Navidea
BIOPHARMACEUTICALS

Precise Identification and Treatment of Macrophage-Mediated Diseases

June 2017

Disclaimer

The private securities litigation reform act of 1995 (the act) provides a safe harbor for forward-looking statements made by or on behalf of the company. Statements in this presentation, which relate to other than strictly historical facts, such as statements about the Company's plans and strategies, expectations for future financial performance, new and existing products and technologies, anticipated clinical and regulatory pathways, and markets for the Company's products are forward-looking statements within the meaning of the Act. The words "believe," "expect," "anticipate," "estimate," "project," and similar expressions identify forward-looking statements that speak only as of the date hereof. You are cautioned that such statements involve risks and uncertainties that could cause actual results to differ materially from historical or anticipated results due to many factors including, but not limited to, the Company's continuing operating losses, uncertainty of market acceptance of its products reliance on third party manufacturers, accumulated deficit, future capital needs, uncertainty of capital funding, dependence on limited product line and distribution channels, competition, limited marketing and manufacturing experience, risks of development of new products, regulatory risks and other risks detailed in the Company's most recent Annual Report on Form 10-K and other Securities and Exchange Commission filings. You are further cautioned that the foregoing list of important factors is not exclusive. The Company undertakes no obligation to publicly update or revise any forward-looking statements.

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, cancer and other diseases

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

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

Strong Financials
Sufficient cash and cash flow to support pipeline validation

Management

Michael Goldberg, M.D.

President & CEO

- Member of Navidea's Board of Directors since November 2013
- Managing Partner of Montaur Capital Partners since January 2007
- Previously CEO of Emisphere Technologies
- Previously Vice President of The First Boston Corp., founding member of the healthcare banking group
- BS/MD – Combined 6 year biomedical program, RPI/Albany Med
- MBA finance, Bronfman Fellow – Columbia Grad School of Business

Fred Cope, Ph.D.

Chief Scientific Officer
Senior Vice President

- Appointed Senior VP and Chief Scientific Officer in May 2013
- Previously served as Assistant Director for Research and Head of Program Research Development for The Ohio State University Comprehensive Cancer Center, The James Cancer Hospital and The Richard J. Solove Research Institute
- Serves as editorial reviewer for several professional journals
- Advisor/director to the research program at Roswell Park Memorial Cancer Center

Jed Latkin

Chief Financial Officer
Chief Operations Officer

- Previously was a Portfolio Manager at Nagel Avenue Capital beginning 2010 and at ING Investment Management from 2006-2010, Morgan Stanley Investment banking (2002-2006)
- Previously served as CFO of Viper Powersports, CEO of End of Life Petroleum Holdings, CEO of Black Elk Energy, Portfolio Manager of Precious Capital and CFO of West Ventures
- Currently serves on the boards of the Renewable Fuels Association and Buffalo Lake Advanced Biofuels
- MBA finance - Columbia Grad School of Business

William Regan

Chief Compliance Officer
Senior VP, Global Regulatory & Quality

- Served as Principal of Regan Advisory Services (RAS) consulting on all aspects of regulatory affairs within pharma, biotech and diagnostic imaging business, including PET, contrast agents and radiopharmaceuticals
- Prior to RAS, managed radiopharmaceutical manufacturing, quality assurance, pharmaceutical technology and regulatory affairs at Bristol-Myers Squibb (BMS).
- Served as global regulatory head for BMS' Medical Imaging business

Board of Directors

Eric K. Rowinsky, M.D.
Chairman

- **Chairman of the Board of Directors**
  Navidea Biopharmaceuticals
- **Executive Chairman and President**
  Rgenix, Inc.
- Held senior management positions at Stemline Therapeutics, Primrose Therapeutics and ImClone Systems.
- Currently on the board of Biogen

Tony Fiorino, M.D., Ph.D.

- **President and CEO**
  Triumvira Immunologics
- Previously was CEO at BrainStorm Cell Therapeutics and EnzymeRx
- Experienced biotechnology and pharma analyst at JP Morgan and Citigroup
- Buyside experience at Greywall Asset Management and Pequot Capital

Michael Goldberg, M.D.

- **President and CEO**
  Navidea Biopharmaceuticals
- Previously was Chairman and CEO of Emisphere Technologies - multiple patents and publications in drug delivery
- Previously Managing Partner at Montaur Capital Partners, VP Corp Fin- First Boston

Mark Greene, M.D., Ph.D.

- **Director of the Division of Immunology**
  University of Pennsylvania School of Medicine
- John Eckman Professor of Medical Science at University of Pennsylvania School of Medicine
- Previously served as Scientific Advisor to Ception Therapeutics, Antisome PLC and Fulcrum Technologies

Michael Rice

- **Founding Partner**
  Lifesci Advisors, LL and LifeSci Capital, LLC
- Previously co-head of healthcare investment banking at Canaccord Adams
- Previous experience at ThinkEquity Partners and Bank of America
- Currently on the board of RDD Pharma

The Role of Macrophages in Human Biology

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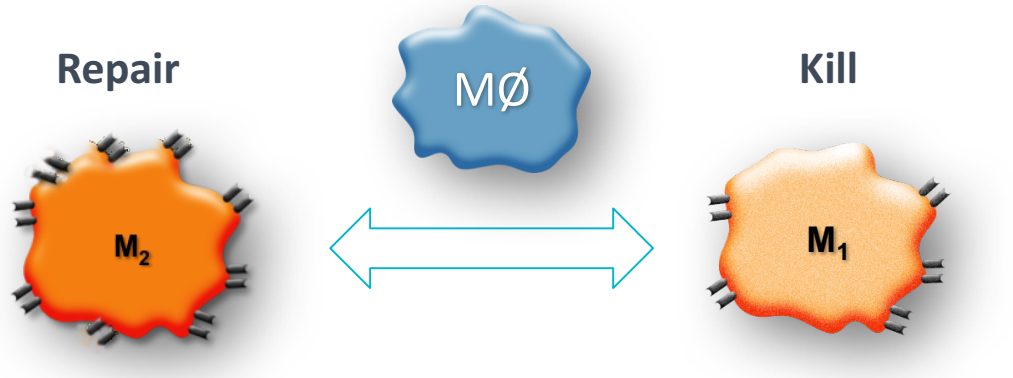
Macrophages are immune system cells that respond to tissue damage or infection

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**

Macrophage Activities



- Heals wounds
- Replaces dead tissue

- Fights Infection
- Stops Cancer

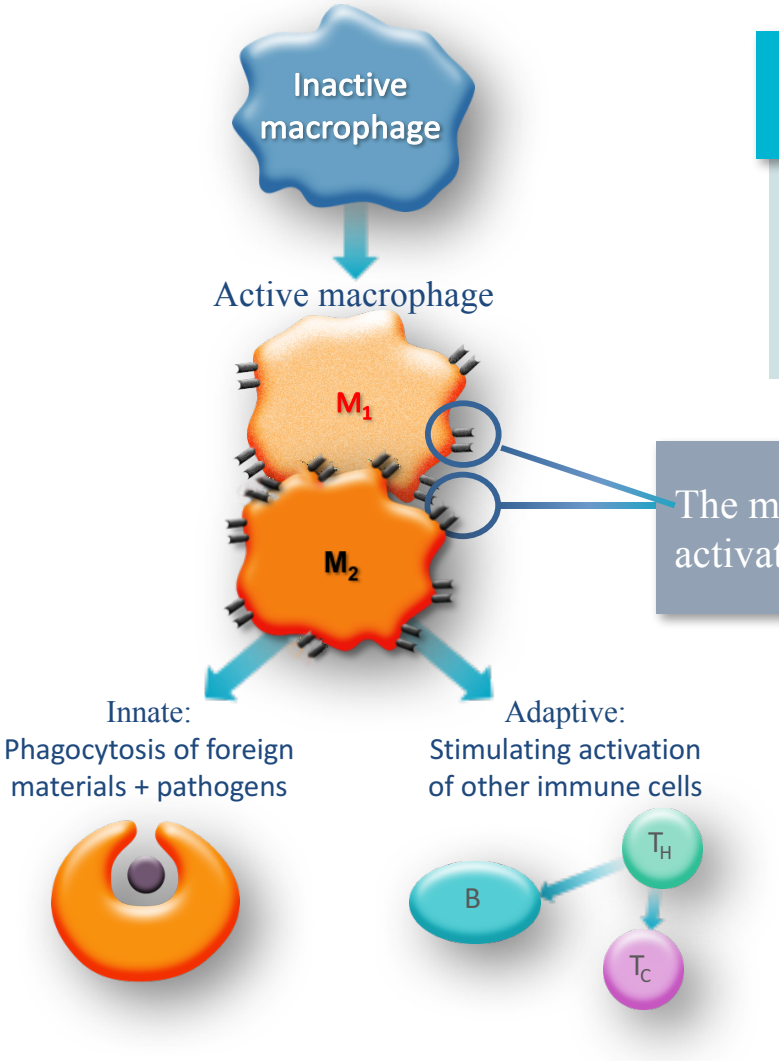
Macrophage biology enables targeting major diseases resulting from inappropriate activity of activated macrophages

Diseases that activate macrophages

- Allergies
- Infections
- Cancer

- Atherosclerosis
- Neurodegeneration
- Autoimmune diseases

Macrophages and CD206 Receptors



Macrophages are activated in multiple ways

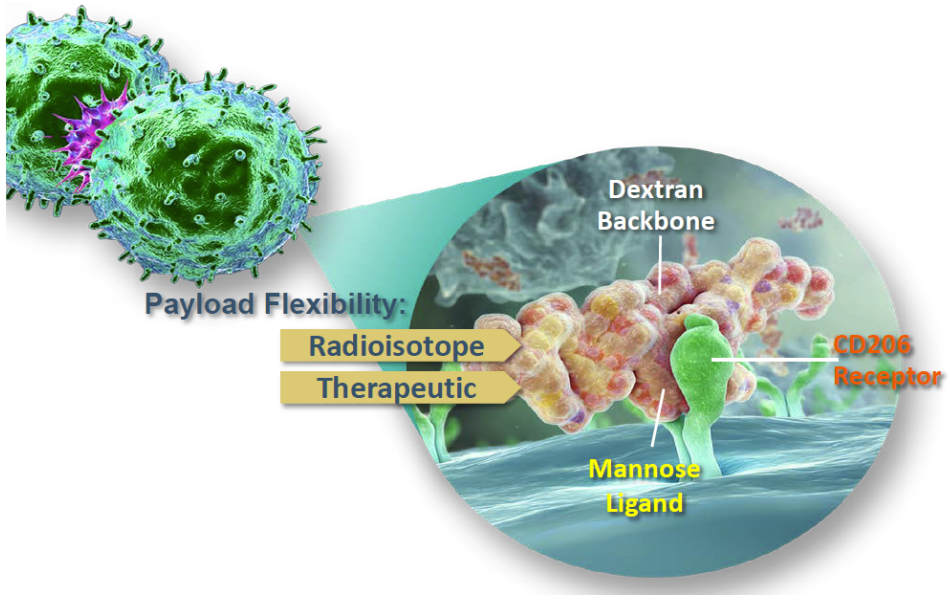
Environmental Exposure
- Viruses
- Other infectious agents
- Drugs/chemicals
- Other (e.g. ultraviolet light)

Hormonal Effects
- Intrinsic and extrinsic
- Variable depending on disease

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

Activated macrophages function in both innate + adaptive immunity

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

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

Tilmanocept combines:

- Mannose ligand for binding CD206 receptors on activated macrophages

→ ✓ **Seek**

✓ **Identify** Radioisotope

✓ **Modify** Therapeutic Agent

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 ▪ Tc^{99} ▪ Other Isotopes

Manocept™ vs Monoclonal Antibodies

Advantages of Navidea's Technology

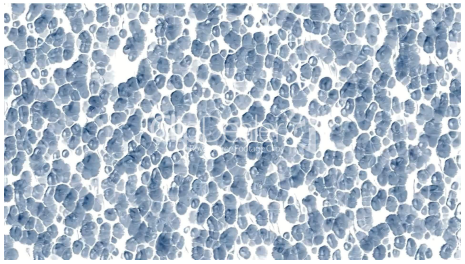
	Manocept™	vs.	mAbs
Molecular Weight	✓ ~2-20 kilo daltons		~150 kilo daltons
Backbone (BB)	✓ natural and synthetic polymers		complex proteins
Cost	✓ negligible		$$$$
Half life	✓ hours		weeks
Binding affinity	✓ 10^{-9}- 10^{-13}		10^{-5} – 10^{-7}
Antigenic	✓ Highly unlikely (not seen with current formulations)		Ab's must be humanized and still not 100% non-antigenic
Delivery options	✓ IV, SC, oral, topical		IV, efforts to create SC in limited indications
Drug loading	✓ Multiple "copies" per BB - inexpensive, effective generic agents enable rapid development		Antibody-drug conjugates being developed primarily to deliver proprietary agents

Manocept™ vs Steroids

Advantages of Navidea's Technology

	MT-2000 Class	vs.	Glucocorticoid
Distribution	Exclusively to CD206-expressing activated macrophages		All cells
Absorption	Receptor-mediated		Concentration-dependent
Safety	TBD- but based on mechanism of action should be safe		Highly toxic due to off-target systemic effects
Efficacy	Designed to address the many safety issues limiting this most powerful anti-inflammatory agent		Most effective anti-inflammatory agent available. Efficacy limited by toxicity at doses required to get adequate levels into inflammatory cells
Binding affinity	10^{-9}- 10^{-13}		No selectivity
Delivery options	IV, SC, oral, topical		IV, SC, oral, topical
Drug loading	Multiple "copies" per BB inexpensive, effective generic agents enable rapid development		Drug not targeted therefore "leaks" into all cells/organs in concentration-dependent manner
Mechanism of Action	Converts M1 to M2 phenotype		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

Glucocorticoid Receptor (GR)



GRs expressed in almost every cell in the body

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)

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 <u>every</u> cell in the body

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

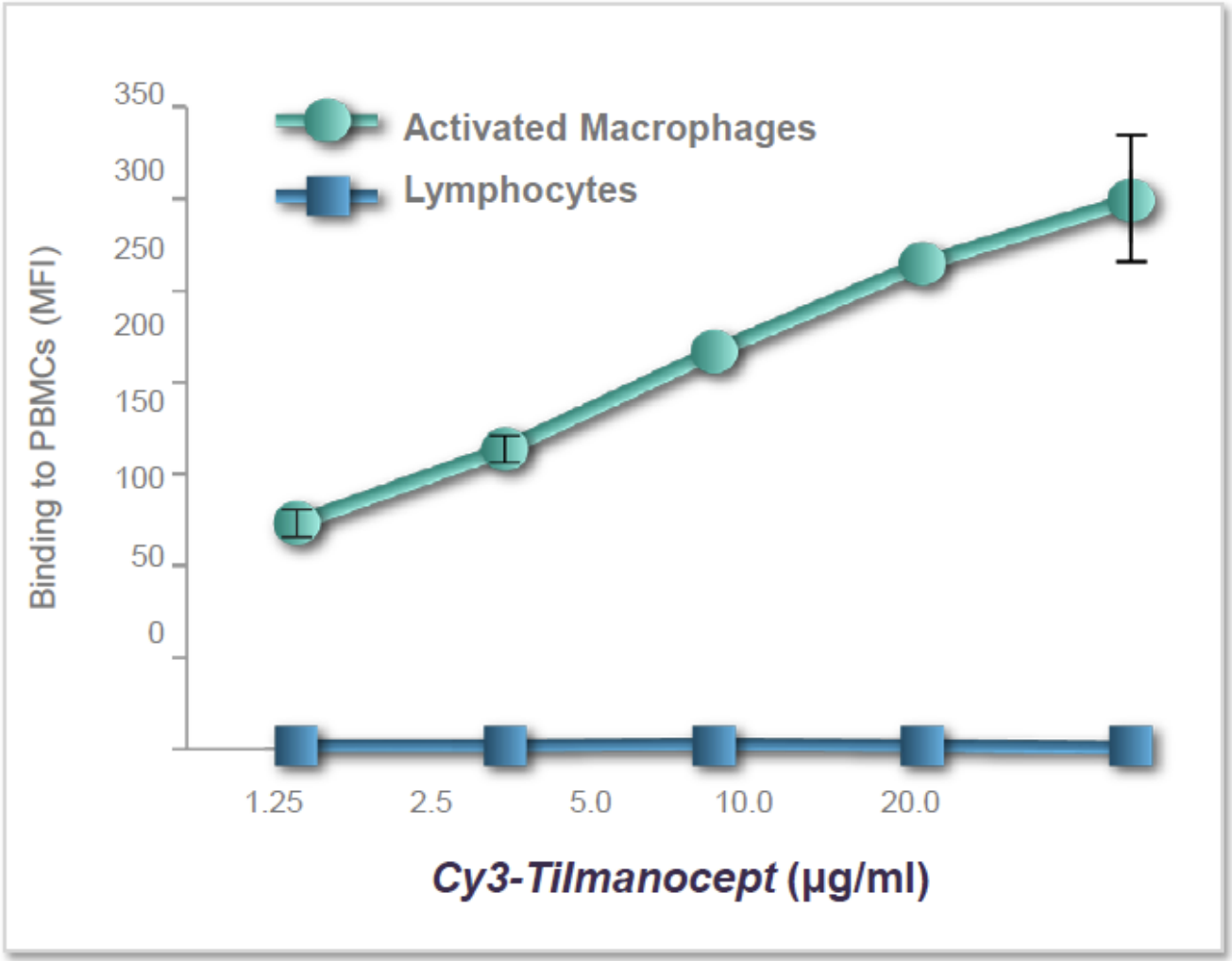
✓ **Achieves full benefits of the drug without the side effects.**

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

Selective Binding Enables Precise Targeting

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

Binding Affinity = $3X10^{-11}$



Product Pipeline

Lymphoseek Technetium Tc-99m tilmanocept

First FDA/EMA-Approved Macrophage-Targeting Platform

FDA-Approved Dx and Imaging Agent

- Approved for sentinel lymph node (SLN) detection & lymphatic mapping
- Lymphoseek remains gold standard for FDA NDA-sNDA approval process

Commercial Expansion

- Approved for commercial sale in North America and Europe
- Approved for single dose vial in Europe, October 2016
- Commercial arrangements in North America, Europe and China

Expanding Clinical Development

- Ongoing clinical immunodiagnostic platforms in expanding indications such as Rheumatoid Arthritis, Cardiovascular Disease, etc.
- Expanding modes of administration under development – subcutaneous, IV and oral

FDA Approval	FDA Approval	FDA Approval	EMA Approval	EMA Approval
Lymphatic mapping in breast and melanoma patients	Squamous cell carcinoma	SLN detection in Breast cancer and melanoma	SLN detection in melanoma, breast and oral cavity cancer	Single Does Vial
Mar. 2013	**Jun. 2014**	**Oct. 2014**	**Nov. 2014**	**Oct. 2016**

YTD

High Selectivity = Better Targeting

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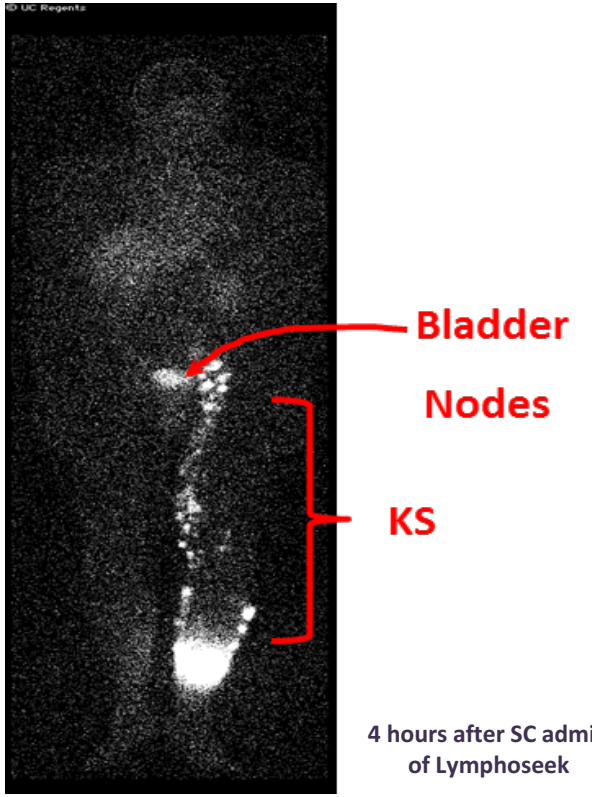
Macrophage depletion with liposomal agents that target all macrophages fail due to toxicity

Manocept Radio-isotope Imaging



4 hours after SC admin of Lymphoseek

PEG-LD Liposomes Radio-isotope Imaging

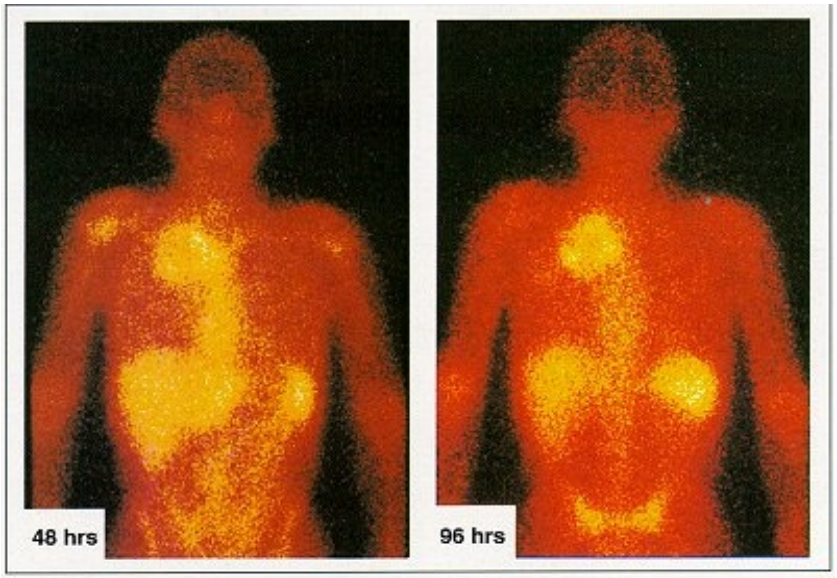


Figure 7: Gamma scintigraphic image of a cancer patient 48 hours (left image) and 96 hours (right image) after administration of PEG-LD liposomes containing ^{111}In. Note that both images are posterior views. Uptake of the radioactive liposomes is seen in certain normal tissues including spleen, liver, 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.

Navidea Imaging Strategy

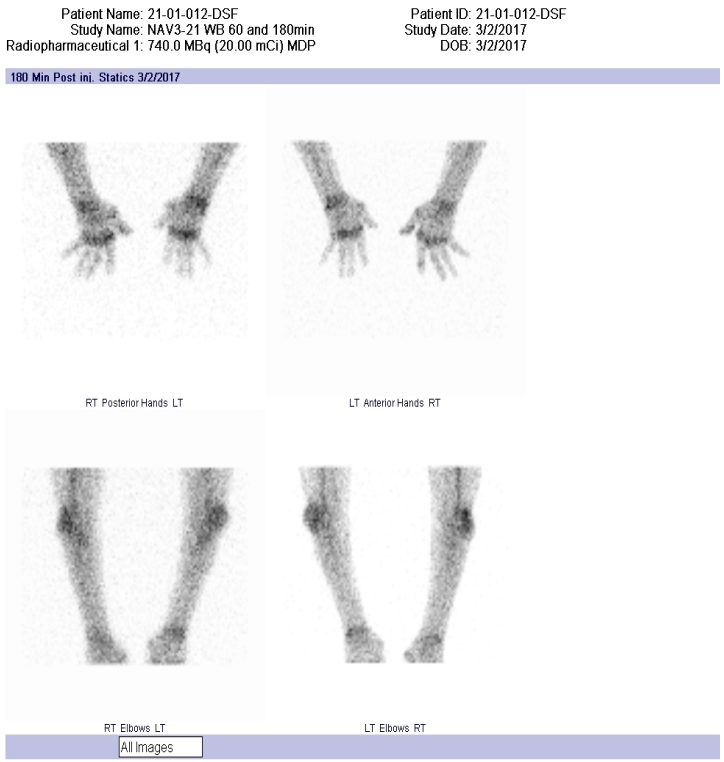
Image M1 or M2 Mediated Disease

Dose it
Same for all indications

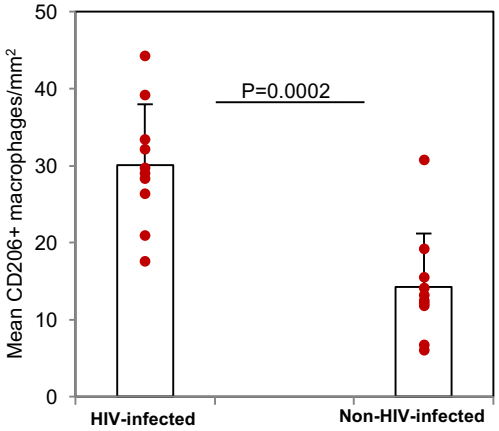
→

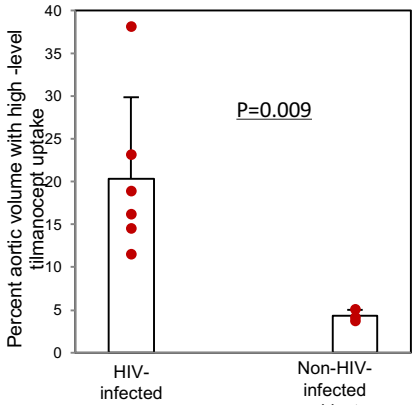
Image it
Focus the camera on area of interest

3 hour image RA



Computer read of CV images



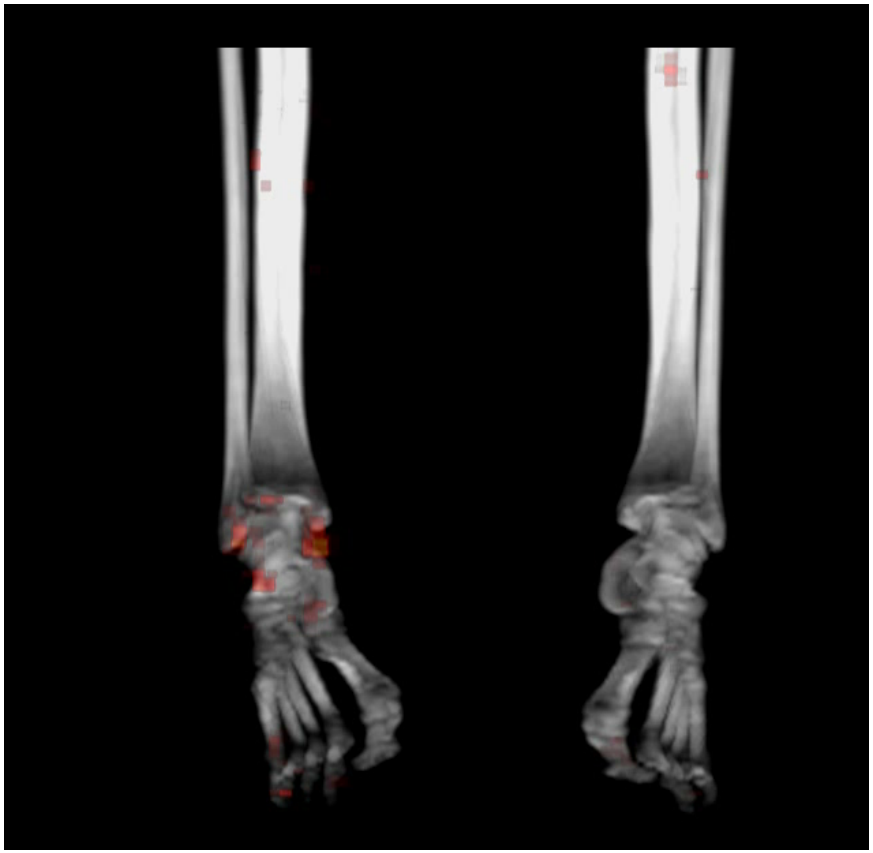


Macrophage Therapeutics Strategy

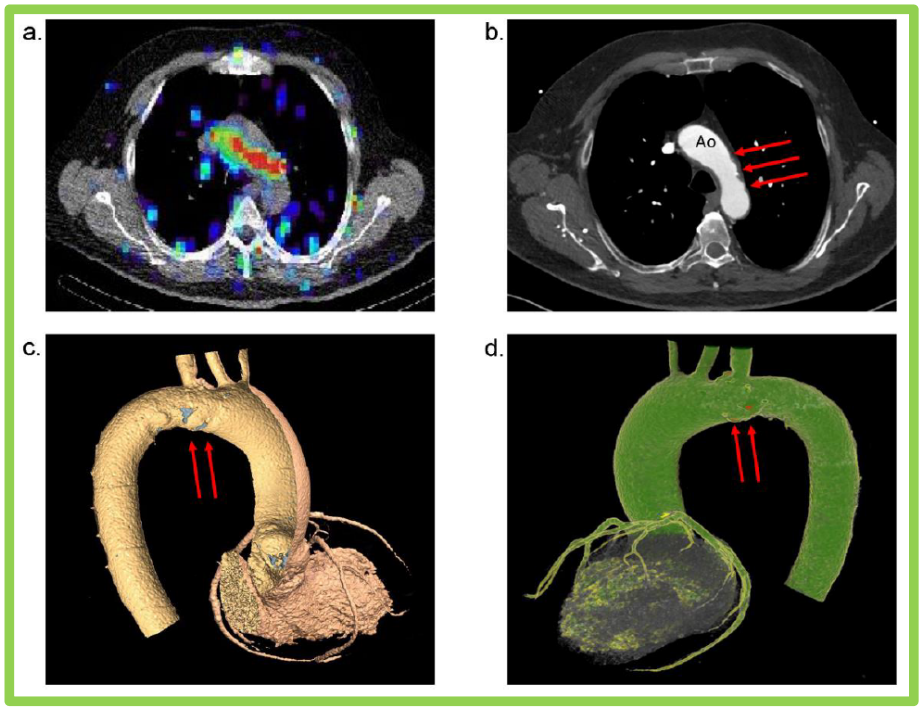
Treat M1 or M2 Mediated Disease

Image it → **Treat it**

Imaging demonstrates we are targeting disease causing cells



Compiled 2D/3D Imaging



Therapeutic Targets

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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

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 Kuppfer 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-inflammation

- 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

Intellectual Property

- Base technology licensed from UCSD
- Imaging IP through 2033
- Therapeutics under Hatch Waxman to extend through 2025
- Clinical results should enable further IP extensions
- New formulations, carriers and delivery systems will enable additional IP protections

Milestones for Remainder of 2017

Imaging

- Complete IV dosing RA study (17dosed/2 consented/6 controls yet to dose)
- Initiate IV dosing CV Study (IRB approval pending, 2nd NIH grant scoring July)
- Initiate IV dosing NASH study (protocol draft in review, Sites ID'd)
- Complete development plan for imaging active M1-mediated inflammation, RA diagnosis and/or monitoring (KOL's interviewed, indication selected, statistical analysis and protocol under review)

Therapeutics

- Complete development plan for treating active M1-mediated inflammation, demonstration for potential partners for systemic applications (extension of imaging study above, same population)
- Complete development plan for orphan disease indication (consultants hired)
- Complete animal testing by 2 corporate entities for possible partnering
- New backbone efforts – lower MW, new polymer with range of MW's (first synthesis in progress, SOP's for other pathways provided to synthetic lab)

New formulations

- Lab up and running, all equipment acquired and on site
- With new lower MW agents, pursue topical as well as oral (background work initiated with current formulation)

Milestones for Remainder of 2017

Imaging

- Seek approval for imaging "activated macrophages"
  - Compare positive image to pathology → TC^{99+} via imaging = $CD206^{+}$ via pathology - RA patients undergoing joint replacement
  - Similar approval pathway as Lymphoseek for SLN
- If approved opens door to sales for ANY IV inflammatory indication. Potential commercial sales PRE approval for research purposes in clinical studies (NASH, CV, autoimmune etc)
- Post approval of generic inflammatory imaging indication, work to obtain partners to develop specific indications to enhance potential for insurance reimbursement.

Therapeutics

- Complete development plan for treating active M1-mediated inflammation, demonstration for potential partners for systemic applications, potential meaningful sales for MT while systemic products are being developed
- Orphan indication for MT - Auto-immune hepatitis
  - ~ 100,000 patients in US
  - Current Tx – high dose oral steroids
    - Poor efficacy ~1/3 patients achieve remission
    - Very significant toxicity – weight gain ~ 100lbs, type 2 diabetes, depression, osteoporosis
  - Business and regulatory models being pressure tested by outside consultants

Financial Projections

$MM (USD)	Year 1 Post Close	Year 2 Post Close
Revenues		
CAH Guarantees	$6.7	$6.7
Grants	$2.0	$2.0
RoW & Other Milestones (range)	$0-0.7	$0-1.3
Total Revenues	**$8.7 – 9.4**	**$8.7 – 10.0**
Research & Development		
Wages & Drug Development	$2.9	$2.9
Total R&D	**$2.9**	**$2.9**
General & Administrative		
Professional Services	$1.9	$1.6
Wages & Other Support Costs	$2.6	$2.5
Total G&A	$4.4	$4.1
Income from Operations	**$2.1 – 1.4**	**$3.0 – 1.7**

Lymphoseek

Cardinal Health Deal

Sale of NA Commercial Rights for Dx Lymph Node Oncology Indications

North American Commercial Rights

- Sale limited to North American rights for diagnostic oncology indications only

Deal Terms

- Navidea received $81M upfront payment
- Sales-based milestone payments up to $227M over 10 years
- $17M in milestone payments guaranteed over next 3 years

Navidea's Takeaway

- Retains development platform of all non-competing diagnostic indications
- Retains rights to develop targeted therapeutics in all indication areas

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Strong Financials
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Thank you

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Contact Details

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