Navidea
BIOPHARMACEUTICALS

Precise Identification and Treatment of Macrophage-Mediated Diseases

June 2018

Disclaimer

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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

The Role of Macrophages in Human Biology

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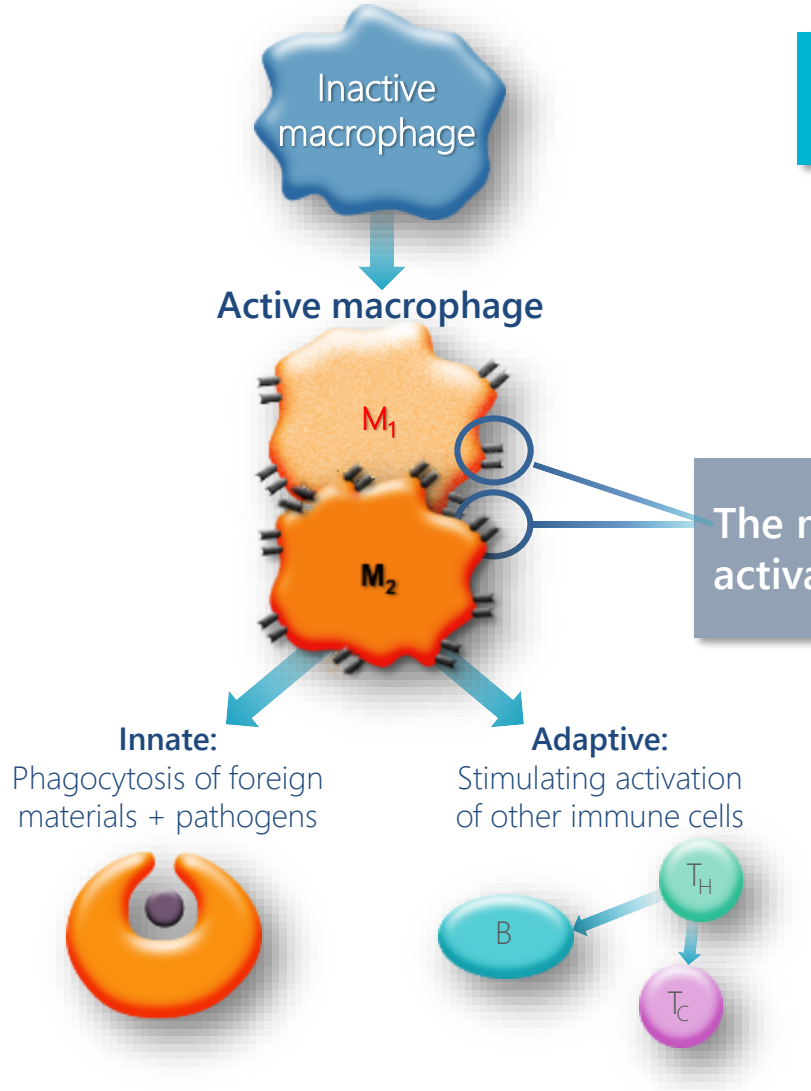
Macrophages are immune system cells that respond to tissue damage or infection

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**

Macrophages and CD206 Receptors



Macrophages are activated in multiple ways

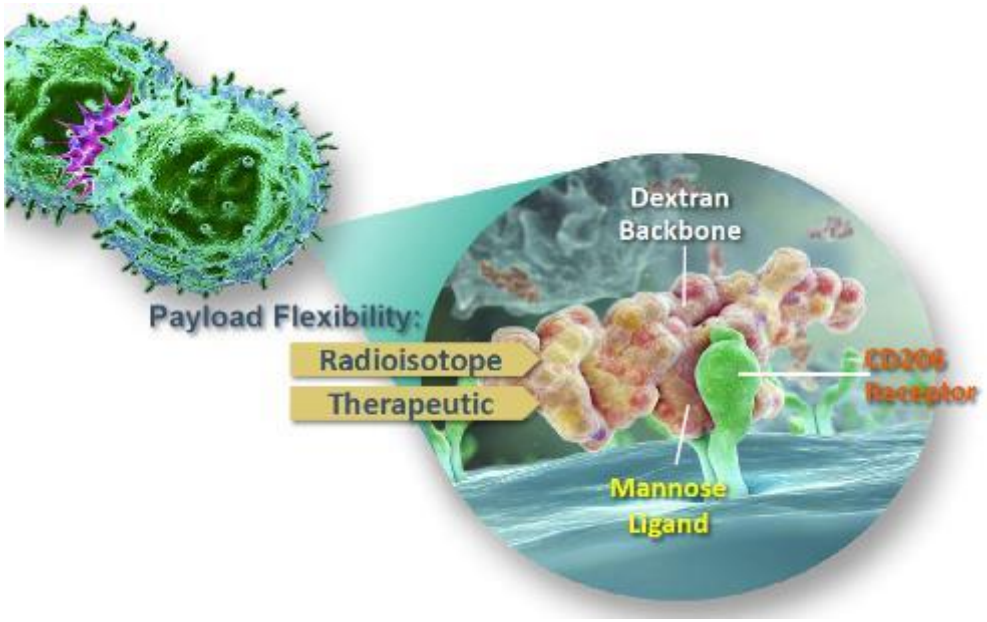
Environmental Exposure
- Viruses
- Other infectious agents
- Drugs/chemicals
- Other (e.g. ultraviolet light)

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

<u>Tilmanocept combines:</u>

- Mannose ligand for binding CD206 receptors on activated macrophages → ✓ **Seek**
- Radioisotope → ✓ **Identify**
- Therapeutic agent → ✓ **Modify**

Therapeutic Concept

Selectively targeting Activated Macrophages

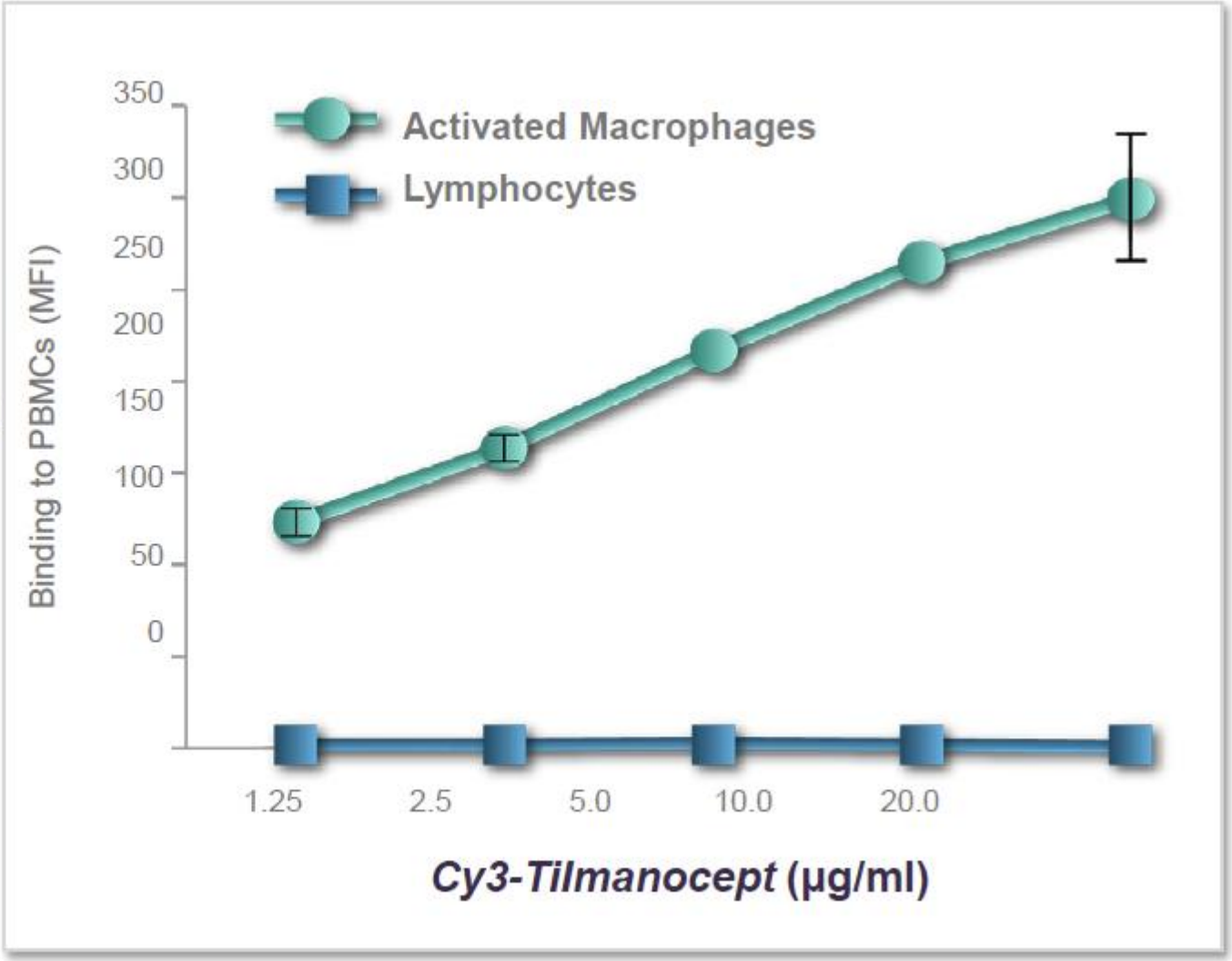
Platform for immuno-constructs that preferentially target CD206+ (and CD209+ dendritic cells) activated macrophages

1 GPS	2 Delivery	3 Payload
		
Mannose Moiety With One Hardwired Address - CD206 Activated Macrophages	Manocept™ Backbone	▪ Chemotherapeutics ▪ Immune-modulators ▪ Tc^{99} ▪ 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 (kuppfer cells, microglial cells, etc.)

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



High Selectivity = Better Targeting

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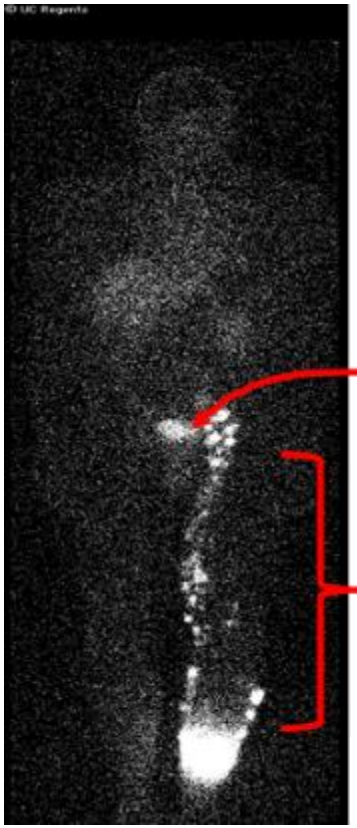
Macrophage depletion with liposomal agents that target all macrophages fail due to toxicity

Manocept Radio-isotope Imaging



4 hours after SC admin of Lymphoseek

PEG-LD Liposomes Radio-isotope Imaging

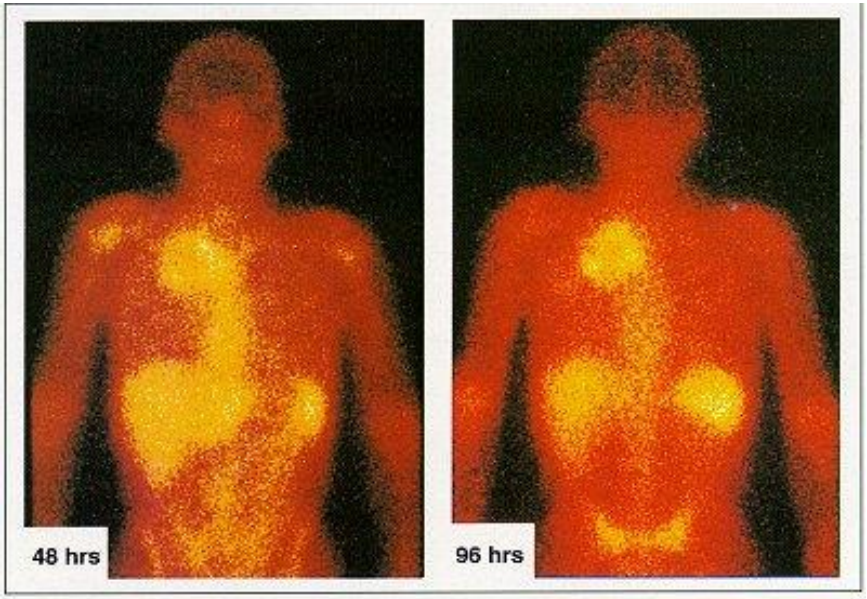


Figure 7: Gamma scintigraphic image of a cancer patient 48 hours (left image) and 96 hours (right image) after administration of PEG-LD liposomes containing ^{111}In. Note that both images are posterior views. Uptake of the radioactive liposomes is seen in certain normal tissues including spleen, liver,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

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

Substantial Unmet Clinical Need

Current Clinical Landscape & Monitoring Market Opportunity

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NASH Clinical Landscape:

103

NASH treatments currently in development

~55

in clinical-stage

Current Scale of Global NASH trial patients

>10,000

Patients currently involved in NASH trials globally

Assuming 2 scans per year per patient

$5,000/imaging agent

NAVB sales price

$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

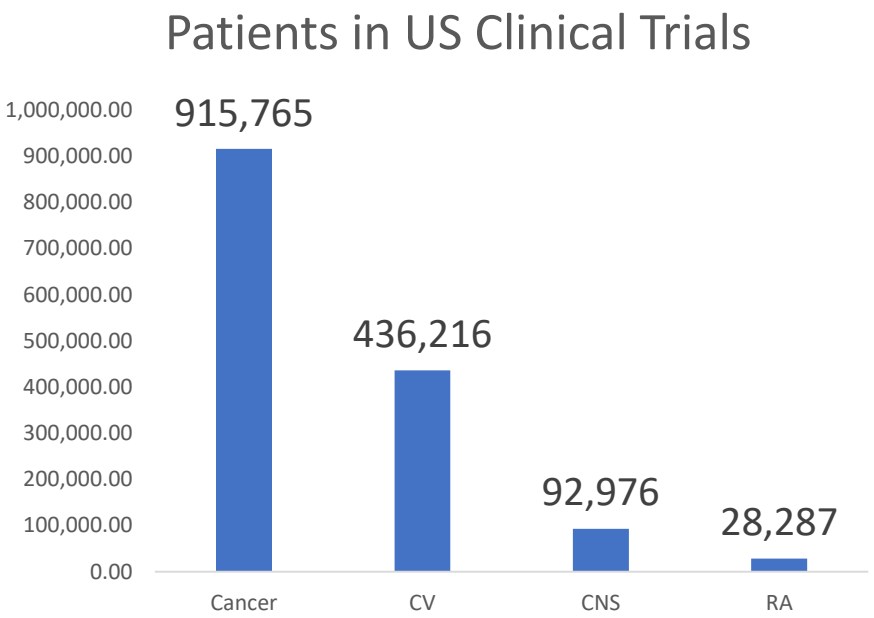
↓ Decrease sample sizes

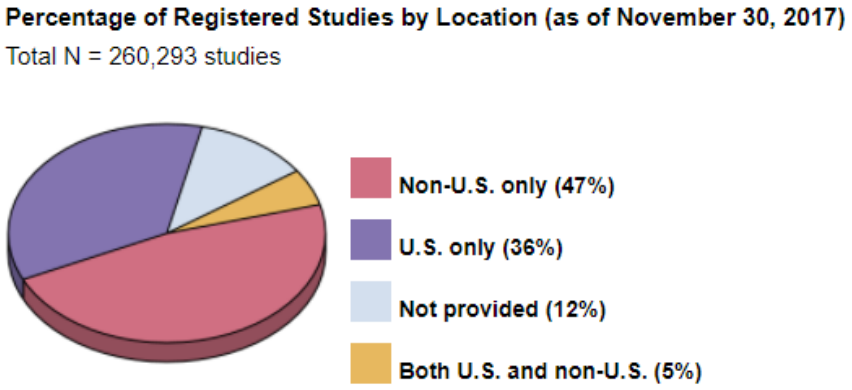
Autoimmune:

- 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

Oncology Trial Monitoring Opportunity

Recruitment, Maintenance, Summary





https://clinicaltrials.gov/ct2/resources/trends

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

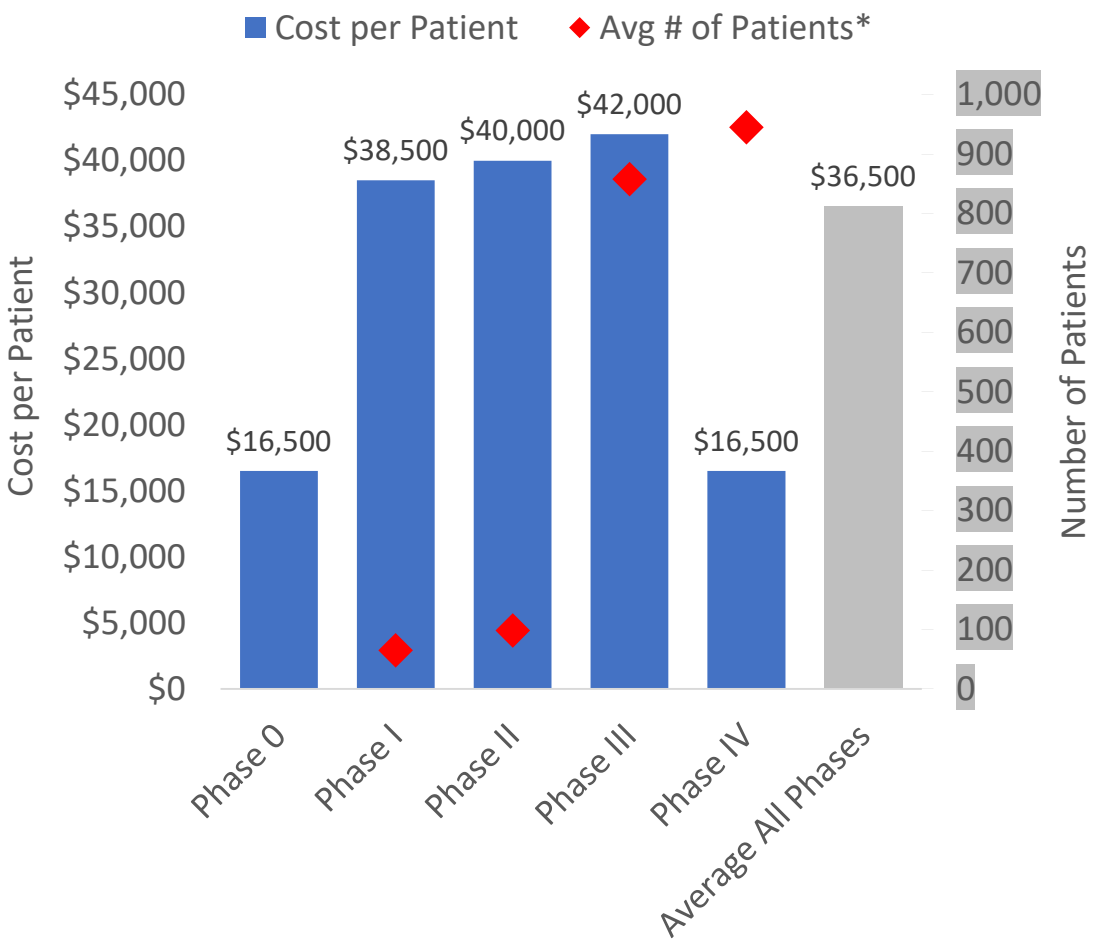
Range of doses given per patient per treatment regiment: 2 - 8

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

Navidea Imaging Strategy

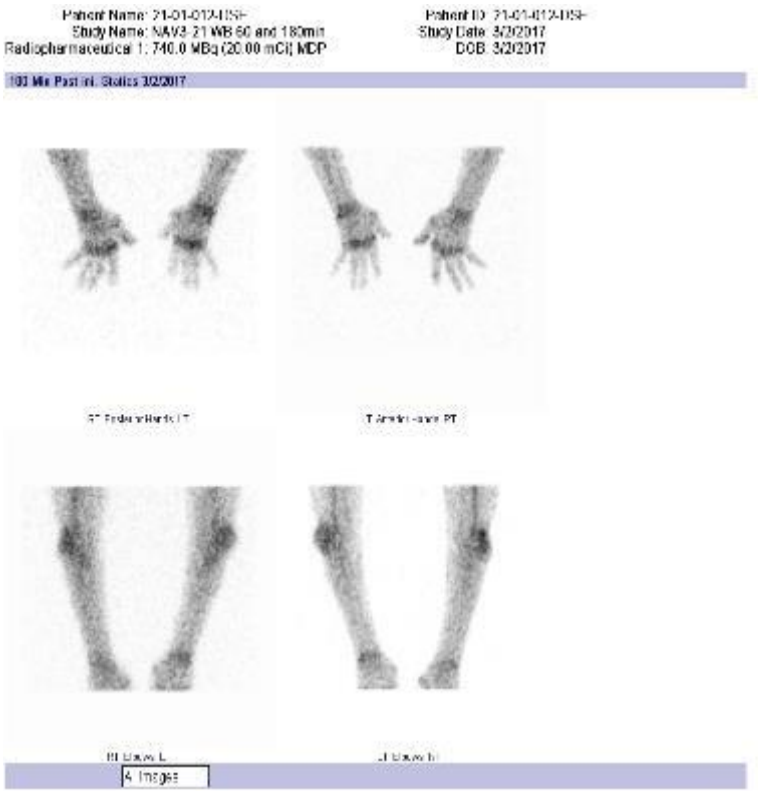
Image M1 or M2 Mediated Disease

Dose it
Same for all indications

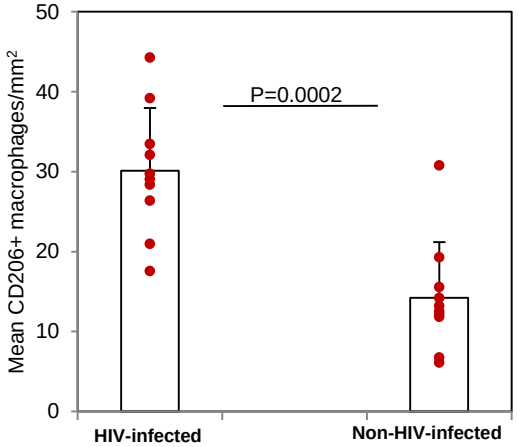
→

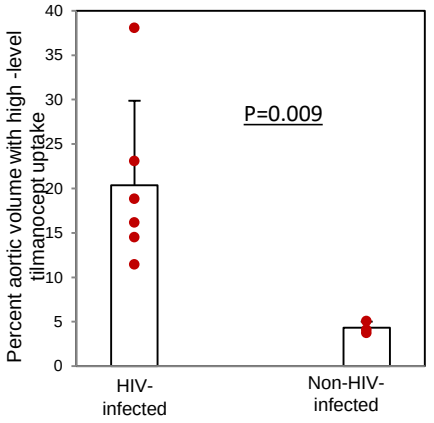
Image it
Focus the camera on area of interest

3 hour image RA



Computer read of CV images

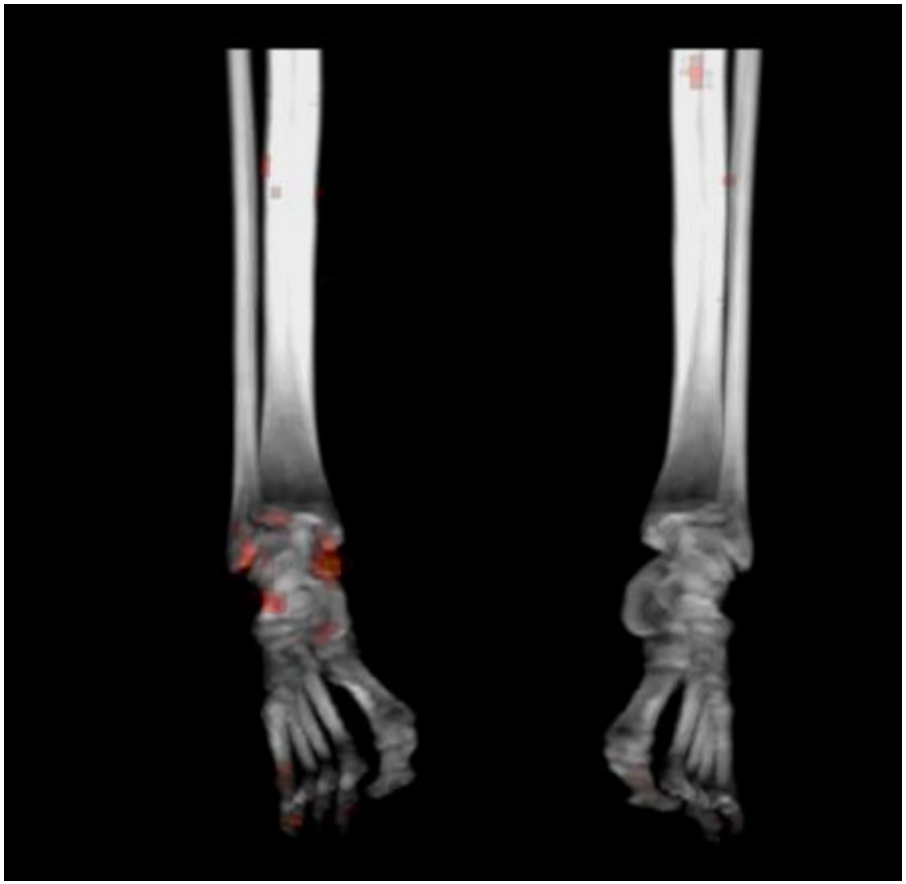




Macrophage Therapeutics Strategy

Treat M1 or M2 Mediated Disease

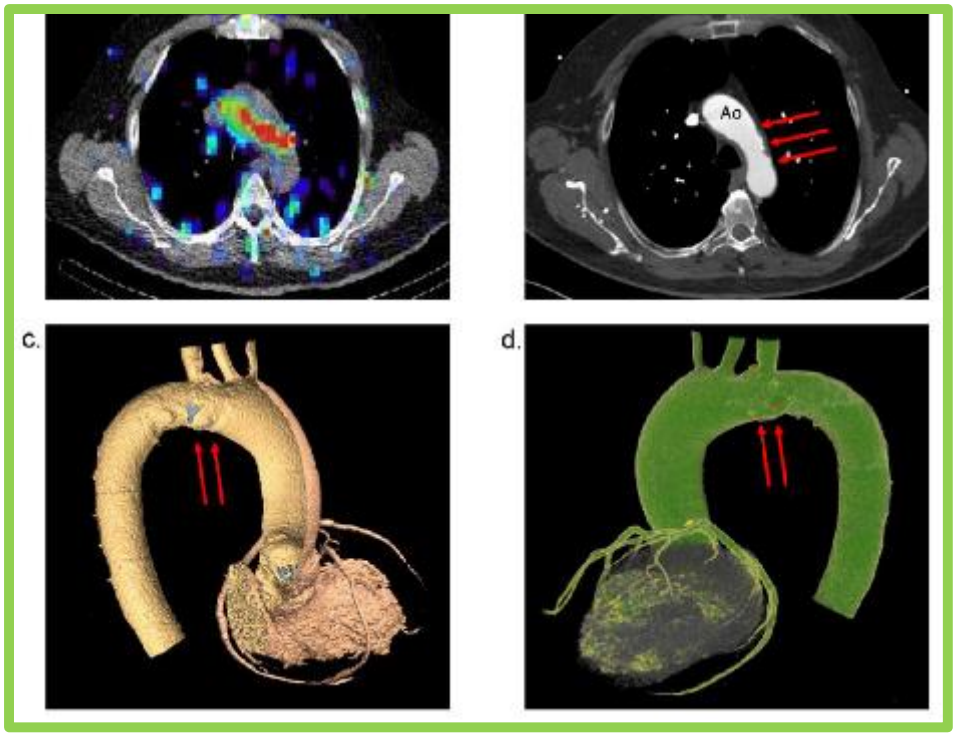
Image it



Treat it

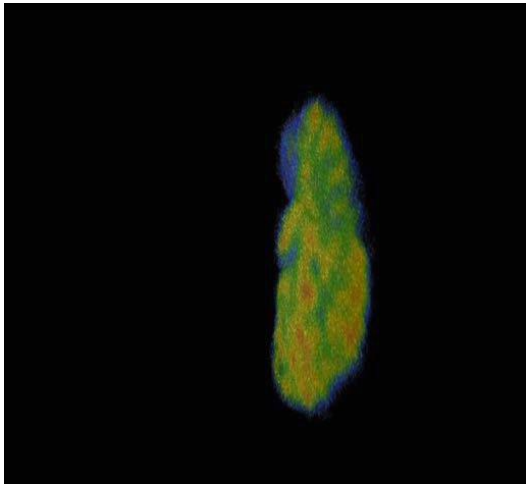
Imaging demonstrates we are targeting disease causing cells

Compiled 2D/3D Imaging

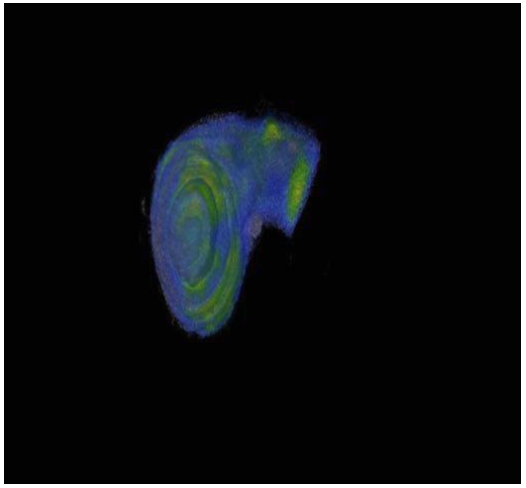


NASH vs. Normal

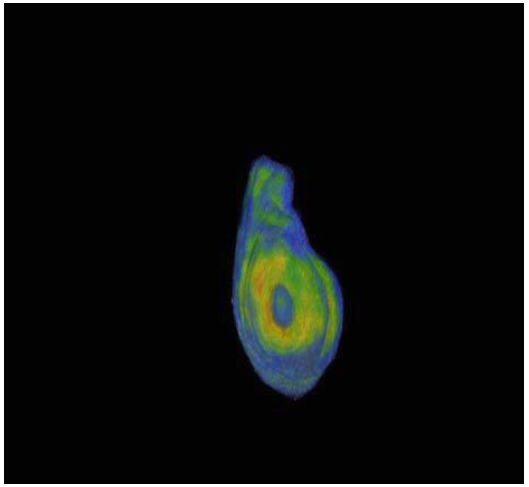
3D Mid Liver Localization



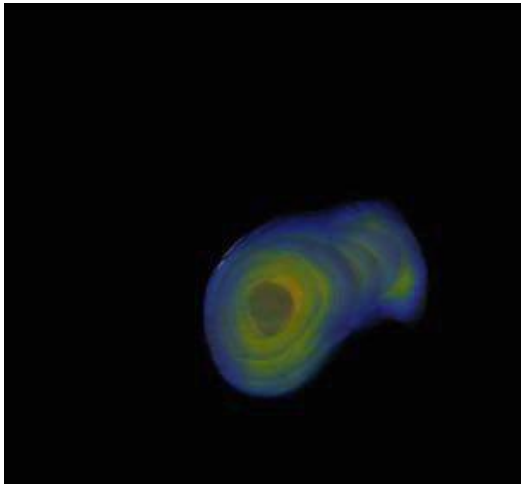
NASH Pt-1



NASH Pt-2

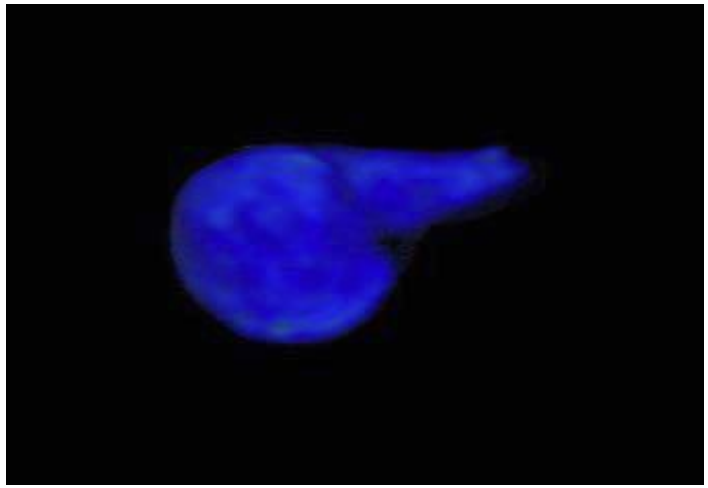


NASH Pt-3



NASH Pt-4

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



Normal Patient

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

Therapeutic Targets

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Aberrant macrophages are associated with several major disease states

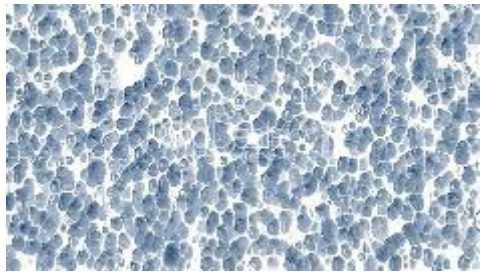
Cancer	**Cancer cells** modify the macrophage to create new cancer cells called **tumor associated macrophages (TAMs)** TAMs enable enhanced angiogenesis and release other tumor enhancing factors for an **immunosuppressive microenvironment**
Infectious Disease	In certain infectious diseases, the macrophage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

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 **every** cell in the body

MT Hypothesis

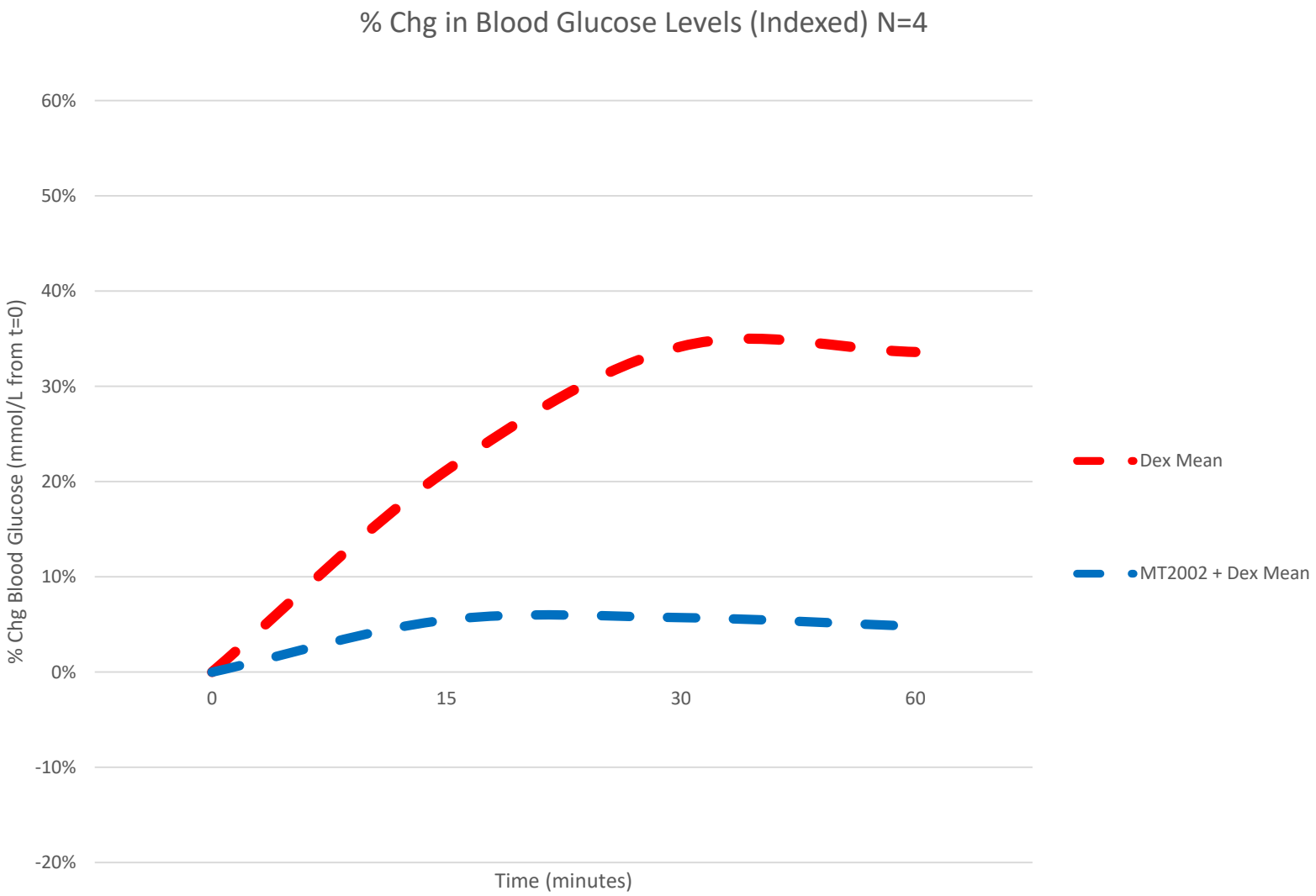
1. Covalently linking dexamethasone to a polymeric backbone with targeting to a cell surface receptor, found on ONLY disease causing cells
2. Receptor (CD206) internalizes the complex
3. pH inside cell causes release of the glucocorticoid in the cytosol where it binds the GC

✓ **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.

Receptor mediated delivery

Equal amount of dex dosed: free vs conjugated



LPS-induced Model of Acute Lung Inflammation

Mouse Model 4 hours post administration of triggering Agent

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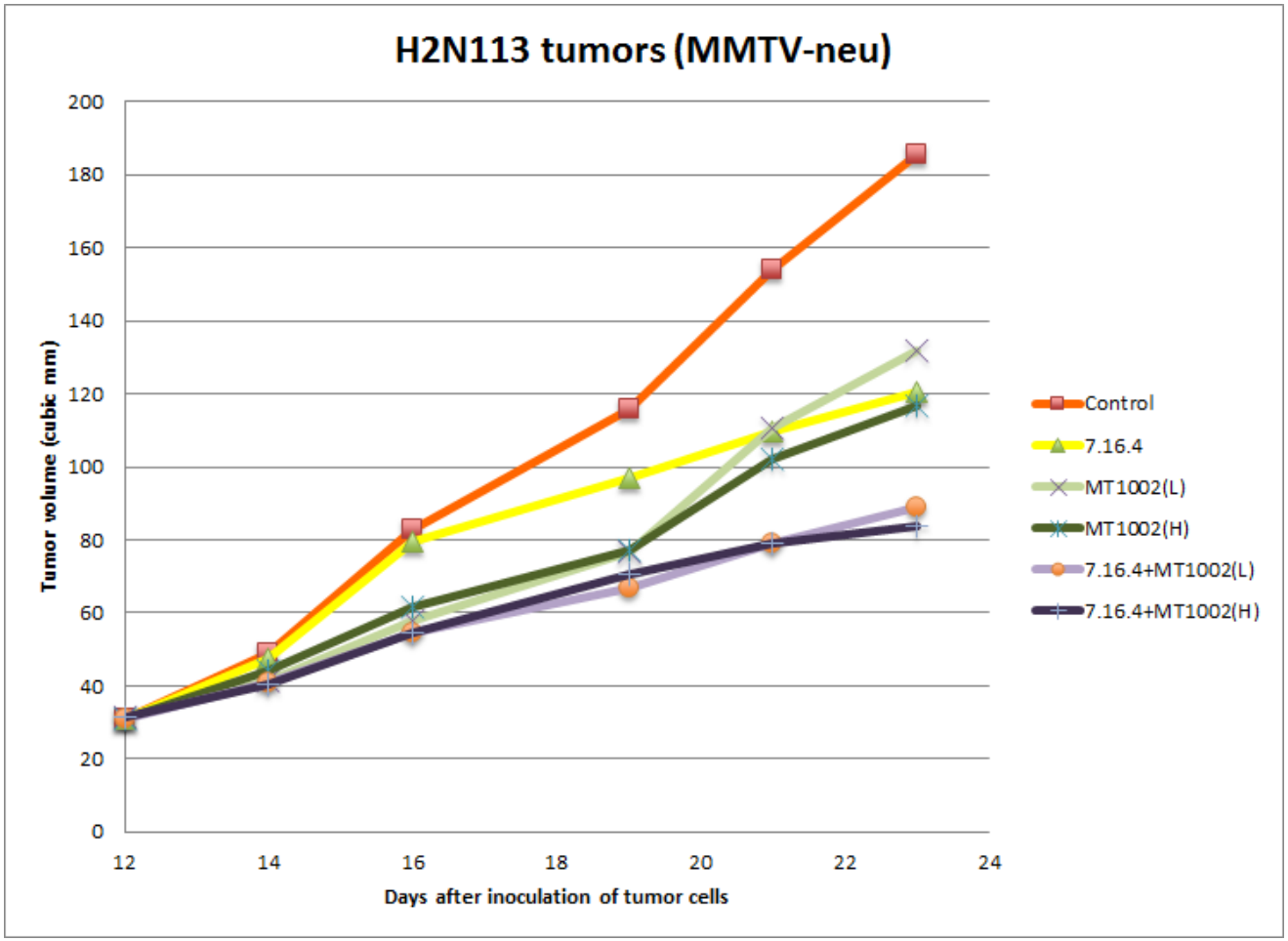
	GM-CSF(pg/ml)	IL-6(pg/ml)	TNF α (pg/ml)	IFN γ (pg/ml)
Vehicle	**129**	**1,615**	**1,443**	
DEX	-99%	-95%	-78% **(-96%)**	**-91%**
MT-2002	-65%	-77%	-66% **(-94%)**	**-87%**

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 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



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)

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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

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Targeting KS with Manocept Conjugates

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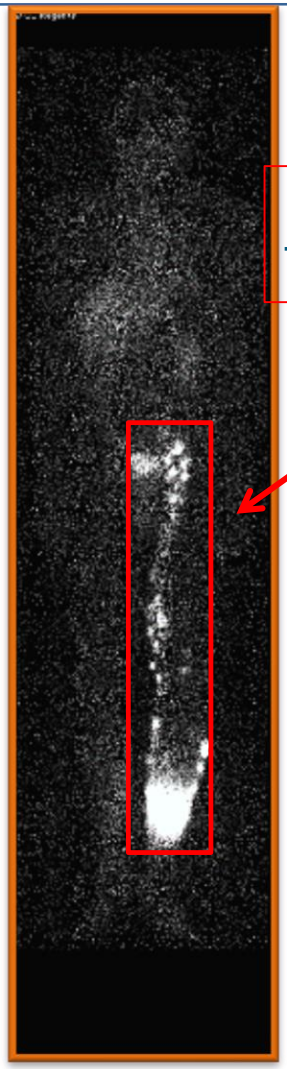
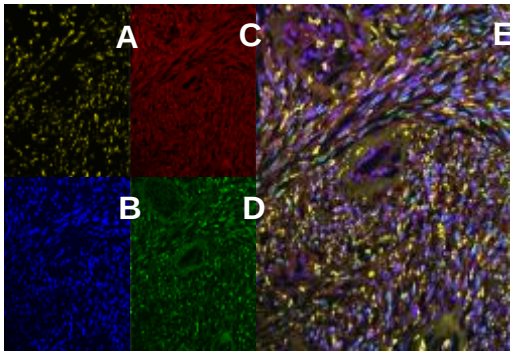


Image KS lesions **(Tilmanocept)**

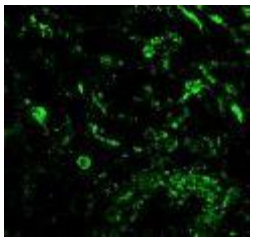
KS tumor and TAMs Take up **Manocept-Cy3**

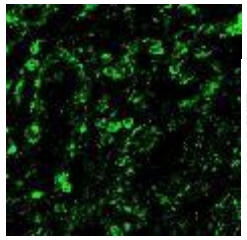


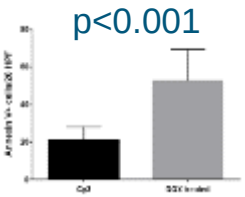
Kill TAMs **(Man-Dox)**

Cont
MAN-Dox

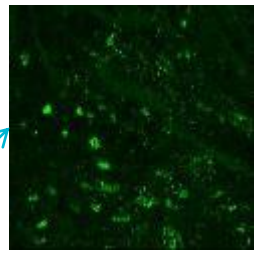
Apoptosis

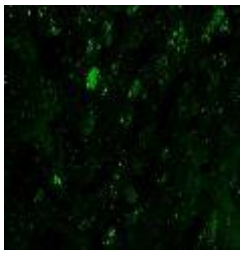


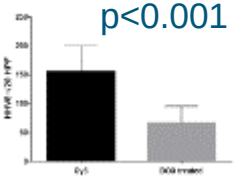




Kill HHV8+ KS tumor cells







Kill HIV+ macrophages

Anti-HIV: IC50= 0.054uM

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

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

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Contact Details

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