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Executive Summary

Developing powerful new treatment approaches to modulate microbial recognition and inflammatory signaling pathways for the treatment of advanced / metastatic cancers

<table>
<thead>
<tr>
<th>Innovative antibodies reshaping innate immunity</th>
<th>Monoclonal Antibodies Against Innate Immune Sensors</th>
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</thead>
<tbody>
<tr>
<td>• Targeting pattern recognition receptors involved in microbial recognition</td>
<td></td>
</tr>
<tr>
<td>• Validated immuno-regulatory receptors implicated in inflammation</td>
<td></td>
</tr>
<tr>
<td>• Differentiated targets, derisked in vitro and in vivo</td>
<td></td>
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</tbody>
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<thead>
<tr>
<th>Next-generation living medicines</th>
<th>Synthetic Microbial Immune Stimulators (sMIST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First-in-class immunotherapy platform based on genetically engineered bacteria for solid tumor indications</td>
<td></td>
</tr>
<tr>
<td>• Safe, non-pathogenic bacteria used as a TB vaccine in children and for the treatment of early stage bladder cancer</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Advance lead candidates to IND-enabling studies, expand IP portfolio</th>
<th>Funding &amp; Capital Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• JLabs NYC Award Winner of QuickFire Challenge NYC: lab space award</td>
<td></td>
</tr>
<tr>
<td>• Angel investment: 2018 &amp; 2020. Raising angel / seed $1M round</td>
<td></td>
</tr>
<tr>
<td>• Grants: NY State, NIH / NCI SBIR Phase I, NSF SBIR Phase I awards</td>
<td></td>
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</tbody>
</table>
Accomplished Management Team

Boris Shor, PhD  
Chief Executive Officer

Robert Easton, MBA  
VP, Business Strategy

William Johnson, M.S.  
VP, Corporate Development
Strong Advisory Board

Yossef Av-Gay, PhD
Scientific Co-Founder
Professor, Infectious Diseases
The University Of British Columbia

Jessica C. Seeliger, PhD
Scientific Advisor
Associate Professor
Stony Brook University

Claudia Gravekamp, PhD
Scientific Advisor
Associate Professor
A. Einstein College of Medicine

Matthew Galsky, MD
Clinical Advisor
Professor, Oncology
Mt Sinai Hospital

Jules Mitchel, PhD, MBA
Regulatory Advisor
Clinical Trials

Jean Kadouche, PhD
Scientific Advisor
Antibody Development

Bruce Zetter, PhD
Scientific Advisor
Professor, Cancer Biology
Harvard Medical School

Barrett McGrath
Advisor
Commercial Development
Changing the Treatment Paradigm for Metastatic Cancers

We aim to halt and potentially prevent metastasis in difficult-to-treat solid tumors

<table>
<thead>
<tr>
<th>colon</th>
<th>breast</th>
<th>bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Colon" /></td>
<td><img src="image" alt="Breast" /></td>
<td><img src="image" alt="Bladder" /></td>
</tr>
</tbody>
</table>

Common sites where cancer spreads
- liver
- lung
- peritoneum
- skin
- bone
- brain
- liver
- lung
- skin
- bone
- liver
- lung

Median survival
- 30 months
- 36 months
- 12 months

Colorectal cancer (CRC) is the 3rd most common cause of cancer death
- 104,270 New colon cancer cases (US)
- 22% Metastatic (mCRC)
- 52,980 Estimated deaths 2021 (US)
- $13.7B Global market size (2018)
- ↓ CGAR of 6.1%
- $18.5B Global market size (2023)
Metastasis is the Predominant Reason For Cancer Death

✓ Chronic inflammation is a driver of tumor progression and metastasis

~70% of cancer deaths due to metastasis

“Inflammatory” cancers often associated with microbiota

Infectious agents
- Lung cancer / pulmonary infections
- Colon cancer
- Gastric cancer
- Pancreatic

Cancers frequently exploit microbial recognition receptors

Our Approaches Target:
- tumor microenvironment
- pre-metastatic niche
- proinflammatory pathways
Approaches To Target Microbial Recognition Pathways

- Focus on microbial recognition receptors expressed in cancers

1. Tumor-Elicited Inflammation
   - chronic inflammation
   - Tumor progression
   - Metastasis
   - Immunosuppression
   - Therapy resistance

2. Anti-tumor Response
   - Acute inflammation
   - Immune-infiltration
   - Immunogenic cell death
   - T-cell priming

- Microbes / Infection
- Danger signals
- Tissue Disruption
Manipulating Innate Immunity & Inflammation In Cancer

- Developing novel approaches to modulate innate immunity and inflammation for the treatment or prevention of cancer

- Leveraging two complimentary therapeutic modalities to target microbial recognition pathways

**Monoclonal antibodies:**
- microbial recognition receptors

**Synthetic Microbes:**
- living drugs programmed to fight cancer
# Current Pipeline Projects at Manhattan BioSolutions

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>INDICATION</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>IND</th>
<th>PARTNER</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABS-PRR1</td>
<td>solid tumors</td>
<td></td>
<td></td>
<td>US (2022)</td>
<td>Inserm Armada DX</td>
</tr>
<tr>
<td>MABS-PRR2</td>
<td>CLL, NHL, T-ALL</td>
<td></td>
<td></td>
<td>US (2023)</td>
<td>Armada DX</td>
</tr>
<tr>
<td>MABS-sMIST1,2</td>
<td>solid tumors</td>
<td></td>
<td></td>
<td>US (2023)</td>
<td>Stony Brook University</td>
</tr>
<tr>
<td>MABS-sMIST3</td>
<td>COVID-19</td>
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</table>

## External / Academic Partnerships

- **PRR1**: Drs Ding Xu and Dhaval Shah (University at Buffalo)
- **PRR2**: Drs Armand Bensusson (INSERM), ARMADA Dx
- **sMIST**: Dr Jessica Seeliger (Stony Brook University)
Monoclonal Antibodies Against Microbial Recognition Receptors:

anti-RAGE mAb
RAGE Signaling Bridges Chronic Inflammation & Cancer

- **RAGE** is a key innate immune sensor that mediates the cellular response to a range of DAMPs including advanced glycation end-products (AGEs), HMGB1, S100s, β-amyloid, phospholipids, CpG DNA, RNA, LPS.

- **Expressed at low levels** under normal physiology (lungs), but it is highly upregulated under chronic inflammation because of the accumulation of various RAGE ligands.

- **Well-validated target**
  - Key role in colon, breast cancer progression
  - Invasion & Metastasis to the Lung, Bones
  - Cigarette smoke-induced inflammation in COPD
  - Neuroinflammation, & Aging, Sepsis

Genetic ablation or mAb blockade of RAGE reduces cancer growth and pulmonary metastasis in multiple models.

Breast cancer model

Lung Metastasis

Pancreatic cancer

Ronit Vogt Sionov et al., OncoImmunology 2019 & other publications
Novel Antibody Validated In Vitro & In Vivo

- **Heparan Sulfate** is essential for RAGE signaling; it stabilizes dimeric interface of RAGE
- **Novel mechanism & epitope**: mAb blocks Heparin Sulfate - RAGE interactions

- Potent and specific binding
- B2 mAb blocks liver lysate induced neutrophil chemotaxis in vitro
- B2 mAb is effective in protecting mice from liver damage
- Inhibits Osteoclastogenesis in vitro. Potential utility for cancers that metastasize to bones
- Experiments in cancer models ongoing

**Novel MOA**

**Protection against liver damage**

- **mAb Inhibits Osteoclastogenesis**

- Heparan Sulfate is essential for RAGE signaling: it stabilizes dimeric interface of RAGE
- Novel mechanism & epitope: mAb blocks Heparin Sulfate - RAGE interactions

- Potent and specific binding
- B2 mAb blocks liver lysate induced neutrophil chemotaxis in vitro
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- Experiments in cancer models ongoing
Targeting Advanced / Metastatic Cancers

Cancers with bone or lung metastases: breast, colon, kidney, prostate

DLBCL KIRC

Significance in additional subpopulations (mRNA clusters)

LUAD PP KIRC Cluster 2

RAGE is overexpressed and is the prognostic marker in KIRC: kidney renal clear cell carcinoma

Kidney Cancer (Clear Cell Renal Cell Carcinoma) is the only tumor type identified in Oncomine with RAGE overexpression

Affymetrix Chip Data: consistent with TCGA
Applying Complimentary Modalities To Eradicate Cancer

✔ Leveraging additional technologies: ADCs, Bispecifics and AI-optimized mAbs to ensure maximum success of each program

Bispecific Abs (novel format)
Collaboration with Atlante Bio

AI / ML Optimized mAbs
Collaboration with EVQLV

Antibody Drug Conjugates
Dr Dhaval Shah (UB)

Leveraging additional technologies: ADCs, Bispecifics and AI-optimized mAbs to ensure maximum success of each program.
# Development Plan

<table>
<thead>
<tr>
<th>Drug</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
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<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>αRAGE mAb</td>
<td>![Humanization (completed)]&lt;sup&gt;ло&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>![efficacy in 2-3 models (colon, breast, kidney)]&lt;sup&gt;ло&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IND-Enabling Studies</td>
<td>![Exploratory safety, PK]&lt;sup&gt;ло&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>αCD5 mAb</td>
<td>![Validation of 2 novel clones (biology, immunology)]&lt;sup&gt;ло&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>![POC efficacy (CLL, MCL, T-ALL)]&lt;sup&gt;ло&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>![PK/PD, CMC, Tox, Establish GMP]&lt;sup&gt;ло&lt;/sup&gt;</td>
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## Capital Requirement, Valuation and Financials

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Capital Requirement</th>
<th>Expected Valuation Upon Completion of Milestone</th>
</tr>
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<tbody>
<tr>
<td>• Complete preclinical studies with αRAGE, αPRR-2 mAbs (efficacy in 2-3 models, PK, safety in mouse models)</td>
<td>$2M</td>
<td></td>
</tr>
<tr>
<td>• IND-enabling studies with αRAGE mAb and IND-filing</td>
<td>$5M</td>
<td>$25M</td>
</tr>
<tr>
<td>• Ph 1 Dose escalation study of αRAGE mAb in advanced metastatic tumors (colon, breast, prostate)</td>
<td>$3M</td>
<td>$100M (target stage for option or partnership)</td>
</tr>
<tr>
<td>• Ph 2 Advanced RCC design / inception</td>
<td>$3M</td>
<td></td>
</tr>
<tr>
<td>• Ph 2 Advanced RCC study</td>
<td></td>
<td>$500M (licensing or acquisition)</td>
</tr>
</tbody>
</table>

- **Raising a seed round, current Valuation <$10M**
- **Expected valuation representing ~4X ROI within 3 yrs (assuming favorable Ph 1 results)**
Synthetic Microbial Immune Stimulators (S-MIST)

Oncology Applications & COVID-19
Innate Memory or “Trained Immunity”: Emerging Concept

Pathogens can induce Innate Immune Memory to provide an increased but non-specific response to reinfection.

Trained innate immunity mediates protection against heterologous infections and is mediated by epigenetic and functional reprogramming of myeloid cells and innate lymphoid cells such as NK cells.
Epidemiological Evidence In Cancer

Vaccination with Bacteria Enhances Survival Of Cancer Patients

Prior immunization is associated with better survival

Preexisting BCG-specific immunity improves the antitumor response


Biot et al., 2012. Science Trans Med
S-MIST: First-In-Class Microbe-Based Living Medicines

1. Genetic modification enables secretion of immuno-enhancing factors or targeting commonly expressed cancer antigens

2. Rational design options with re-usable parts
   - Expression of cancer-related proteins, immuno-modulatory factors, antibodies
   - Episomal or chromosomal integration
   - Secreted or membrane-localized
   - Options for host strains

• Potential to target multiple cancers
• Utility in prime boost combinations, combination with other therapies

- Genomes integrated
- Secretion of cytokines (Immunomodulation)
- Display of mutated antigen (Vaccine)
- Secretion of mutated antigen (Vaccine)

- sMIST-Cytokine
- sMIST-FGFR3mut
Efficacy Study Demonstrates Strong Anti-tumor Effects

**sMist-FGFR3mut**: potential to become an adjuvant or neoadjuvant therapy in advanced / metastatic bladder cancer patients

- MB-49 syngeneic model of bladder cancer
- Subcutaneous injection of S-MIST-FGFR3mut

-14  0  +7  +14  +21  d>40

sMist  sMist  sMist  sMist  sMist

*Study ongoing in syngeneic model of colon cancer with sMist-Cytokine*
Significant Market Opportunity In Oncology Indications

**Primming Vaccines**
- Novel modality
- High reward

**Local Therapy**
- Lower risk
- Some cancers

**Prime-Boost**
- New approach
- Combos

Expansion to multiple cancer types: advanced bladder, head & neck, colon, lung, pancreatic, cutaneous tumors

**S-MIST-FGFR3mut**
- Subcutaneous and/or intravesical (prior the surgery)
  - Muscle-Invasive Bladder Cancer
  - Advanced / Metastatic Bladder Cancer

**rMIST-Cytokine**
- Intratumoral or Intrallesional
  - Cutaneous cancers
  - Cutaneous metastatic cancer (breast, lung, ovarian and colon)
  - Advanced Solid Tumors

81,400 new bladder cancer cases: ~28,490 MIBC, Metastatic $1B Global Market

>$1B Global Market

Global cancer vaccine market is anticipated to reach $12.8B by 2023 with CAGR ~ 17%
BCG Protects Against Other Infections Via Trained Immunity

☑️ Most widely administered: given to ~3 billion people: newborn babies, children and adults
☑️ Standard or care for the treatment of early-stage bladder cancer around the world

**Tuberculosis – Live BCG**

- Schistoma mansoni
- Leprosy
- Buruli ulcer
- YFV vaccine virus

**Heterologous Protection**

- Malaria
- Staph. a sepsis
- Candida albicans
- Influenza
- Helminth infection
- HSV Infection

**COVID-19**

- 35 trials around the globe
  - Preventative
  - Therapeutic
How to Create Safe & Effective Vaccine Against COVID-19

- Genetically engineering BCG bacteria to express and target SARS-CoV-2 protein(s)
- Inducing specific protective responses against SARS-CoV-2 via subcutaneous or mucosal vaccination: targeting structural proteins S, N, and M

- Platform designed
- Genome integration system or ectopic
- Combination of promoters and signal sequences
- Bacterial transformation
- Selection of clones with highest transgene expression

First vaccine candidates selected and are currently validated in preclinical experiments