Implicyte

Next generation neuro-oncolytic virotherapy
Investment thesis

TECHNOLOGY

- A novel and proprietary armed neuro-oncolytic virotherapy platform that efficiently destroys tumor cells without harming normal brain tissue.
- Chimeric VSV expressing IL-12 and CD40L, combining direct tumor lysis with potent and targeted immune stimulation.
- Replication competent viruses travel safely through the brain to destroy distal tumors and heavily glycosylated glycoprotein prevents antibody neutralization.

INDICATIONS AND CLINICAL PLAN

- Rapid path to clinic and proof-of-concept; initial targeting of recurrent glioblastoma lowers barriers and allows expedited initiation of Phase 1 safety trials as no effective treatments currently exist; opportunity to observe early efficacy signals.
- Once safety confirmed, will quickly expand into other gliomas and ovarian cancer.
- Broad infectious tropism of chimeric VSV further expands opportunity to a wide range of malignancies, including skin, colon and lung cancers.

ENTERPRISE

- Experienced founding team, key advisors, contractors and development partners.
- Company owns exclusive rights to proprietary IP portfolio including broadly protective foundational IP licensed from Yale University
- Currently raising $30 million to achieve product proof-of-concept and reach exit opportunities by Year 4 with Phase 2 data.
## Team

### Founders

**Lutz B. Giebel, PhD**  
Chairman

- CEO, Co-Founder & Director, Delinia, Inc.
- Managing Partner, SV Life Sciences
- CEO, Director & Co-Founder Cythera Inc. (now ViaCyte)
- Co-Founder & VP Research, MetaXen

**John S. Swartley, MBA, PhD**  
President

- Associate Vice Provost for Research and Managing Director, Penn Center for Innovation
- General Partner, BCM Technologies
- Associate Director of Licensing, Yale OCR
- Director of Multiple Startups

### Advisors

**Donald O’Rourke, MD**  
Chief Clinical Advisor

- Professor of Neurosurgery, University of Pennsylvania
- Leading world expert on brain malignancies
- Director of Penn’s Human Brain Tumor Tissue Bank and Glioblastoma Translational Center of Excellence

**Thomas Monath, MD**  
Chief Development Advisor

- Managing Partner, Crozet BioPharma
- Led multiple innovative viral vaccines through clinical development, licensure and commercialization, including VSV Ebola vaccine.
- Served as the Chief Medical Officer for numerous companies

**Dung “Zung” Thai, MD, PhD**  
Chief Medical Advisor

- 19+ years clinical director including numerous clinical trials, including first in human study of REMD-477
- Numerous leadership roles in biopharma including Atara, Anza Biotherapeutics, and Gilead Sciences

### Management

**Matthew Stremlau, PhD**  
Vice President Research and Development

- Harvard-trained virologist
- Winner Science Magazine’s Grand Prize for Young Life Scientists (2007)
Opportunity

+ Implycye has **exclusively licensed Yale University’s oncolytic rVSV platform** for the treatment of brain malignancies and other cancers.

+ The Van den Pol research group demonstrated that **chimeric VSV diffuses readily through tissue** to attack and eliminate both primary and distant tumors.

+ Our lead chimeric VSV incorporates the heavily glycosylated Lassa virus envelope protein, which **prevents the formation of neutralizing antibodies**.

+ We are further enhancing this platform by arming these neuro-oncolytic viruses with **potent immune-stimulating transgenes**.

+ We have **filed additional patents** covering our novel “armed” immunostimulatory chimeric VSVs.

The late Dr. Anthony van den Pol
Implicyte’s non-neurotoxic chimeric virus has been engineered by replacing the wild type vesicular stomatitis virus (VSV) glycoprotein with the Lassa fever virus glycoprotein, which also makes it less immunogenic.

Additional candidate viruses include non-neurotoxic chimeric VSV with either the Ebola virus glycoprotein or the Chikungunya virus glycoprotein substituted for the wild type G-protein.

### Implicyte’s Lead Therapeutic Candidates

<table>
<thead>
<tr>
<th>Chimeric Virus</th>
<th>Glycoprotein</th>
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<tbody>
<tr>
<td>VSV-Lassa</td>
<td>Lassa</td>
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<tr>
<td>VSV-Ebola</td>
<td>Ebola</td>
</tr>
<tr>
<td>VSV-Chikungunya</td>
<td>Chikungunya</td>
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**VSV-Lassa:** 3’ → N → P → M → LASV-GP → L → 5’

Lassa virus glycoprotein replaces VSV glycoprotein.
CB17 SCID mice with xenografts of human RFP-expressing rU87 glioma were treated with a single intravenous injection of either VSV-Lassa or saline (control) 15 days after tumor placement.

VSV-Lassa destroys brain glioma and prolongs life indefinitely.
VSV-Lassa diffuses safely through brain to seek out and destroy multiple tumors

+ A major challenge in effectively treating high-grade gliomas and other brain malignancies is **tumor cell migration** within the brain causing multiple tumors.

+ To model this challenge, both the **left and right side of the SCID mouse brain** was implanted with U87 human gliomas.

+ Fifteen days later, **VSV-Lassa was injected into the tumor on the right side** of the brain.

+ Eight days later, **VSV-Lassa** had destroyed the inoculated tumor on the right side of the brain, and the virus had **migrated to the contralateral left tumor (abscopal effect)** and begun the **process of infection** and destruction without adversely affecting the intervening normal brain tissue.

*Wollmann et al., J. Virology, 2015*
VSV-Lassa efficiently destroys ovarian cancer after systemic injection

+ A single administration of LASV-VSV eliminates detectable ovarian cancer cells. Fluorescence imaging of mice who received an injection of ovarian tumor cells are shown in Figure A.

+ Mice treated with a single intraperitoneal injection of VSV-Lassa (center panel) completely eliminates ovarian tumors; in contrast, treatment with cisplatin only partially eliminates the tumors.

+ VSV-Lassa causes a rapid reduction in tumor size and presence. In Figure B, the graph shows the relative size of human ovarian tumors in mice at different stages of tumor development.

+ Tumors in untreated or cisplatin treated mice continue to expand until mice are euthanized at Day 50; by way of contrast, tumors in the VSV-Lassa treated cohort were completely eliminated and treated mice survived >210 days.

van den Pol et al, Virology, 2020, 12(555):44-55
Clinical development plan

+ Phase 1a safety testing and proof-of-concept in patients with recurrent glioblastoma.
+ Phase 1b expansion to other brain gliomas.
+ Phase 2 to include glioblastoma, other brain gliomas, and ovarian cancer.
+ Opportunity for accelerated approval based on Phase 2 results. Fully eligible for both Orphan Disease Designation and Biological Exclusivity.
+ Future expansion potential to other solid tumors, such as skin, lung and colon cancers.

**Proof-of-concept in brain malignancies**

**Phase 1a**
- Glioblastoma

**Phase 1b**
- Glioblastoma
- Other gliomas

**Phase 2**
- Glioblastoma
- Other gliomas
- Ovarian cancer

**Expand to additional cancer indications**
- Lung
- Skin
- HCC
- Colon
- Renal
- Head and Neck
- Pancreatic
- Others based on basket outcome

+ Implycyte is also developing a set of novel virotherapy biomarkers, which can be performed by qPCR on patient tumor samples, to stratify patient population and significantly improve clinical trial success.
## Approach Advantages

<table>
<thead>
<tr>
<th>Innovation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Non-neurotoxic</td>
<td>Permits targeting of brain tumors with potent oncolytic and immunostimulatory activity, without damaging healthy tissue.</td>
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<td>Rapid clearance of secondary tumors</td>
<td>Chimeric viruses diffuse rapidly and safely through tissue to seek out and destroy multiple distal tumors.</td>
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<td>Armed with IL-12 and CD40L</td>
<td>Transforms an inherently ‘cold’ tumor into one that is ‘hot’ and activates a potent anti-tumor immune response. Transgenes stimulate T lymphocytes and natural killer cells that help to eradicate primary tumors and prevent growth of secondary ones.</td>
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<td>No neutralizing antibodies</td>
<td>Highly glycosylated heterologous glycoproteins shield virus from neutralizing antibodies.</td>
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<td>Safe and effective against multiple cancers</td>
<td>Effective against a wide range of malignancies including glioma, brain metastases, ovarian, melanoma and colon with potential for further expansion to other solid tumor indications</td>
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Contact

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