Precise Identification and Treatment of Macrophage-Mediated Diseases

June 2018
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# The Navidea and Macrophage Opportunity

## Three Primary Commercial Drivers

### I. Biomarker

Near-term opportunity to capitalize on Tilmanocept’s unique ability to target and identify activated macrophages

Will be a key tool, useful in assessing the immune system’s activity, in vast majority of therapeutic trials ranging from oncology to auto-immune from CV to infectious diseases

### II. Diagnostic Opportunities

- NASH imaging
- Auto-immune imaging (RA nearest term opportunity)
- Cardiovascular imaging

### III. Near Term Therapeutic Opportunities

- Direct into joint injection to safely replace existing standard of care
- Auto-immune hepatitis
- Cancer – Targeting the Tumor Microenvironment, specifically TAMS, which removes the physical and immunological force field created by most tumors to protect itself
Macrophages are immune system cells that respond to tissue damage or infection.

Activated macrophages are stimulated by cytokines or bacteria to respond to invading or infected cells:

- Help clear infectious agents, repair damaged tissue
- Alter microenvironment to suppress or promote disease-causing cells
- **Have unique receptors that enable cellular targeting**
- **May be used as drug-delivery agents to identify and treat disease**
Macrophages and CD206 Receptors

Innate:
- Phagocytosis of foreign materials + pathogens

Adaptive:
- Stimulating activation of other immune cells

Activated macrophages function in both innate + adaptive immunity

The mannose receptor, CD206, is only expressed on activated macrophages and dendritic cells (CD209)

Macrophages are activated in multiple ways

- Environmental Exposure
  - Viruses
  - Other infectious agents
  - Drugs/chemicals
  - Other (e.g. ultraviolet light)

- Hormonal Effects
  - Intrinsic and extrinsic
  - Variable depending on disease
Our Technology

Target CD206 macrophage receptor

Activated macrophages can be depleted (MT1000 class) or converted from pro-inflammatory M1 to healing M2 macrophages (MT2000 class). Developing new class to convert M2 to M1 specifically for cancer indications.

Platform Concept

Tilmanocept combines:
- Mannose ligand for binding CD206 receptors on activated macrophages
- Radioisotope
- Therapeutic agent

Enable’s specific therapeutic activity without systemic and long term immune suppression

✓ Seek

✓ Identify

✓ Modify
Therapeutic Concept
Selectively targeting Activated Macrophages

Platform for immuno-constructs that preferentially target CD206+ (and CD209+ dendritic cells) activated macrophages

1. GPS
2. Delivery
3. Payload

- Mannose Moiety
- With One Hardwired Address - CD206 Activated Macrophages

- Manocept™ Backbone

- Chemotherapeutics
- Immune-modulators
- Tc⁹⁹
- Other Isotopes
Selective Binding Enables Precise Targeting

Tilmanocept selectively binds only to activated macrophages without targeting lymphocytes (non-activated macrophages), or non-activated tissue resident macrophages (kupffer cells, microglial cells, etc.)

Binding Affinity $= 3 \times 10^{-11}$
High Selectivity = Better Targeting

Macrophage depletion with liposomal agents that target all macrophages fail due to toxicity

Manocept Radio-isotope Imaging

PEG-LD Liposomes Radio-isotope Imaging

Figure 7: Gamma scintigraphic image of a cancer patient 48 hours (left image) and 96 hours (right image) after administration of PEG-LD liposomes containing $^{111}$In. Note that both images are posterior views. Uptake of the radioactive liposomes is seen in certain normal tissues including spleen, liver, bone marrow. The activity visible in the central chest (substernal) and upper abdomen represent liposomes that are still circulating in the heart and major vessels at these time points. The liposomes are taken up by a large tumor in the left upper lung. The density of radioactivity is as high or higher in the tumor than in any normal organ.
## Manocept™ vs Monoclonal Antibodies

### Advantages of Navidea’s Technology

<table>
<thead>
<tr>
<th></th>
<th>Manocept™</th>
<th>vs.</th>
<th>mAbs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>✓ ~2-20 kilo daltons</td>
<td></td>
<td>~150 kilo daltons</td>
</tr>
<tr>
<td><strong>Backbone (BB)</strong></td>
<td>✓ natural and synthetic polymers</td>
<td></td>
<td>complex proteins</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>✓ negligible</td>
<td></td>
<td>$$$$</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>✓ hours</td>
<td></td>
<td>weeks</td>
</tr>
<tr>
<td><strong>Binding affinity</strong></td>
<td>✓ $10^{-9}$ to $10^{-13}$</td>
<td></td>
<td>$10^{-5}$ – $10^{-7}$</td>
</tr>
<tr>
<td><strong>Antigenic</strong></td>
<td>✓ Highly unlikely (not seen with current formulations)</td>
<td></td>
<td>Ab’s must be humanized and still not 100% non-antigenic</td>
</tr>
<tr>
<td><strong>Delivery options</strong></td>
<td>✓ IV, SC, oral, topical</td>
<td></td>
<td>IV, efforts to create SC in limited indications</td>
</tr>
<tr>
<td><strong>Drug loading</strong></td>
<td>✓ Multiple “copies” per BB - inexpensive, effective generic agents enable rapid development</td>
<td></td>
<td>Antibody-drug conjugates being developed primarily to deliver proprietary agents</td>
</tr>
</tbody>
</table>
Substantial Unmet Clinical Need
Current Clinical Landscape & Monitoring Market Opportunity

NASH Clinical Landscape:

Current Scale of Global NASH trial patients

>10,000
Patients currently involved in NASH trials globally

103
NASH treatments currently in development

Assuming 2 scans per year per patient

$5,000/imaging agent
NAVb sales price

~55
in clinical-stage

$100M
Potential annual revenue for research purposes only

Cardiovascular:
Much larger sample size than NASH
Provides drug developers with ability to better dose
Increase success rates
Decrease sample sizes

Autoimmune:
• Very large, highly competitive market exacerbated by introduction of biosimilars
• Navidea’s imaging agents can prove useful in indication assessment, competitive assessments and dose selection
The Tumor Microenvironment (TME) is critical to a tumor’s defenses vs the host’s immune system.

CD206+ Macrophages are one of the most important constituents of the TME

Revenue per dose: $5,000

Range of doses given per patient per treatment regiment: 2 - 8

Number of patients in oncology clinical trials: 915k

represents a large % of the total cancer patient population, thus making it difficult and expensive to recruit new patients to all the planned combination studies

Addressable market - $1B+ for every 5% penetration of the US oncology clinical trial market.
**Unique Commercial Opportunity**

**Improvement in Savings for Clinical Trial Costs and Preventative Screening**

- **Average cost per patient in clinical trials today:** $36,500
- **Site monitoring, recruitment and retention account for approximately one-third of trial costs**
  - Focused recruitment and patient screening to optimize trial outcomes and minimize SAE’s and reduce overall patient mortality
  - Ongoing patient monitoring and dose optimization
  - End of trial scanning for outcomes
  - Cut overall spend and time to market

Subscription (recurring revenue) model

- Patient enrollment numbers reflect oncology trials
- Source: ClinicalTrials.gov
# Product Pipeline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Diagnostics</th>
<th>Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Solid Tumors Lymphatic Mapping</td>
<td>MT-1002</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Sentinal Node Biopsy</td>
<td>MT-2002</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Rheumatoid Arthritis</td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Cardiovascular Diseases</td>
<td></td>
</tr>
<tr>
<td>FDA Approved</td>
<td>FDA-approved in 2014</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast, Melanoma, oral cavity, head &amp; neck cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kaposi’s Sarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NASH</td>
<td></td>
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</table>

**MT-1002**

An FDA-approved agent for sentinel lymph node detection in breast cancer, melanoma, oral cavity, head & neck cancer.

**MT-2002**

A Phase 2 candidate for imaging Kaposi’s sarcoma and NASH.
Navidea Imaging Strategy

Image M1 or M2 Mediated Disease

**Dose it**
Same for all indications

**Image it**
Focus the camera on area of interest

3 hour image RA

- Mean CD206+ macrophages/mm²
  - **P=0.0002**

- Percent aortic volume with high-level tilmanocept uptake
  - **P=0.009**

Computer read of CV images

HIV-infected vs Non-HIV-infected

- P=0.0002
- P=0.009
Macrophage Therapeutics Strategy

Treat M1 or M2 Mediated Disease

Image it

Treat it

Imaging demonstrates we are targeting disease causing cells

Compiled 2D/3D Imaging
NASH vs. Normal

3D Mid Liver Localization

NASH Pt-1

NASH Pt-2

NASH Pt-3

NASH Pt-4

Normal Patient

Link to video files found at www.ir.navidea.com

HOTTER
(Greater Tc99m-Tilmanocept Uptake)*

*Based on Image-J Analysis and Tc99m-Tilmanocept Uptake Assessment
Therapeutic Targets

Aberrant macrophages are associated with several major disease states

**Cancer**
Cancer cells modify the macrophage to create new cancer cells called **tumor associated macrophages (TAMs)**
TAMs enable enhanced angiogenesis and release other tumor enhancing factors for an **immunosuppressive microenvironment**

**Infectious Disease**
In certain infectious diseases, the macrophage acts as an incubator for the proliferation of the ingested material
- HIV, HPB, HPC, Zika, Ebola, etc.
- TB, Leishmaniasis, assorted drug-resistant bacteria

**Inflammation/Fibrosis**
Activated macrophages stimulate **excessive inflammation, fibrosis and autoimmune diseases**
- NASH, nephropathies, fibrotic disorders
- RA, IBD, Lupus, MS, myocarditis

**CNS**
Activated macrophages stimulated by improper clearance of amyloid and cause the associated inflammation typically seen in **Alzheimer disease** and implicated in **MS, Parkinson’s and other CNS diseases**

**Cardiovascular**
Lipid-containing macrophages exacerbate **atherosclerosis**, an inflammatory condition
### Manocept™ vs Steroids

#### Advantages of Navidea’s Technology

<table>
<thead>
<tr>
<th></th>
<th>MT-2000 Class</th>
<th>VS.</th>
<th>Glucocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>Exclusively to CD206-expressing activated macrophages</td>
<td>All cells</td>
<td></td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>Receptor-mediated</td>
<td>Concentration-dependent</td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>TBD- but based on mechanism of action should be safe</td>
<td>High toxicity due to off-target systemic effects</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Designed to address the many safety issues limiting this most powerful anti-inflammatory agent</td>
<td>Most effective anti-inflammatory agent available. Efficacy limited by toxicity at doses required to get adequate levels into inflammatory cells</td>
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</tr>
<tr>
<td><strong>Binding affinity</strong></td>
<td>$10^{-9}$ - $10^{-13}$</td>
<td>No selectivity</td>
<td></td>
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<td><strong>Delivery options</strong></td>
<td>IV, SC, oral, topical</td>
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<td><strong>Drug loading</strong></td>
<td>Multiple “copies” per BB inexpensive, effective generic agents enable rapid development</td>
<td>Drug not targeted therefore “leaks” into all cells/organs in concentration-dependent manner</td>
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<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Converts M1 to M2 phenotype</td>
<td>Depending on cell type will have multiple activities leading to the very high side effect profile limiting dose and extended use of these highly efficacious agents</td>
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Glucocorticoid Receptor (GR)

Controls
- Development
- Metabolism
- Immune Response

Primary immune mechanism of action is the regulation of gene transcription.
- The activated GR complex up-regulates the expression of anti-inflammatory proteins in the nucleus
- or represses the expression of pro-inflammatory proteins in the cytosol (by preventing the translocation of other transcription factors from the cytosol into the nucleus)

MT Hypothesis
1. Covalently linking dexamethasone to a polymeric backbone with targeting to a cell surface receptor, found on ONLY disease causing cells
2. Receptor (CD206) internalizes the complex
3. pH inside cell causes release of the glucocorticoid in the cytosol where it binds the GC

✔ Achieves full benefits of the drug without the side effects.

Efforts are underway to create multiple formulations to provide IV, SC, oral, topical and significant sustained release options.

15-70 Trillion
Cells in the body

60 mg/day or 1E+20 molecules = 1 High dose of prednisone

Therefore, 1-3 million
Molecules of prednisone per every cell in the body
Receptor mediated delivery
Equal amount of dex dosed: free vs conjugated

% Chg in Blood Glucose Levels (Indexed) N=4

- % Chg Blood Glucose (mmol/L from t=0)
- Time (minutes)

- Dex Mean
- MT2002 + Dex Mean
CONCLUSION: Oral gavage of dexamethasone could significantly inhibit cytokine production and leukocyte recruitment compared with vehicle group. IV injection of test item MT-2002 at an equivalent dose of dexamethasone has similar effects as dexamethasone did, and could inhibit the loss of CD206+ macrophages compared with vehicle.

IFNγ and TNFα were repeated in a different experiment with different doses.
Combination therapy (subQ) – MT1002 + anti-HER2 MAb

H2N113 tumors (MMTV-neu)

Control (PBS)
7.16.4 (33ug/mouse)
MT1002 (0.035mg/mouse)
MT1002 (0.07mg/mouse)
7.16.4+MT1002 (33ug/mouse+0.035mg/mouse)
7.16.4+MT1002 (33ug/mouse+0.07mg/mouse)
Key Findings

Selective targeting of macrophages by MT1002 alters tumor’s immunological milieu and results in enhanced tumor shrinkage via:

- Lowering tumor-promoting M2 macrophages
- Increasing pro-inflammatory M1 macrophages
- Lowering T-regs and CD4+ cells
- Increasing NK cells and cytotoxic CD8+ cells

Combination of MT1002 with anti-cancer MAb results in increased efficacy via promoting ADCC
Targeting KS with Manocept Conjugates

KS tumor and TAMs Take up **Manocept-Cy3**

**Kill TAMs**

(Man-Dox)

**Image KS lesions (Tilmanocept)**

**Apoptosis**

**Kill HHV8+ KS tumor cells**

**Kill HIV+ macrophages**

Anti-HIV: IC50 = 0.054uM

**Cont MAN-Dox**

p<0.001

p<0.001
Preclinical Models Validate Macrophage Strategy

**Arthritis**
- Results report clear statistically significant anti-inflammatory activity with no apparent significant clinical signs relating to off target effects.

**Asthma**
- Results show a decrease in all three pro-inflammatory markers evaluated that are secreted by disease causing macrophages that successfully demonstrates an anti-inflammatory effect.
- Study repeated by large pharma collaborator with comparable results with different mix of pro-inflammatory markers.

**NASH**
- Results demonstrate statistically significant reduction in NASH related inflammation
- No evidence of damage to resident liver macrophages called Kupffer cells or other liver damage
- Three doses of MT1002 tested in NAFLD-NASH model and 1 dose of MT 2002 and MT 1002 tested in NASH fibrosis model
- All doses of both compounds had statistically significant effects

**Neuro-inflammatory**
- Results confirmed the anti-inflammatory construct very effectively crosses the blood brain barrier

**Cancer**
- Results showed an immediate effect on the rate of tumor growth and in the slower growing tumor the inhibition in tumor growth rate remained throughout the duration of the study
- Synergy demonstrated with addition of a targeted antibody resulting in the ability to significantly reduce the dose of the companion antibody
- This offers the potential for lower side effects, reduced resistance and dramatically lower cost
Corporate Overview
Targeting Activated Macrophages to Detect, Monitor and Treat Disease

FDA/EMA-approved diagnostic product
Lymphoseek® – funding new product development

Technology platform applicable to therapeutics:
RA, CV, NASH, cancer and other diseases

Targeting CD206 receptors on activated macrophages
Enables higher affinity and better drug delivery than MAbs

Evolving corporate strategy
Creates and maximizes shareholder value through new collaborations, entities and partnerships

Strong Financials
Sufficient cash and cash flow to support pipeline validation
Thank you

Navidea

BIOPHARMACEUTICALS

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