Combining Bi-specific Antibodies and Oncolytic Virus Therapy

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Company Overview

- **BCM spin-off company at JLABS@Houston**
- **Technology**: Oncolytic virus therapies
- **Lead Program**: T-cell Engager-Armed oncolytic virus expressing bi-specific antibodies (TEA-OV)
- **Short Timeline to Clinic With Lead Program**: ppIND meeting has been held regarding IKT-901, which is expected to enter Phase I in Q3 2018
- **Manufacturing & Trial Execution Leverages Leading OV Experts**: BCM & UPMC experts for GMP production and trial execution
- **Strong IP Portfolio**: Robust and growing portfolio of filed 4 patents

## Company Overview & Key Highlights

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology</th>
<th>Indication</th>
<th>Research</th>
<th>IND Enabling</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKT-901</td>
<td>FAP-TEA-VV</td>
<td>Solid tumors</td>
<td></td>
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<tr>
<td>IKT-902</td>
<td>EpCAM-TEA-VV</td>
<td>Solid tumors</td>
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<tr>
<td>IKT-903</td>
<td>EphA2-TEA-VV</td>
<td>Solid tumors</td>
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<tr>
<td>IKT-904</td>
<td>HER2-TEA-VV</td>
<td>Solid tumors</td>
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<tr>
<td>IKT-905</td>
<td>GPC3-TEA-VV</td>
<td>Solid tumors</td>
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<tr>
<td>IKT-906</td>
<td>GD2-TEA-VV</td>
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<tr>
<td>IKT-907</td>
<td>FAP-TEA-HSV</td>
<td>Solid tumors</td>
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</table>

### TEA-OV Candidates

### VV Expressing Checkpoint Inhibitors

### CAR (Chimeric Antigen Receptor)-T: VV Loaded & Next Gen NK

<table>
<thead>
<tr>
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<th>Technology</th>
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<tbody>
<tr>
<td>IKT-701</td>
<td>VV-loaded CAR-T</td>
<td>Solid tumors</td>
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<tr>
<td>IKT-702</td>
<td>CD19-CAR-NK</td>
<td>Blood tumors</td>
<td></td>
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<tr>
<td>IKT-703</td>
<td>GD2-CAR-NK</td>
<td>Solid tumors</td>
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</table>
# Oncolytic Viruses: Validated through recent approvals and multiple strategic partnerships

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>ONYX-015 approved by CFDA for head &amp; neck cancer</td>
</tr>
<tr>
<td>2006</td>
<td>BioVex first reports efficacy of OncoVEX in Phase 2 study for melanoma</td>
</tr>
<tr>
<td>2008</td>
<td>BioVex was acquired by Amgen for $1 billion</td>
</tr>
<tr>
<td>2010</td>
<td>FDA issued guidance for OV clinical trials</td>
</tr>
<tr>
<td>2012</td>
<td>Amgen’s T-VEC was approved by FDA for melanoma</td>
</tr>
<tr>
<td>2016+</td>
<td>&gt;7 OV Deals</td>
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## Licensor/Acquiror - Target

<table>
<thead>
<tr>
<th>Licensor/Acquiror</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td>BMS</td>
<td>PsiOxus</td>
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<tr>
<td>Pfizer</td>
<td>Ignite</td>
</tr>
<tr>
<td>Merck</td>
<td>Viralytics</td>
</tr>
<tr>
<td>Merck</td>
<td>DNAtrix</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Licensor/Acquiror</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer</td>
<td>ViraTherapeutics</td>
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<tr>
<td>Pfizer</td>
<td>Western Oncolytics</td>
</tr>
<tr>
<td>Celgene</td>
<td>Oncorus</td>
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# Immuno-oncology: Despite recent advances, limitations remain

<table>
<thead>
<tr>
<th>Therapy Class</th>
<th>Examples</th>
<th>% (CR+PR)</th>
<th>Limitations</th>
<th>IKT Approach to Overcome Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Antigen mAb</td>
<td>AVAST Vectibix, Eributax</td>
<td>- Solid 12.2-32.5%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Minimal Immune Stimulation</td>
<td>• Vaccinia Mediated Oncolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Liquid</td>
<td>• Side effects</td>
<td>• T Cell Stimulation/Recruitment</td>
</tr>
<tr>
<td>Bi-specific T cell</td>
<td>BLINCYTO</td>
<td>- Solid 88%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• Suboptimal solid tumor penetration</td>
<td>• Expression restricted to tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Liquid</td>
<td>• T Cell Stimulation/Recruitment</td>
<td>• Increase local expression of BiTE</td>
</tr>
<tr>
<td>Cytokines</td>
<td>PROLEUKIN</td>
<td>- Solid 25%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>• Systemic Side effects</td>
<td>• Transgene expression limited to tumor</td>
</tr>
<tr>
<td>Checkpoint Inhibitors</td>
<td>KEYTRUDA, YERVOY</td>
<td>- Solid 6-25%&lt;sup&gt;4&lt;/sup&gt;</td>
<td>• Safety, esp. in combo w/ other IO</td>
<td>• Local expression to avoid systemic effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Liquid</td>
<td>• Safety, esp. in combo w/ other IO</td>
<td></td>
</tr>
<tr>
<td>DC/CIK Therapy</td>
<td>sipuleucel-T PROVENGE</td>
<td>- Solid 0%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>• Minimal efficacy to date</td>
<td>• Off the shelf approach</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Liquid</td>
<td>• Not an ‘off the shelf’ product</td>
<td></td>
</tr>
<tr>
<td>Oncolytic virus</td>
<td>IMLYGIC</td>
<td>- Solid 10-26.4%&lt;sup&gt;7&lt;/sup&gt;</td>
<td>• Potency as monotherapy</td>
<td>• Armed with I/O potentiation biologics against multiple unique targets</td>
</tr>
<tr>
<td>CAR-T cell therapy</td>
<td>Tisagenlecleucel-T</td>
<td>- Solid 83-95%&lt;sup&gt;8&lt;/sup&gt;</td>
<td>• Safety, not an ‘off the shelf’ product</td>
<td>• CAR-T’s loaded with OV expressing biologics against solid tumor targets</td>
</tr>
</tbody>
</table>

Sources:

<sup>4</sup> Villahermosa et al. JCO Precis. 2016 July 6;12:30;
<sup>6</sup> Bilsland et al. F1000Res 2016 30;5
<sup>7</sup> https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567385.pdf
<sup>8</sup> https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567385.pdf
TEA-OV: A novel modality leveraging established IO approaches

Program Highlights

**Multi-technology approach targeted to novel tumor-specific antigens:**
- Oncolytic vaccinia virus expressing bi-specific antibodies
- Targeting FAP, EpCAM, EphA2, HER2, GPC3, and GD2

**Superior to other modified VVs:**
- Expression and activity does not depend on development of an endogenous antitumor response (absent/compromised in many patients)
- Directly engages T cells to kill non-infected tumor cells
- Induces anti-tumor immunity without overdriving innate viral immunity

**Addresses limitations of BiTE solid tumor therapy:**
- TE continually produced locally within VV-infected tumor translating to high tumor penetration
- High local TE concentrations reduces the systemic side effects and toxicity
- Viral oncolysis prevents antigen loss variants

Diagram:
- CD3 Ab → Target Ab → Tumor cell
FAP-TEA-VV: Overview

**Mechanism of Therapeutic Effect**

- **Targeting FAP enhances antitumor activity**
  - Improve virus spread within tumor tissue by targeting CAF
  - Overcome immune suppressive tumor environment by targeting TAM
  - Enhance bystander killing of FAP+ tumor

- **FAP-CAR-T and FAP tumor vaccine have been evaluated in clinical studies**
  - The safety of FAP-CAR-T therapy is being validated in phase 1 clinical study
  - A clinical study of FAP-IL2 fusion protein has been launched

**FAP Expression in Tumor Environment**

- **Cancer-Associated Fibroblasts:** FAP is overexpressed in stroma of >90% of epithelial tumors, and is not expressed in healthy adult tissues outside of wound repair
- **Tumor-Associated Macrophages**
- **Tumor Cells:**

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1. Cancer-Associated Fibroblasts: FAP is overexpressed in stroma of >90% of epithelial tumors, and is not expressed in healthy adult tissues outside of wound repair.
PROBLEM: Spread of Virus Limited by Tumor Environment

The antitumor effects of systemic delivery of vaccinia virus is limited by its low virus delivery efficacy (limited virus access to tumor), and suboptimal virus spread within the tumor tissue.

Role of Cancer associated Fibroblasts:
- CAFs produce collagens, laminins, fibronectins, proteoglycans, and hyaluronan, forming a dense extracellular matrix (ECM) around tumor cells.
- CAFs combined with ECM provide physical barriers to oncolytic viruses, forming a shield surrounding tumor nests.
- Oncolytic viruses have limited autonomous motility and can only be spread through cell-to-cell contact or soluble diffusion across concentration gradients, both of which can be blocked by CAF and ECM.
  - First, viruses could potentially adhere to any surfaces of CAFs where they are first administered and then fail to spread since CAFs are rather resistant to virus infection.
  - Second, oncolytic VV has a diameter > 200 nm and physically does not fit through the strands of the ECM, preventing passive diffusion across concentration gradients to reach the tumor.

*IKT's FAP-targeted virus provides an alternative and unique strategy to improve the efficacy of systemic administration of oncolytic virus, by promoting virus spread and replication within tumors.*
Solution: Targeting the ECM through CAFs

Targeting elements of the ECM improves local replication of systemically delivered virus:

- Using matrix-degrading enzymes to remove physical ECM barriers is currently the foremost option as a study of HSV (a large virus over 100 nm) showed that coinjection of matrix-degrading collagenase improved viral spread within the tumor.
- However, CAFs could produce ECMs continuously and thus the efficacy of matrix-degrading collagenase could rely on the speed of production and degradation of ECMs.
- *Despite the limited gains, this provides compelling proof of principle to continually target CAFs as a means to improve systemic efficacy of OVs.*

FAP-TEA-VV provides an alternative and unique strategy to improve systemic therapy of OV by:

- Destroying CAFs and removing physical barriers to oncolytic virus in a more permanent manner,
- Allowing small amount of virus to replicate effectively within tumor, and leading to enhanced antitumor effects.

*We observed that administration of FAP-TEA-VV in mouse models significantly enhanced viral titer within tumors, leading to enhanced antitumor effects and the increase of viral titer is correlated with the destruction of FAP-positive stromal cells.*
Fibroblast Activation Protein (FAP)

Hofmeister et al; Cancer Immunol Immunother 2006
**FAP-TEA-VV: Construction**

### Production of Recombinant FAP-TEA VV

1. Recombinant insertion of TE into TK gene of ∆VGF-VV
2. Plaque purification (YFP+); YFP deletion (Cre/loxp)
3. Production of FAP-TEA-VV in permissive cell lines

**Diagram:**
- FAP Ab
- CD3 Ab
- CD3+ T-Cell
- FAP+ Tumor cell
- CD3 Ab
- FAP Ab
- FAP
Mouse Version FAP-TEA-VV

A

FAP-TEA-VV

EphA2-TEA-VV

GM-CSF-VV

B

EphA2-CD3 protein

M 0.5µg 1µg 2.5µg FAP-TEA-VV EphA2-TEA-VV GFP-VV

C

GM-CSF expression (pg/ml)

0 10 20 30 40 50 60

B16 GL-261

0 0.1 1 5 MOI
FAP-TEA: Enhanced *in vitro* Killing with T cells

**A**

MOI- multiplicity of infection (measure of virus concentration in assay)

**B**

MOI 1

EphA2-TEA-VV  FAP-TEA-VV  EphA2-TEA-VV  FAP-TEA-VV

T cells

GL261- mFAP

GFP Expressing FAP+ Target Cells

Tumor cells

MOI 0.1

30.4%  1.67%

16.4%  0.67%

37.4%  28.6%

32.8%  19.1%

**graphical representation**

**Murine Construct**
FAP-TEA-VV: Bystander Killing of Tumor Cells

**Experiment Design**

Grow VV (FAP or Control) in Tumor cells

Harvest culture medium (no infected cells present)

Add to FAP+ cells w/ T cells

**Results**

![Graph showing the results of the experiment with different VV types and cell lines.](image-url)
FAP-TEA-VV: Inhibition of B16 Tumor Growth

FAP-TEA-VV demonstrates robust tumor inhibition in the B16 tumor model

**Experiment Design**

1. Implant 1x10^6 B16 cells in right flank

2. Implant 5x10^4 B16 cells in left flank

3. PBS or 1x10^8 PFU VV into right flank

**Results**

**Right Flank**

- PBS
- EphA2-TEA-VV
- mFAP-TEA-VV
- GM-CSF-VV
- mFAP-TEA-VV

**Left Flank**

**FAP-TEA-VV inhibited growth of primary and secondary tumors**
FAP-TEA-VV: Inhibition of Tumor Metastases in vivo

FAP-TEA-VV inhibits surface metastases and tumor growth in the B16 tumor model

**Experiment Design**

1. Intravenous injection of $2 \times 10^5$ B16 cells
2. Inject PBS or $1 \times 10^8$ PFUs VV
3. Sacrifice and harvest lungs

**Results**

Inhibition of Tumor Metastases

In the same tumor model, FAP-TEA-VV inhibited tumor metastases compared to virus alone

Murine Construct
FAP-TEA-VV: T cell infiltration *in vivo*

**B16 subcutaneous tumor model**
3 intratumor VV injections (D7, D10, D13), Tissue harvest and assay (D15)

A&B) Infiltrating T cells by flow cytometry

C) Infiltrating T cells by fluorescent microscopy
**FAP-TEA-VV: T cell activation in vivo**

**B16 subcutaneous tumor model**
3 intratumor VV injections (D7, D10, D13) Tissue harvest and assay (D15)

D) Intracellular staining of tumor infiltrating T cells

E) ELISPOT IFNγ of splenic CD8+ or CD4+ T cells against dendritic cells presenting FAP or TRP2 (a B16 tumor antigen)
**FAP-TEA-VV: Correlation of Stromal Destruction & Virus Spread**

**B16 subcutaneous tumor model**
3 intratumor VV injections (D7, D10, D13). Tissue harvest and assay (D15)

A) Fluorescent microscopy of FAP+ cells

B) % of FAP+ cells in tumor tissue

C) VV titer per gram of tumor tissue

D) Relationship between FAP+ cells and VV titer
FAP-TEA: mTEA-VVs have no systemic anti FAP activity

B16 s.c. & i.v. tumor model

Serum was collected from mice treated with PBS or GFP-VV or EphA2-TEA-VV or mFAP-TEA-VV for both i.v. and s.c. models \((n = 5)\). Supernatant was collected from MC-38 cells infected with GFP-VV or EphA2-TEA-VV or mFAP-TEA-VV at MOI 5 for 24 h. Supernatant served as positive control. Medium served as negative control. GL-261-FAP-GFP cells were co-cultured with Con A-activated mouse splenocytes in presence of supernatant or serum for 24 h. The killing activity was analyzed by flow cytometry.
mFAP-TEA-VVs do not affect the total cell number of mice bone marrow and mice weight in systematic metastasis B16 model. $2 \times 10^5$ B16 cells were i.v. injected through tail vein of C57/BL6 mice ($n = 5$). The mice were injected $1 \times 10^8$ VV through tail vein on day 1 and 3. (a) On day 15, bone marrow was collected for counting of total bone marrow cell numbers. (b) Mice body weights were monitored at the different time points.
**FAP-TEA-VV (IKT-901) Development Plan: Ongoing IND enabling studies support planned Phase I commencement in 2018**

- **2015-2017**
  - Licensed TEA-VV patent from BCM & filed 3 additional patents
  - IKT is working with Novella to file IND application in 2018
  - IKT’s lead product (clinical grade VV) will be produced in Q4 2017

- **2018-2019**
  - Initiate phase I studies (IT/IV injection) in USA in Q2 2018

- **2019+**
  - Complete Phase I/II trials
<table>
<thead>
<tr>
<th>Limitations</th>
<th>HSV-GMCSF</th>
<th>VV-GMCSF (Wyeth Strain)</th>
<th>FAP-TEA-VV (WR Strain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Stroma</td>
<td>▼ Limits viral spread/oncolysis</td>
<td>▼ Limits viral spread/oncolysis</td>
<td>▲ Targeted by FAP-TE, enhancing viral spread/oncolysis</td>
</tr>
<tr>
<td>Endogenous anti-Tumor T cell</td>
<td>Required ▲ Enhanced by GMCSF</td>
<td>Required ▲ Enhanced by GMCSF</td>
<td>▲ Not required ▲ TE redirects any T cell to target</td>
</tr>
<tr>
<td>Anti-viral Immunity</td>
<td>▼ Enhanced by GMCSF</td>
<td>▼ Enhanced by GMCSF</td>
<td>▲ Anti-viral T-cells may be redirected to antigen target</td>
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<tr>
<td>Immune Suppressive MDSCs</td>
<td>▼ Enhanced by GMCSF</td>
<td>▼ Enhanced by GMCSF</td>
<td>▲ Targeted by FAP-TE</td>
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<tr>
<td>Infectious Spread</td>
<td>Receptor mediated</td>
<td>▲ Efficient cell-cell</td>
<td>▲ Efficient cell-cell</td>
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<tr>
<td></td>
<td></td>
<td>▼ Limited by CAF</td>
<td>▲ Enhancing spread through CAF</td>
</tr>
<tr>
<td>Viral Replication</td>
<td>▼ Requires nuclear translocation</td>
<td>▲ In cytoplasm within 2 hours</td>
<td>▲ In cytoplasm within 2 hours</td>
</tr>
</tbody>
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For more information, please contact:
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