existing inhibitors of glycolysis
Biology

- Tumors rely preferentially on glycolysis even in the presence of abundant oxygen.
- For example: PET diagnostic imaging relies on a modified glucose with a radio-tracer ($F^{18}$DG).
  - Tumors over-consume $F^{18}$DG because of their dependence on glycolysis.
- Cutting off this “fuel supply” (inhibiting glycolysis) results in targeted tumor cell death.
Chemistry – Improving the Drug-Like Properties of 2-DG and Targeting Brain Cancers

Example of heroin
Heroin is the diacetyl ester of morphine that increases by 100-fold levels of morphine in the brain

WP1122 is the diester of 2-DG of our design, which greatly enhances CNS uptake and levels 2-DG in the brain

[Diagram showing chemical structures of morphine, heroin, and WP1122]
Pharmacology (PK/PD)

- 2-DG CNS distribution and retention was measured after oral administration of equimolar amounts of 2-DG and its diacetate WP1122
- CNS distribution and retention of 2-DG is dramatically higher when generated from WP1122
- No observed systemic toxicity
In Vivo Findings - WP1122 is Effective *In Vivo* against Gliomas

- WP1122 used alone has at least the same or greater activity than temozolomide (Temodar®), a current *standard of care* in patients diagnosed with glioblastoma.
- We used temozolomide to create our clinical development strategy.

Orthotopic Glioblastoma Model in Mice
Intellectual Property

• Composition of matter and its uses protection for WP1122
• Priority date: 7/11/2008
• Broader protection of chemical space in progress
• Additional patents are being processed to cover design platform technology
• Worldwide exclusive license from MD Anderson
  – Sublicense granted in Poland and lesser neighboring countries to facilitate ~$5 million development grant for brain tumors. Separate license to explore topical dermatology use granted to USA company.
Appendix

- Development Plan Overview thru Major Inflection Points
- Clinical Development Path to NDA
- Phase I/II Protocol Highlights – Proof of Concept
- Highly Experienced Development Team
- Drug design platform
Development Plan Overview

Year: 0  1  2  3  4  5

- Manufacturing / Scale Up
- Toxicology Package
- File IND
- Phase I/II Trials
- Registration Clinical Trial
- NDA Approval
- Marketing

Funding:
- Year 1: $7.5mm
- Year 2: $10mm
- Year 3: $15mm

- Grant & Equity Round
- Efficacy
- Revenue

Strategic exit 2 to 5 years from funding

Grant & Equity Round
Efficacy
Revenue

www.braintumor.org
Clinical Development Path

- Proof of concept generated within 3 years
- Provides major valuation inflection point for funding
- Accelerated approval path allows for registration on expanded Phase II trial
- Approval = mandatory use, hence small team capable of achieving full distribution
- Strategic sale or license most likely exit

IND within 12 months
2013/2014

Phase I/II trial with 65 patients
1-2 years

Expanded Phase II registration trial
2 years

NDA and revenue from drug sales
2017 – 2018
Phase I/II Protocol Highlights

• 65 Patients with recurrent high-grade glioma (for Phase I component and glioblastoma for Phase II)
• 3 X 3 design for Phase I dose escalation trial
• Standard Inclusion/ exclusion criteria; screening F\(^{18}\)-DG PET for inclusion
• Select dosing based on animal toxicology studies
• Pharmacokinetic blood draws on days 1 and 14 with repeat PET scan on day 14 to look for “Biologically Effective Dose” (BED)
• Standard dose limiting toxicities with 1 out of 3, Grade 3 or 4 with cohort expansion of 6; then 2 out of 6, Grade 3 or 4 DLT’s; define maximum tolerated dose (MTD) at one cohort below
• Patients enrolled must be evaluated by a dietician and agree to adhere to a low carbohydrate diet
• Based on animal PK and toxicology – the preliminary dosing schedule would be: oral, twice daily dosing continuously
• Once MTD is reached, if much different than “Biologically Effective Dose”, then discussion from a panel of “experts” to decide the dose to be used for the Phase II trial
## Highly Experienced Development Team

(working together for last 8 years – took early stage project from discovery to Phase II clinical activity with $10 million in equity financing)

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<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Experience</th>
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<tbody>
<tr>
<td>Waldemar Priebe, PhD</td>
<td>Founding Partner and CSO</td>
<td>• Award-winning professor at MD Anderson Cancer Center</td>
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<td>• Inventor of multiple clinically evaluated drugs</td>
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<td></td>
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<td>• Discovery used to launch $100 million Nasdaq company</td>
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<td>• Discovery used to form Reata, $1 billion drug company</td>
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<td>Walter V. Klemp</td>
<td>Founding Partner and CEO</td>
<td>• First company returned 49 times original investment</td>
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<td>• Took next company public and grew to #1 on INC 500</td>
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<tr>
<td></td>
<td></td>
<td>• $400 million annual revenues, 2,500 employees, 7 countries</td>
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<td>• Last 8 years developing FDA approved drugs and devices</td>
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<td>Don Picker, PhD</td>
<td>COO</td>
<td>• Led team to develop $500 million cancer drug</td>
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<tr>
<td></td>
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<td>• 25 years drug development experience</td>
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<td></td>
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<td>• Wide range of disease targets from bench to NDA</td>
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<td>• Put first generation of platinum drugs through FDA</td>
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<td>Charles Conrad, MD</td>
<td>Principal Investigator</td>
<td>• Professor of Neuro-oncology at MD Anderson Cancer Center</td>
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<td>• Physician scientist with &gt;10 years clinical trial design experience</td>
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<td>• PI or co-PI on over 70 clinical trials</td>
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<td>• Inventor/founder of several drug development start-ups</td>
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Long-Term Strategy - Drug Design Platform

- WP1122 is the first in a line of drugs that can be derived from our “design platform”
- Our initial focus is on CNS malignancies to obtain rapid approval
- IP is in process for a broader range of esterase enhanced therapies