July 2021

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," "forecast", "goal" "future", "intent", "will", "may", "could" and similar expressions, as well as the negatives of thee words or comparable words, 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 and uncertainty of future profitability, 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, our ability to successfully complete research and further development of our drug candidates, the timing cost, and uncertainty of obtaining any required regulatory approvals of our drug candidates, our ability to successfully commercialize our drug candidates, 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.

We are a precision immuno-diagnostics and therapeutics company focused on solving the many problems presented by inflammatory conditions

We are leveraging our platform technology to create a robust pipeline of immuno-diagnostics and immuno-therapeutics

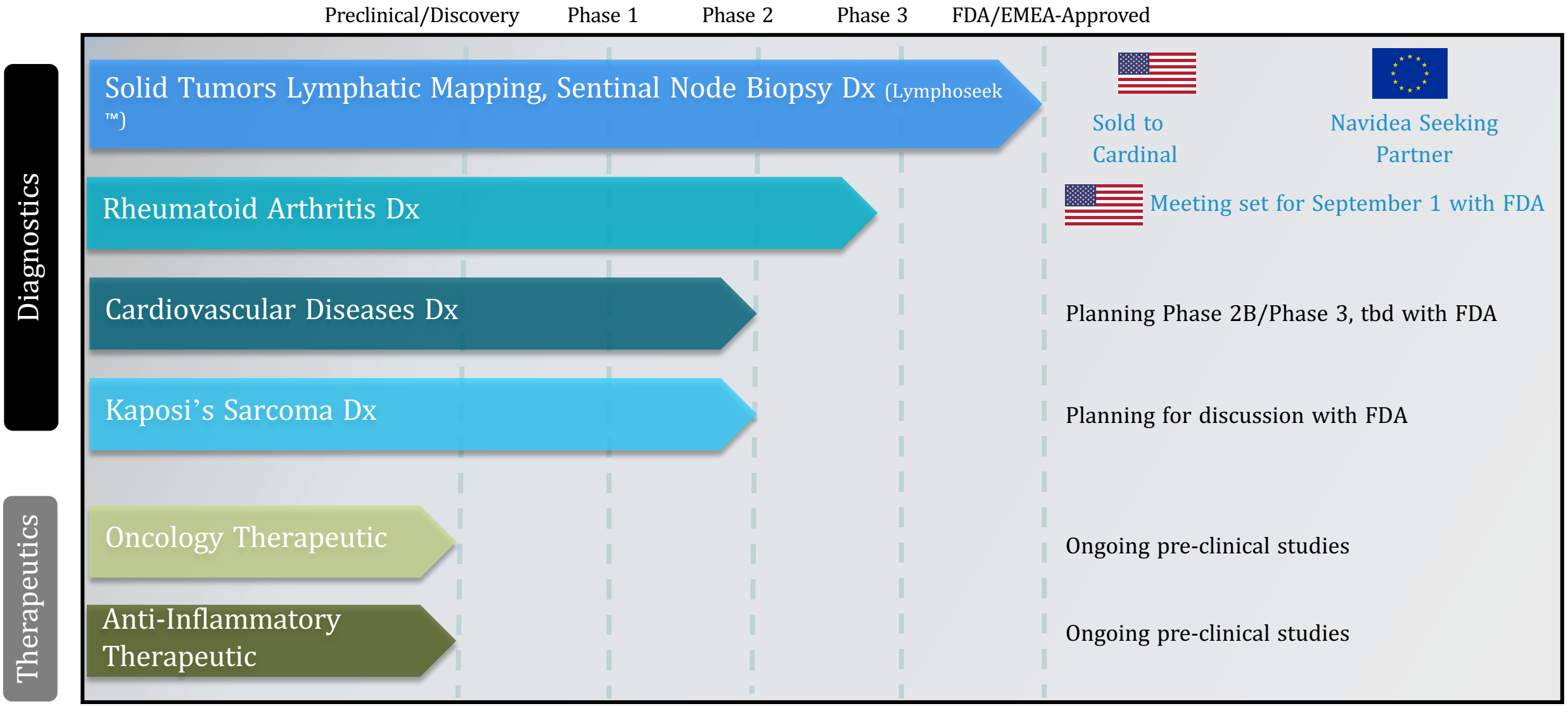
Navidea® BIOPHARMACEUTICALS

Corporate Overview

A precision immuno-diagnostics company focused on inflammatory diseases

1. Building off FDA/EMA-approved diagnostic product Lymphoseek® (technetium Tc 99m tilmanocept) Injection
2. Non-invasive imaging targeting CD206 receptors on Activated Macrophages
3. Initial focus on personalized Rheumatoid Arthritis Diagnostics
4. Proprietary Manocept™ platform applicable to multiple disease states in both Diagnostics (Dx) and Therapeutics (Tx)

Our Diagnostics and Therapeutics Pipeline



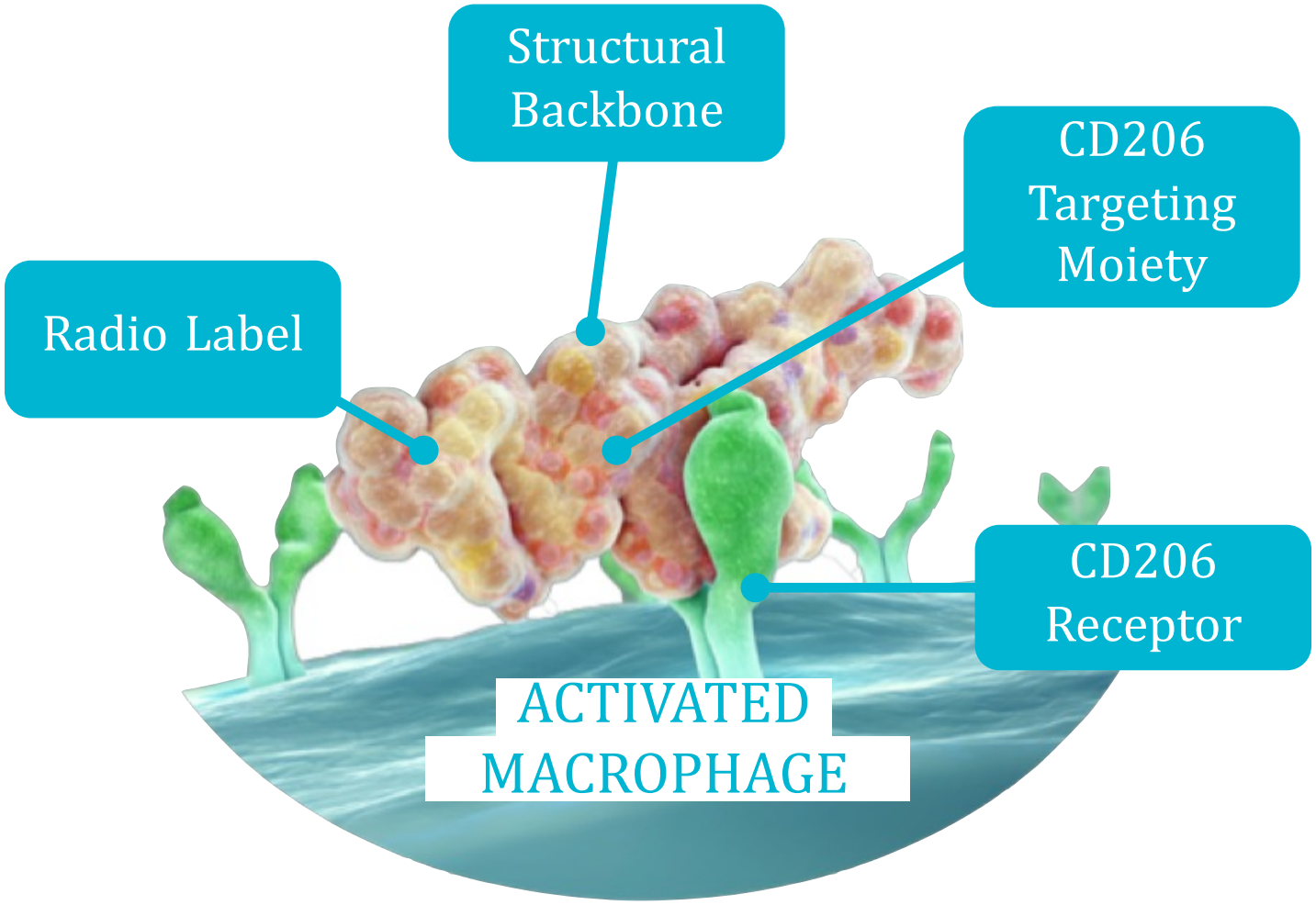
Our Core Tilmanocept Technology

Targeted Binding to Activated Macrophages

Best-in-class CD206 affinity allows sensitive detection of all types of activated macrophages in vivo

Disease agnostic provides robust pipeline beyond RA

FDA/EMA approved (favorable regulatory pathway)



The Tilmanocept Difference (Diagnostics)

	Manocept™	Key Differentiator
Target	Activated Macrophages	Highly specific target correlated to active inflammatory response
Molecular Weight	~2-20 kilo-daltons	Able to penetrate circulating and deep tissue macrophages while maintaining industry leading specificity
Backbone (BB)	Natural and synthetic polymers	Negligible cost and ability to achieve robust gross margin profile
Half life	minutes	Clearance limits radiation exposure, and allows for recurrence and monitoring applications
The Tilmanocept Difference (Diagnostics)	10^{-9}- 10^{-13}	Binding affinity greater than or equal to the best mAbs – highest levels of specificity but at much lower cost
Drug loading	Multiple “copies” of radiolabel can be added to Tilmanocept backbone	Increases resolution of diagnostic imaging

Why Focus on Rheumatoid Arthritis?

+1M

Patients in the US are living with RA

$39B

$39 billion drag to the US Economy

20-50%

20-50% of patients respond adequately to any RA treatment

2nd

RA is the 2nd largest drug category globally

Why are Current Dx & Treatment Paradigms Failing?

1. Measurement of treatment response relies on subjective assessments.

2. Lack of biomarkers to guide treatment selection and/or monitor response

3. Development of tolerance to current therapies[1]

(1) Sidiropoulos PI, Boumpas DT. Differential drug resistance to anti-tumor necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006;65(6):701–703. doi:10.1136/ard.2005.049890

Our Solution and Value Proposition

Quantitative Imaging of Activated Macrophages in Rheumatoid Arthritis Patients

1. Increasing evidence of the role of activated macrophages in therapy response.
2. Selecting most appropriate treatment modality for patients based upon pathotype.
3. Convenient safe, rapid, non-invasive detection.

What the Experts Think
(KOL Testimonials)

"Tilmamocept not only provides the opportunity to objectively measure and follow RA disease activity in my patients' joints, but it also may eventually…predict which therapy… will be most effective for that patient, a tool that is desperately needed in today's rheumatology clinic."

- Key Opinion Leader at a leading university with a large RA patient population

"If I had a tool that could give me early information regarding how my patient is responding to treatment, or not responding, it would be a game changer."

L. Moreland
Chief of the Division of Rheumatology and Clinical Immunology at the University of Pittsburgh School of Medicine

Our First Rheumatoid Arthritis Indication

Quantitative Imaging with Tc 99m Tilmanocept for candidates of Anti-TNF Therapy

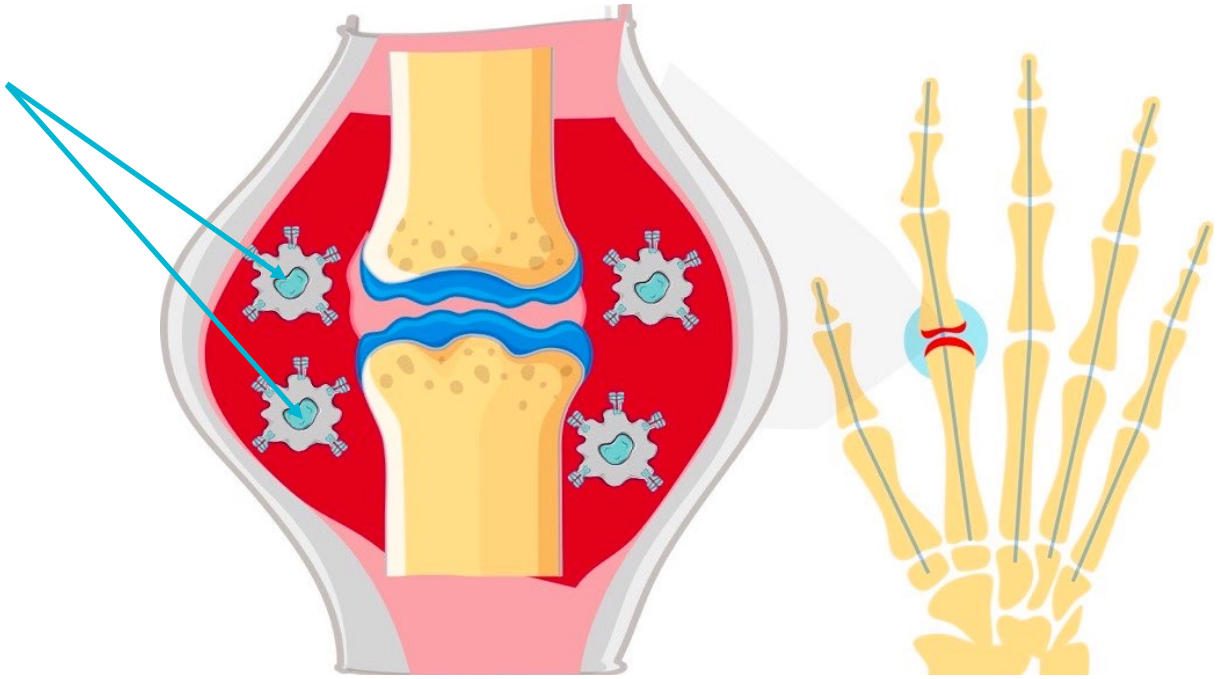
Choosing an Effective Therapy: Imaging before treatment

Early Indication of Treatment Effectiveness: Imaging shortly after initiation of a new Rx

Objective Therapy Monitoring Tool: Imaging later in Rx duration to evaluate effectiveness of current treatment

Tilmanocept Detects and Quantifies Disease Burden by Detecting Activated Macrophages

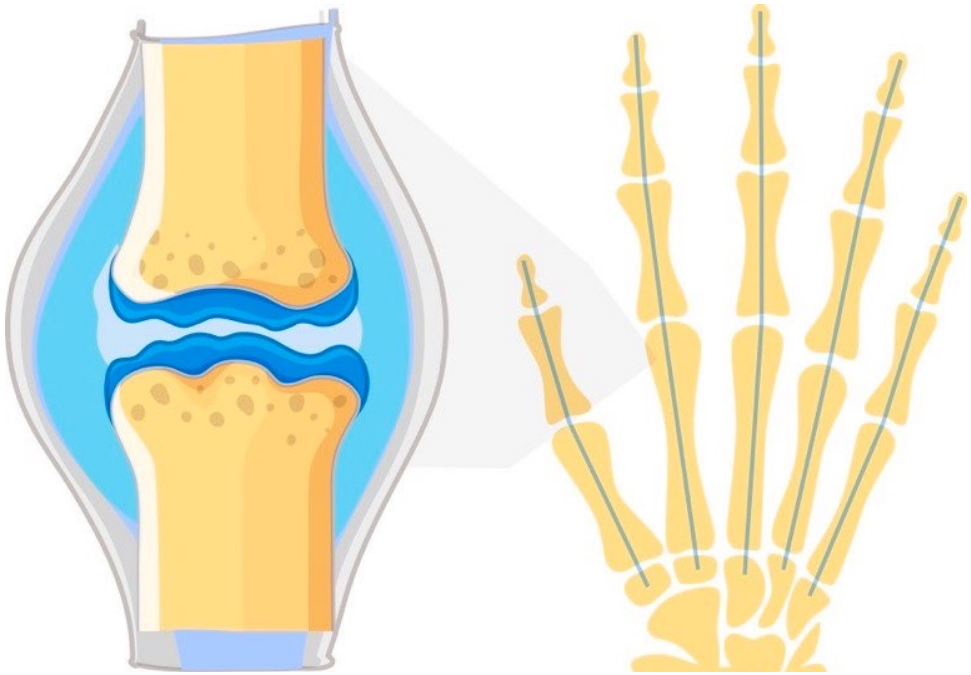
Activated Macrophages



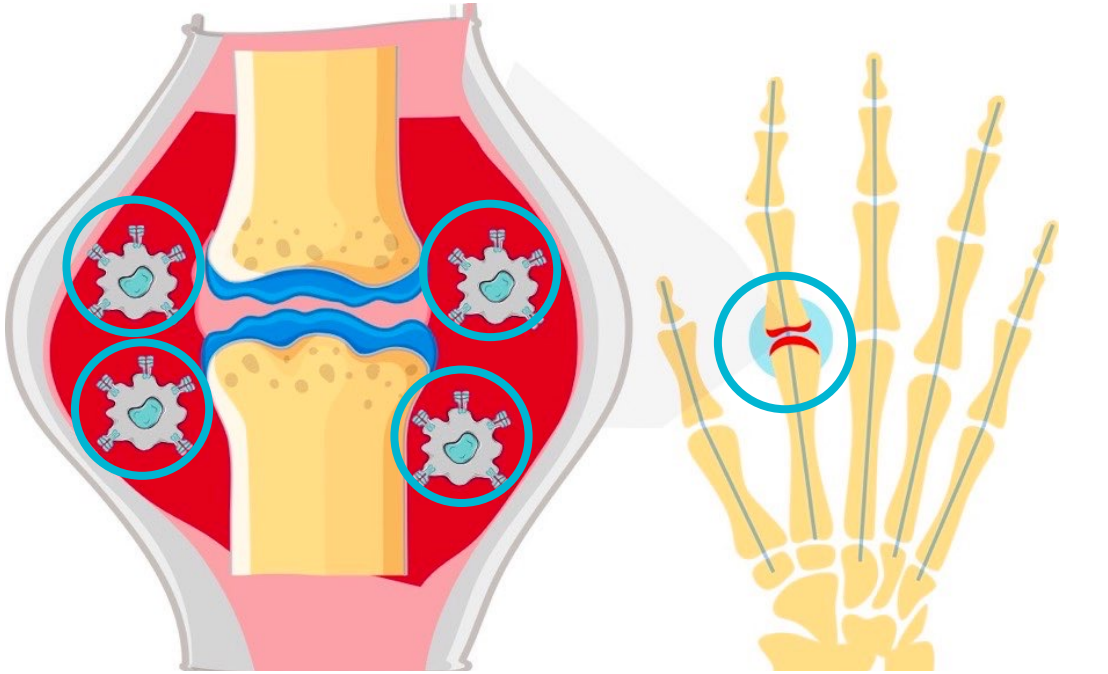
- Source: vecteezy.com (brgfx)

Activated Macrophages are Typically Present in RA Joints

Normal Joint

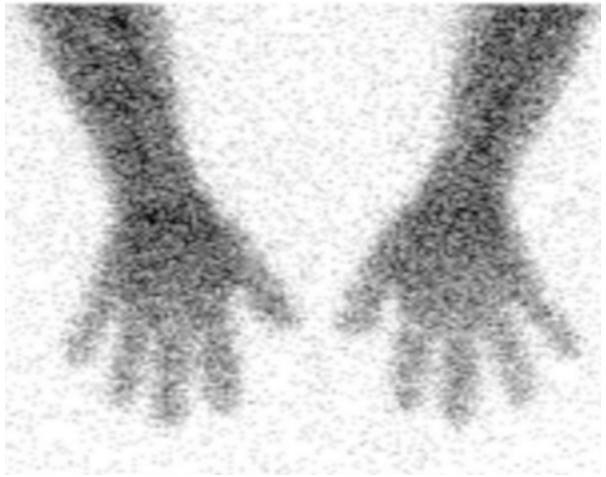


RA Joint



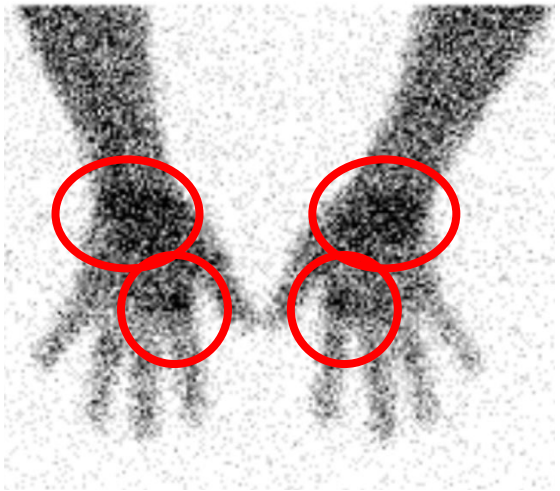
Tilmanocept consistently localizes in areas of macrophage driven inflammation*

Healthy Control Joint

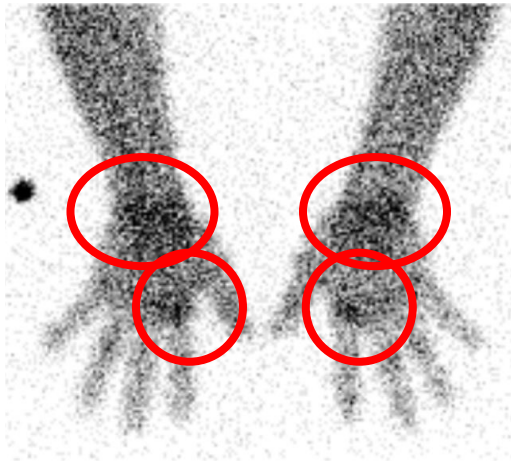


RA Joint

RA Patient Day 0



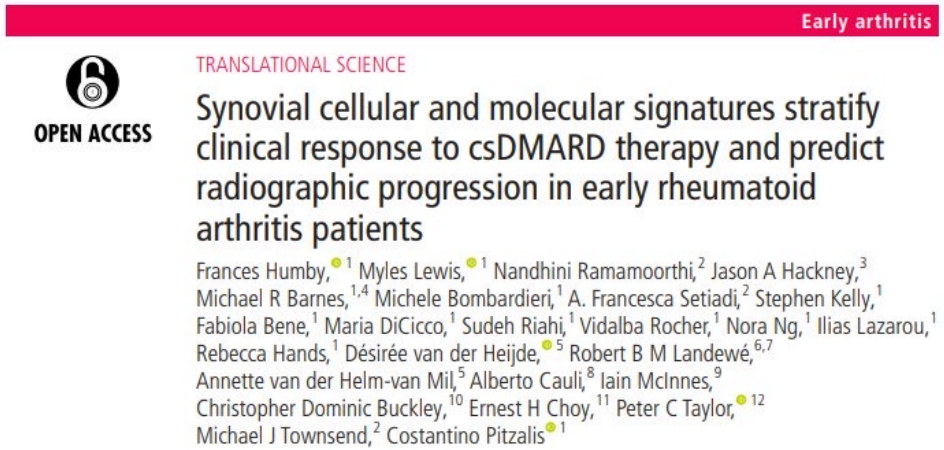
RA Patient Day 8



Patient exhibited reproducible localization over a 1 week period

*Select images from NAV3-31 Trial

Activated Macrophages are Important in RA Joints



Early arthritis

OPEN ACCESS

TRANSLATIONAL SCIENCE

Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients

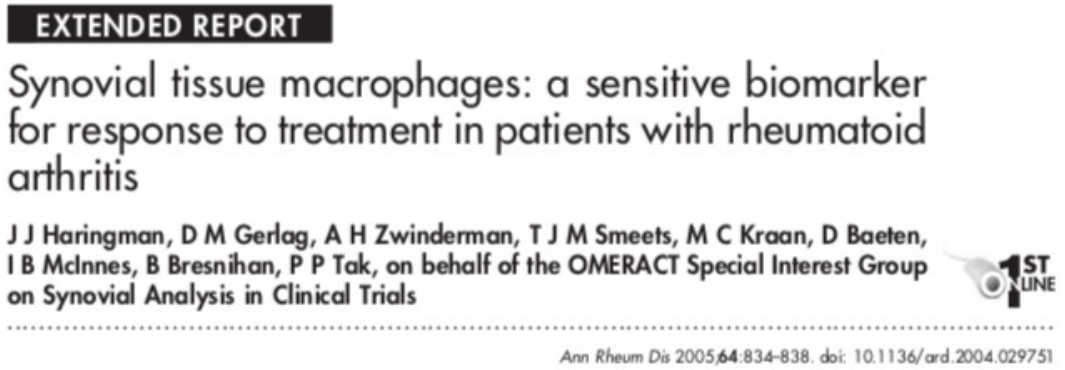
Frances Humby,[1] Myles Lewis,[1] Nandhini Ramamoorthi,[2] Jason A Hackney,[3] Michael R Barnes,[1,4] Michele Bombardieri,[1] A. Francesca Setiadi,[2] Stephen Kelly,[1] Fabiola Bene,[1] Maria DiCicco,[1] Sudeh Riahi,[1] Vidalba Rocher,[1] Nora Ng,[1] Ilias Lazarou,[1] Rebecca Hands,[1] Désirée van der Heijde,[5] Robert B M Landewé,[6,7] Annette van der Helm-van Mil,[5] Alberto Cauli,[8] Iain McInnes,[9] Christopher Dominic Buckley,[10] Ernest H Choy,[11] Peter C Taylor,[12] Michael J Townsend,[2] Costantino Pitzalis[1]

frontiers in IMMUNOLOGY

Macrophages in synovial inflammation

*Aisling Kennedy[1,2], Ursula Fearon[2,3], Douglas J. Veale[2,3] and Catherine Godson[1,2]**

[1] School of Medicine and Medical Sciences, University College Dublin Conway Institute, Dublin, Ireland
[2] University College Dublin, Dublin, Ireland
[3] Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland



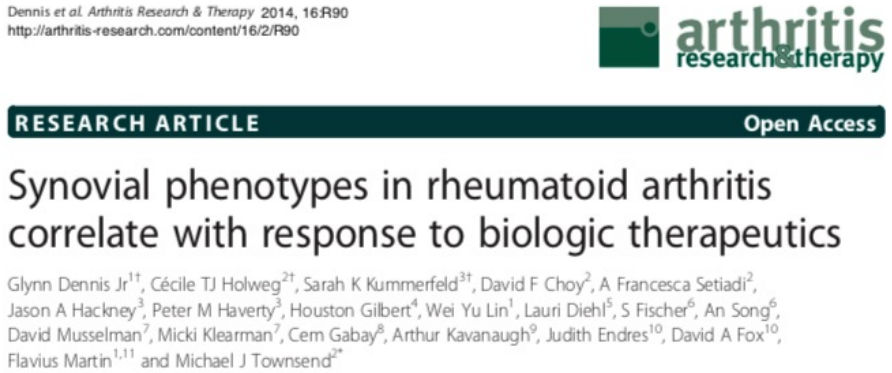
EXTENDED REPORT

Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis

J J Haringman, D M Gerlag, A H Zwinderman, T J M Smeets, M C Kraan, D Baeten, I B McInnes, B Bresnihan, P P Tak, on behalf of the OMERACT Special Interest Group on Synovial Analysis in Clinical Trials

1ST LINE

Ann Rheum Dis 2005;64:834–838. doi: 10.1136/ard.2004.029751



Dennis et al. Arthritis Research & Therapy 2014, 16:R90
http://arthritis-research.com/content/16/2/R90

arthritis research&therapy

RESEARCH ARTICLE Open Access

Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics

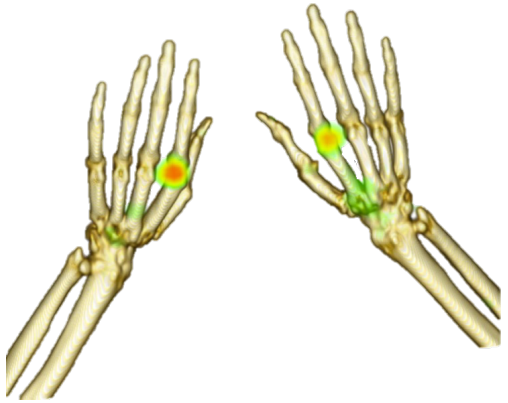
Glynn Dennis Jr[1†], Cécile TJ Holweg[2†], Sarah K Kummerfeld[3†], David F Choy[2], A Francesca Setiadi[2], Jason A Hackney[3], Peter M Haverty[3], Houston Gilbert[4], Wei Yu Lin[1], Lauri Diehl[5], S Fischer[6], An Song[6], David Musselman[7], Micki Klearman[7], Cem Gabay[8], Arthur Kavanaugh[9], Judith Endres[10], David A Fox[10], Flavius Martin[1,11] and Michael J Townsend[2*]

Tilmanocept Localization

Objective Diagnostic Scoring

Tilmanocept localization to joints in patients with active RA

These images are quantified for determination of macrophage disease activity



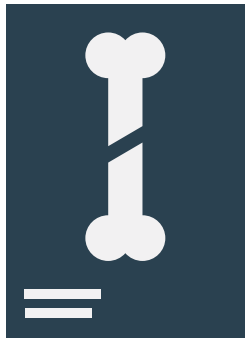
3D SPECT/CT- Orange/green areas show high RA inflammation

2D Planar- Darker regions are RA inflammation

RA Diagnostic Commercial Workflow

1. Rheumatologist Orders Imaging

Imaging Order



2. Radiologist Acquires Images

Images

Report

Quantitative Imaging Report & Score

3. Images Analyzed by Navidea's Core Lab

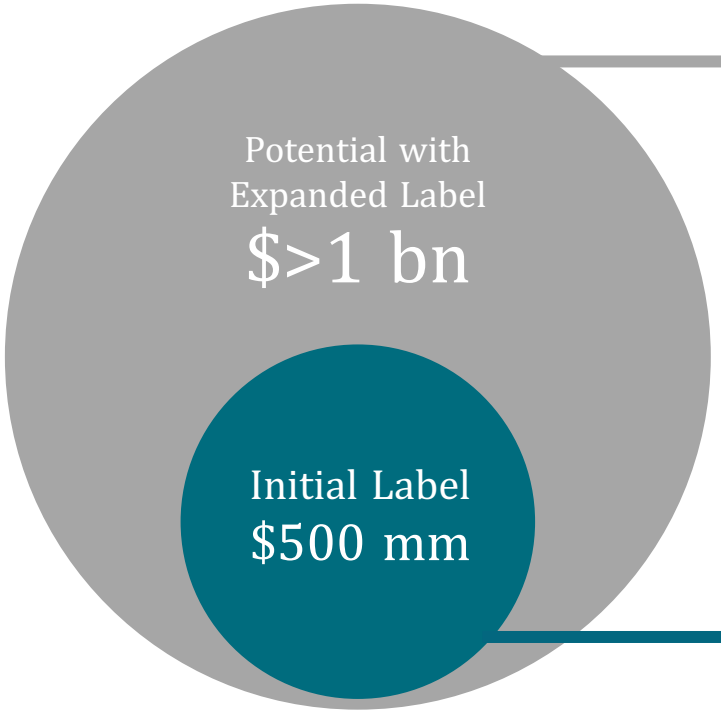
Treatment

4. Report informs:

- The Likely Efficacy of Anti-TNF Rx
- Early Indication of Effectiveness of Anti-TNF Rx
- Monitoring Treatment Efficacy

Source: vecteezy

US RA Market Opportunity is Large & Untapped



Includes:
(1) Initial label, (2) Early detection of RA
(3) Therapy-indiscriminate treatment response

Quantitative imaging with Tc 99m Tilmanocept for candidates of anti-TNF therapy

The Goal of Our Ongoing and Upcoming RA Studies*

Confirm reproducibility
(NAV3-31 P2B)

Correlate with Immuno-histochemistry
(NAV3-32 P2B)

Establish Normative Database
(NAV3-35 P2B)

Correlate with Symptomatology
(NAV3-32 P2& NAV3-33 P3)

- *Specific trial designs are under discussion

Encouraging analyses of NAV3-31

Overview of 3 arm phase 2B Trial for our Rheumatoid Arthritis Diagnostic

Arm	Design	Goal
Arm 1	healthy controls imaged on day 0	confirm the repeatability, reproducibility, and stability of Tc 99m tilmanocept imaging and further establish the quantitative determinants of healthy joints vs. those with RA-involved inflammation
Arm 2	active but stable RA patients imaged day 0 and day 8	
Arm 3	anti-TNF alpha patients imaged pre-treatment (day 0), week 5, week 12, and week 24	pilot arm of the upcoming Phase 3 trial assessing the ability of Tc 99m tilmanocept to provide an early indicator of efficacy of anti-TNF alpha treatment in RA patients

Encouraging interim analyses of NAV3-31

Interim data corroborated our hypothesis in Rheumatoid Arthritis

IA	Date	Results
IA 1	October 2019	<u>18 healthy controls and 12 patients with RA (Arm 1 & 2)</u> • Data demonstrated that this imaging is stable, reproducible, and can define joints with and without RA-involved inflammation.
IA 2	May 2020	<u>15 subjects with active moderate-to-severe RA (Arm 3)</u> • Positively predicted treatment response in 7 out of 8 (88%) subjects with 12-week clinical assessment available • Wide dynamic range of more than one order of magnitude (>10-fold) for calculated global uptake values in joints with RA-involved inflammation • **Signals declined by 58%** from baseline to week 5 in anti-TNF alpha responders • **Signals increased by 79%** from baseline to 5 weeks in anti-TNF alpha non-responders

Encouraging interim analyses of NAV3-31

Interim data corroborated our hypothesis in Rheumatoid Arthritis

IA	Date	Results

IA 2 (follow-on)	November 2020	<u>16 subjects with active moderate-to-severe RA (Arm 3)</u>
		
		• Tc99m tilmanocept imaging from baseline to week 5 was predictive of clinical outcome at 24 weeks in 13 out of 16 patients (81.3%)
		
		• Change from baseline to week 5 in Tc99m tilmanocept imaging had high positive and negative predictive value (PPV & NPV)
		  • Week 12 - PPV= 100%, NPV= 83%
		  • Week 24 - PPV= 100%, NPV= 77%
		
		• Early results also support the hypothesis that, in a subset of RA patients, the baseline scan alone can be a reliable predictor of non-responsiveness to anti-TNF alpha therapy.

Encouraging full analysis of Arm 3 NAV3-31

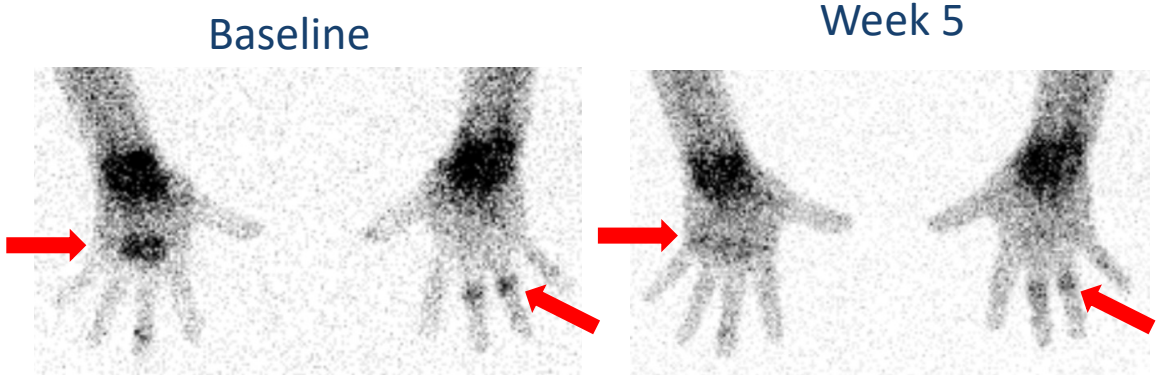
Full dataset corroborates our hypothesis in Rheumatoid Arthritis

Arm	Date	Results
3	June 2021	<u>30 subjects with active moderate-to-severe RA with 12-week follow up, 28 with 24-week follow up</u> • Tc99m tilmanocept imaging from baseline to week 5 was predictive of clinical outcome in 90% of patients at 12 weeks and 86% at 24 weeks. • Results also support the hypothesis that, in a subset of RA patients, the baseline scan alone can be a reliable predictor of non-responsiveness to anti-TNF alpha therapy.

Tc99m Tilmanocept Prediction of Treatment Response

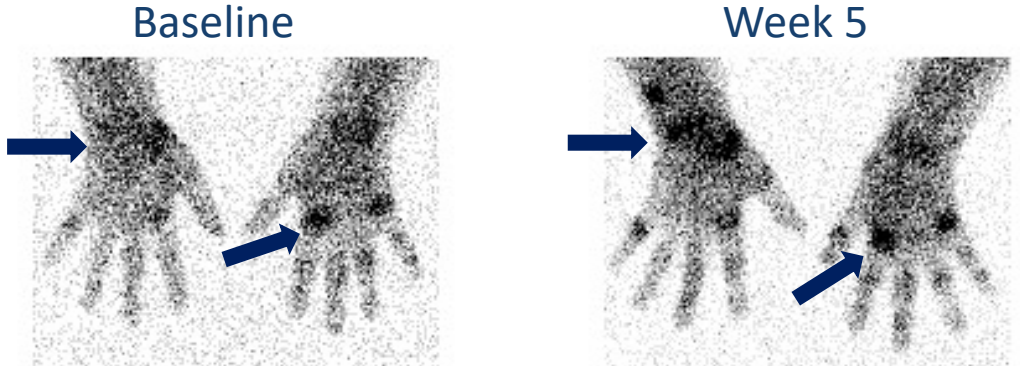
Arm 3 NAV3-31

A



	Week 0	Week 5	Week 12	Week 24
ACR50				
Global TUV				

B



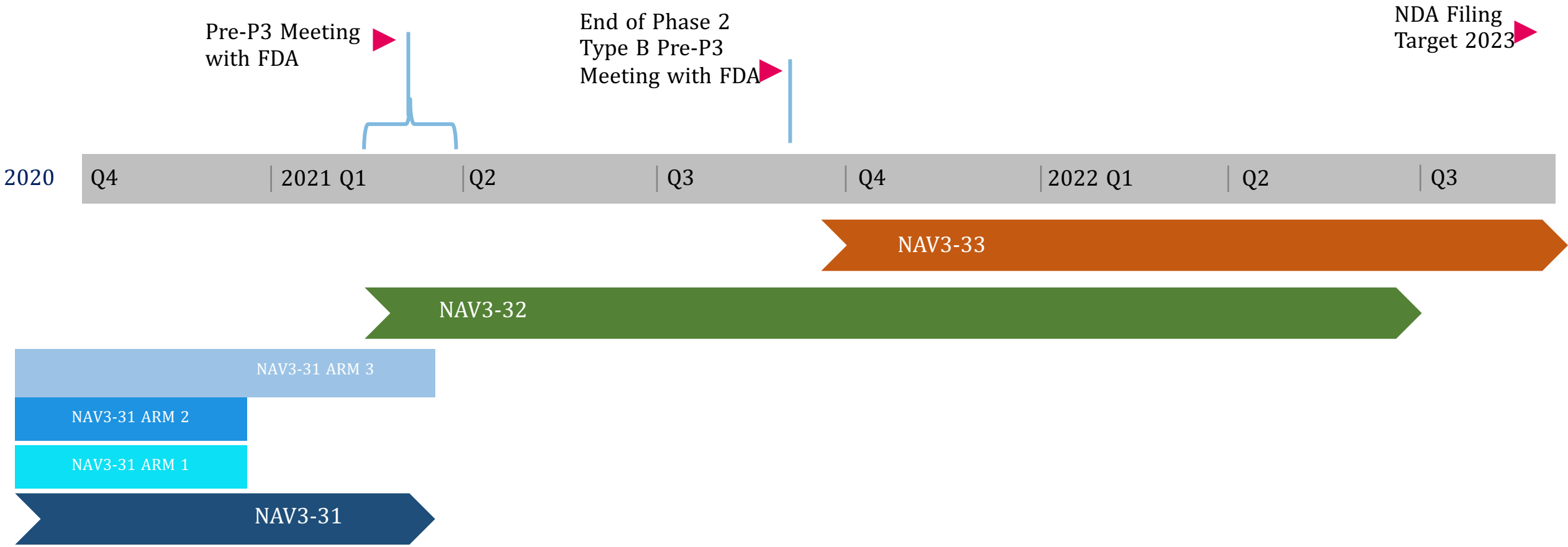
	Week 0	Week 5	Week 12	Week 24
ACR50				
Global TUV				

Legend	
Responder	
Non-Responder	

RA Path to NDA Submission

1. FDA discussion & review of Phase 3 meeting set for September 1
2. Begin Phase 3 Second Half 2021
3. NAV3-32 Phase 2b correlation of imaging to biopsy readout commenced 2q21
   - not on critical path for FDA approval
4. Aim for completion of Phase 3 by end of 2022
5. NDA submission to follow
6. NDA approval target 2023

RA Clinical Timeline*



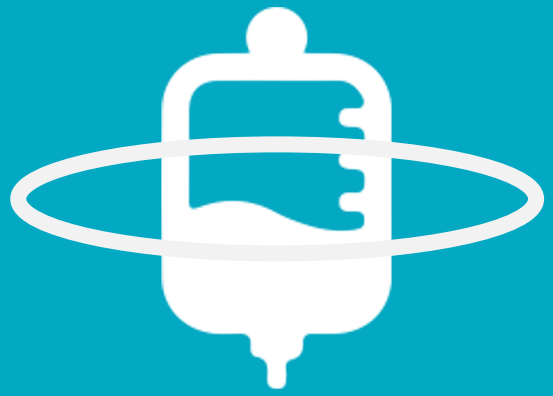
*Estimates as of July 2021

Our Diagnostics Pipeline

Cardiovascular Disease (CVD)

92 million Americans living with Cardiovascular disease

Ph 2 Study ongoing



Kaposi Sarcoma (KS)

Orphan Disease that is highly life threatening in a minority of patients

Ph 2 Study ongoing

CVD is Another Blockbuster Dx Opportunity

CVD is the leading cause of death in the US

1 in 3

U.S. Adults are living with Cardiovascular Disease

=

92 M

Americans

Ongoing CVD Phase 2 Trial at Mass General

Evaluating imaging and detection of vulnerable plaque

- Phase 1 study completed
- Published J Infection Diseases 16 Jan '17
- Additional study funded to expand to IV administration

NIH grant with

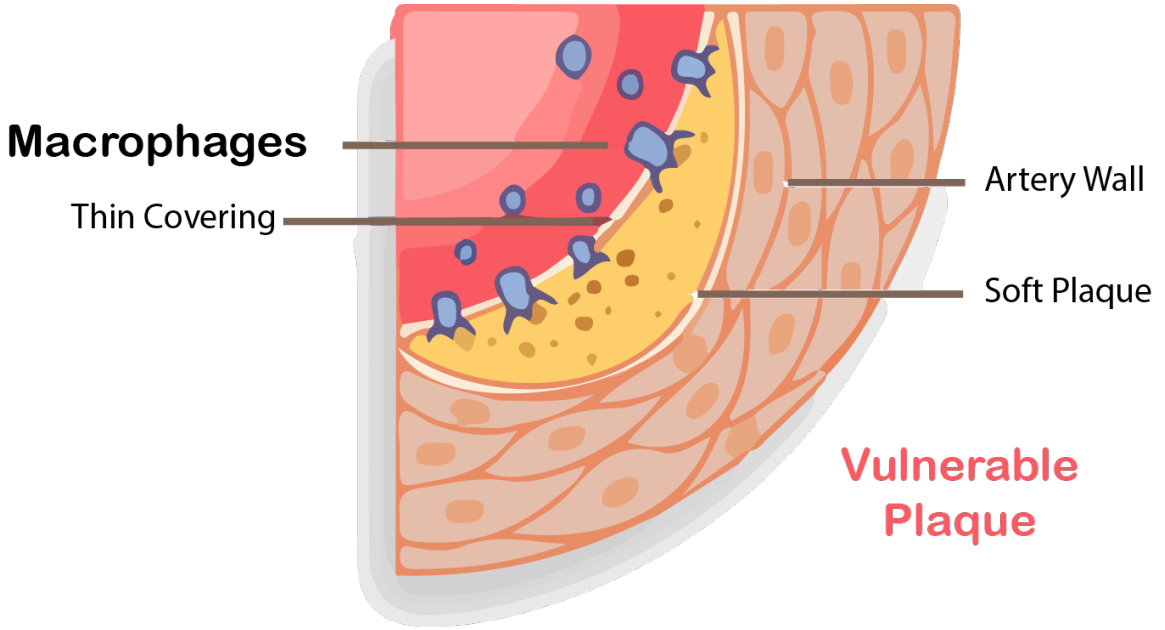
MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

Timanocept as CVD Detection Tools

Detecting High Risk Plaque

Atherosclerosis is an Activated Macrophages Mediated Disease

Activated Macrophages are Potential Markers of CVD Risk and Response to Therapy



Therapeutics Optionality

Leveraging our core Manocept platform to deliver therapeutics.

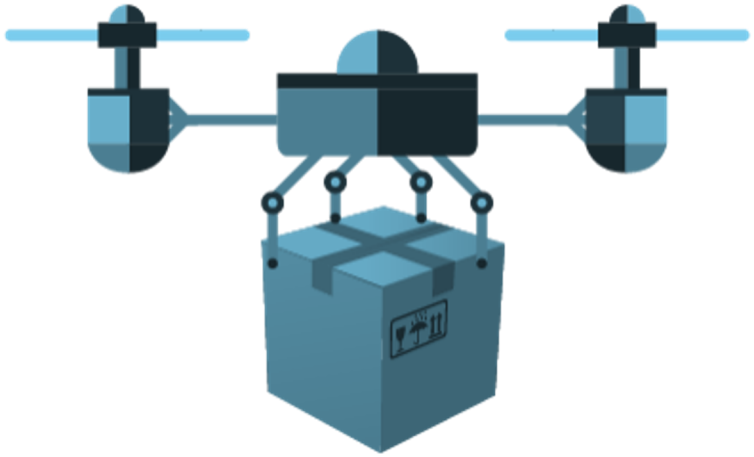
Therapeutics Concept

Platform for Therapeutics that target CD206+ (and CD209 dendritic cells) Activated Macrophages

GPS

Mannose Moiety
With One Hardwired
Address - CD206 Activated
Macrophages

Delivery



Manocept™ Backbone

Targeted Payload

Immune-modulators,
Chemotherapeutics, Tc^{99},
Other Isotopes

Therapeutics Pipeline

1000 CLASS

(Oncology/Fibrosis)

Killing TAMs & Altering the Tumor Microenvironment to Enhance Immunotherapies

- Depleting Through Apoptosis
- Depletes disease causing M2 Macrophages

2000 CLASS

(Anti-inflammatory)

Altering Activated Macrophage Function & Treating the Mechanism of Disease

- Inhibiting Inflammatory Activity
- Targeted steroid converts M1 to M2

Therapeutics Program Focus

Aberrant macrophages are associated with several major disease states

Current Programs

Inflammation

Aberrant activated macrophages can drive excessive inflammation and autoimmune diseases (RA, OA, Lupus, MS, Myocarditis, Uveitis

CNS

Improper clearance of certain compounds are responsible for macrophage driven inflammation seen in Alzheimer disease and implicated in MS, Parkinson's, Lipid Storage, and CNS diseases.

Cancer

Tumors convert anti-tumor macrophages to pro-tumor macrophages, called Tumor Associated Macrophages (TAMs). TAMs inhibit the endogenous immune system from effectively fighting the tumor and also drive angiogenesis.

Pipeline

Fibrosis

Overactive M2 macrophages are a key driver of fibrosis (NASH, Nephropathies, Fibrotic Disorders.

Cardiovascular

Lipid-containing macrophages can exacerbate atherosclerosis, an inflammatory condition

Infectious Disease

The macrophage acts as an incubator in certain infectious diseases (HIV, TB, Assorted Drug Resistant Bacteria)

Key Management

Jed A. Latkin

Chief Executive Officer, Chief Financial Officer and Chief Operating 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, Portfolio Manager of Precious Capital and CFO of West Ventures

MBA Finance - Columbia Grad School of Business

Michael Rosol

Chief Medical Officer

Prior to Navidea, Dr. Rosol served as Associate Director in the Clinical and Translational Imaging Group at Novartis Institutes for BioMedical Research from Nov 16 to Dec 18, and as Head of its Translational Imaging Group from 2012-2015.

He was also Senior Director of Business Development at Elucid Bioimaging, Inc. where he drove adoption of its Computer-Aided Phenotyping applications from May 16 to Nov 16, and CSO of MediLumine, Inc. from Oct 2015 to May 2016,

Dr. Rosol holds a PhD from Boston University School of Medicine.

William Regan

Chief Compliance and Regulatory Officer

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