Next Generation Personalized Cancer Immunotherapy

November 2016
Cancer Vaccines – an Important Addition to the Armamentarium for Cancer Treatment

- They stimulate the body’s immune system to recognise tumor cells as non-self
- Unlike chemo and radiation they are not toxic
- Cancer vaccines not only kill tumor cells, they may also induce an immunological memory
- Cancer vaccines may be whole cell, or contain specific peptide/protein antigens
  - Whole cell vaccines can overcome need to know which antigen targets (mutations) are critical in each patient, and can be used irrespective of patient’s HLA type
  - Dendritic cells (DC) are the master orchestrators of the immune system and are often used to prime an anti-tumor response
- Cancer vaccines may be used in combination with a new class of drug known as checkpoint inhibitors, or other strategies, for overcoming the means by which cancer cells may evade the immune system
- Antigen type, DC culture and maturation method, DC loading are key variables in the development of a DC cancer vaccine
  - Antigen types used include peptides, protein, mRNA, tumor lysates
  - Different cocktails of cytokines have been used to culture and mature DCs leading to various features
  - Loading may be passive via co-incubation or active via electroporation
ET-08: A Novel Neoantigen Targeted Platform

ET-08 has been rationally designed to be a best-in-class personalised cancer vaccine

- **Our IL-15 matured dendritic cells** are uniquely empowered to generate **robust** anti-tumor cytotoxic T cell and NK cell responses

- **We use tumor-derived exosomes** as a source of tumor neoantigen
  - Exosomes are lipid-encapsulated vesicles shed by cancer cells into body fluids
  - 30 – 100 nanometers in size they contain neoantigens* in the form of protein, DNA and RNA that represent the malignant fingerprints of the tumors they derive from
  - Unique opportunity to harvest the neoantigen repertoire of a patient’s entire tumor burden (primary and secondary tumors)
  - Tumor antigens stimulate a significantly stronger immune response when presented in the context of exosomes, compared to tumor lysate or soluble antigen
  - Because exosomes are constantly shed from tumors, and can be harvested from body fluids, they may be employed in a dynamic vaccination strategy matching evolving tumor mutations to vaccine over time

- **We load exosomes into dendritic cells using flow electroporation** from MaxCyte, Inc.
  - This can lead to 5-20x more tumor antigen specific cytotoxic

*Neoantigens are personal, exquisitely tumor-specific mutations and unique to each tumor*
ET-08 is Differentiated From Other Neoantigen Companies

<table>
<thead>
<tr>
<th></th>
<th>ExoCyte Therapeutics</th>
<th>Neon Therapeutics</th>
<th>Gritstone Oncology</th>
<th>Caperna</th>
<th>BioNTech</th>
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<tbody>
<tr>
<td><strong>Neoantigen source</strong></td>
<td>Exosomes</td>
<td>Biopsy</td>
<td>Biopsy</td>
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<tr>
<td><strong>Potential to target all mutations in primary tumor</strong></td>
<td>✔️</td>
<td>✗</td>
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<tr>
<td><strong>Potential to target all mutations in metastases</strong></td>
<td>✔️</td>
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<tr>
<td><strong>Vaccine contains</strong></td>
<td>Peptides, proteins, mRNA</td>
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<td>Peptides</td>
<td>Synthetic RNA</td>
<td>mRNA</td>
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<td><strong>Vaccine can be easily updated</strong></td>
<td>✔️</td>
<td>✗</td>
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<tr>
<td><strong>Clinical studies</strong></td>
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<td>Ph I</td>
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<td><strong>Partnerships</strong></td>
<td>BMS – combo with anti-PD-1</td>
<td>Immune Design</td>
<td>Genentech $310M near-term</td>
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ET-08 Development with World Leading Collaborators

Antwerp University Hospital
The process for manufacturing IL-15 dendritic cells and subsequent electroporation will be optimised at UZA by the team of Prof. Zwi Berneman

La Trobe University
The process for harvesting and enriching tumor-derived exosomes (TEX) will be developed and optimised at La Trobe University by the team of Prof. Richard Simpson

National Cancer Center Singapore
The IL-15 DC and TEX manufacturing processes will be tech-transferred to the GMP cell processing suite at NCCS where staff from UZA and La Trobe will assist in the validation of the full ET-08 manufacturing process. A clinical study will then be undertaken in Singapore.
- Tumor-derived exosomes (TEX) are harvested from the patient (plasma, urine, ascites etc.) and enriched from non-tumor vesicles.

- Dendritic cells, isolated from the patient’s blood as PBMCs, are matured using a unique cocktail of cytokines to become potent activators of CTLs and NK cells.

- Dendritic cells are **electroporated** with TEX in an ex-vivo process.

- The autologous vaccine is administered to the patient and immune responses to tumor neoantigens are monitored.

- Other agents are co-administered with the vaccine in order to reverse immunosuppression and provide access to the tumor microenvironment.

- Additional cycles of therapy are adjusted to deal with emergent tumor neoantigens.
Pre-clinical Data Supports ET-08 Approach

- **Research showing superiority of TEX over tumor lysate**
  - DC-TEX elicits significantly greater glioma specific cytotoxicity than DC-lysate (ex vivo human)\(^1\)
  - Survival rate substantially increased in DC-TEX compared to DC-lysate, despite 60% less antigen loading material (in vivo mouse model of mesothelioma)\(^2\)
  - Co-incubated DC-TEX is superior to co-incubated DC-lysate: increased survival, reduced tumor size, and immune response (in vivo mouse models of renal cell carcinoma and myeloid leukemia)\(^3\)

- **Research showing superiority of electroporation over co-incubation**
  - Electroporated mature DC-lysate more potent than electroporated or coincubated immature DC-lysate (ex vivo human)\(^4\)
  - Electroporated DC-lysate elicited greater anti-tumor responses than co-incubated DC-lysate, using less lysate (in vitro and in vivo mouse)\(^5\)

- **Research showing superiority of IL-15 enhanced DCs**
  - Large body of work published by our collaborators at UZA\(^6\)
The Program to Clinical POC

- Optimise and validate processes for:
  - Tumor exosome harvest and enrichment
  - IL-15 DC production and electroporation
- Conduct 3x IND-enabling non-clinical studies
  - To demonstrate the superiority of electroporation over co-incubation for loading dendritic cells with the contents of tumor exosomes or lysates prepared from tumor exosomes or whole tumor cells
  - To demonstrate the effect of non-tumor exosome contamination in a TEX preparation on the ability of electroporated DCs to present tumor antigens to stimulate allogeneic T cell responses
  - To demonstrate the synergy between DC loaded with antigens contained in tumor exosomes and checkpoint monoclonal antibody inhibitors in the activation of T cell function
- Meet with FDA and HSA to agree requirements for IND and discuss Ph I study design
- Test ET-08 alone in 10 patients to establish safety and cellular and cytokine responses
- Test ET-08 in combination with a checkpoint inhibitor in 10 patients to establish safety and cellular and cytokine responses

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<tr>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32</td>
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<td>DC process development</td>
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<tr>
<td>Clinical trial part B</td>
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<td>Clinical trial part B read-out</td>
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**EXOCYTE THERAPEUTICS PTE LTD**
Budget vs Milestones and Value Inflection

Pre-Funding
• Acquired patents covering exosome electroporated DCs for cancer therapy
• Technical POC completed with MaxCyte
• Put together world-class Strategic Advisory Board
• Raised $0.5M from founders and friends and family

2016-17
• Develop, optimize and validate CMC protocols
• Complete IND-enabling studies
• Write IND
• Pre-IND meeting with FDA
• Pre-CTA meeting with HSA
• File IND and CTA

2018
• Begin Phase I study
• Read out of Part A results (vaccine alone in 10 patients)

2019
• Read out of Part B results (vaccine plus checkpoint inhibitor in 12 patients)
• First patients dosed in Part C&D

2020
• Completion of Part C (40 patients with NSCLC)
• Completion of Part D (signal searching)

Valuation Inflection

Funding

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<tr>
<th>Valuation Inflection</th>
<th>2016-17</th>
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* Assumes checkpoint inhibitors provided FOC by partner
Key Strengths of the ET-08 Approach

- **Personalized vaccine** offers a wide range of mutations for immune surveillance; by targeting multiple patient-specific neoantigens most likely to confer durable immunity.

- **Exosomes** are harvested from body fluids through a **less invasive** procedure than biopsy and represent a **broader spectrum of neoantigens** from the tumor, biased to clonal neoantigens.

- **Not all tumors are accessible for biopsy** (e.g., 31% of advanced or metastatic NSCLC cannot be biopsied⁹), nor do biopsies contain the full spectrum of neoantigens.

- **Context of antigen presentation is important** – TEX are a more effective source of antigen than tumor lysate in DC vaccines (as shown in mouse models of mesothelioma, fibrosarcoma, leukemia, and RCC, and a human glioma model).

- **Electroporation is 5-20x more effective** than the gold-standard co-incubation technique in the generation of antigen specific CD8+ T cells, and **overcomes immunosuppressive effects of tumor exosomes**.

- **Enhanced DCs** will activate NK cells in addition to CD8+ T cells.

- Using a **checkpoint inhibitor** with ET-08 will release the brake on the immune system, facilitating access of anti-tumor T cells into the tumor microenvironment.

- **Vaccine may be updated over time** with new exosomes to match evolving tumor neoantigens.
The ExoCyte Team

Management

Dr. John Holaday – Executive Chairman
Former: CEO QRxPharma, Founder EntreMed, Founder MaxCyte, Founder Medicis

Dr. Janette Dixon – Chief Executive Officer
Current: Principal BioComm Pacific Ltd
Former: CEO Synergy Pharmaceuticals, Managing Director Pacific Pharmaceuticals (Merck Generics/Mylan)

Dr. Mathew Lo – Chief Scientific Officer
Current: Consultant and Co-founder M & M Lo Consulting, LLC
Former: 25 years with AstraZeneca/MedImmune including in product development team leadership roles

Ms. Louise Bussieres – Chief Financial Officer
Current: Principal L2 Consulting Pte
Former: 35 years accounting and finance experience in the life sciences sector

Scientific Advisory Board

Dr. Toh Han Chong (FRCP FAMS) – Chairman
Deputy Director, National Cancer Centre Singapore

Prof. Zwi Berneman
Professor of Hematology, University of Antwerp, Head, Division of Hematology Belgium

Prof. Richard Simpson (PhD FATSE)
La Trobe University Institute for Molecular Science, Melbourne Australia

Prof. Xandra Breakefield
Massachusetts General Hospital, Harvard University USA

Prof. Horace Loh
Dept of Pharmacology, University of Minnesota Scientific advisor to the govts of Taiwan, China and Hong Kong USA

EXOCYTE THERAPEUTICS PTE LTD
References


Dr. Janette Dixon has extensive start-up and business development experience in the life sciences sector across Asia Pacific, North America and Europe. She previously founded and successfully sold diagnostics companies based in Singapore and Malaysia and has founded/co-founded two biotech companies developing therapeutics, including ExoCyte Therapeutics. As a consultant, Janette has executed several strategic alliance and licensing deals in China, USA, Canada and Israel. Previously, as Managing Director of Pacific Pharmaceuticals Ltd she led the restructuring of New Zealand's largest pharmaceutical manufacturing company, outsourcing production to India, UK, Australia and Columbia. Trained as a medical scientist Janette also has degrees in marketing, finance and a Doctorate in Business Administration - her research focused on commercialisation strategy in start-up drug development companies.

For additional information, please contact:

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