Prothena Corporation plc

PRX003 Investor Update:
Phase 2 Development Strategy

September 29, 2016

Agenda

Dr. Gene Kinney, Chief Operating Officer

- Introduction

Dr. Ken Flanagan, Senior Scientist

- Th17 and Inflammatory Disease
- Proposed PRX003 MOA

Dr. Gene Kinney, Chief Operating Officer

- Planned PRX003 Phase 2 Development Strategy

Q&A

- Dr. Gene Kinney
- Dr. Ken Flanagan

Forward-Looking Statements

This presentation contains forward-looking statements. These statements relate to, among other things, the potential of PRX003 as a new approach for treating Th17 mediated diseases where multiple cytokines drive pathology; the design and proposed mechanisms of action of PRX003; whether PRX003 blocks infiltration of Th17 cells into tissue and sequesters them in the circulation, and specifically blocks migration of CD146 expressing Th17 cells and induces demargination of Th17 cells; the potential for our Phase 1b study of PRX003 to provide a rapid path to proof-of-biology; the timing of announcing interim and final results of that Phase 1b study; our contemplated Phase 2 study of PRX003 in psoriatic arthritis and the potential of PRX003 for the treatment of that disease; the strength of our cash position; and the timing of reporting results from our Phase 1b study of PRX003. These forward-looking statements are based on estimates, projections and assumptions that may prove not to be accurate, and actual results could differ materially from those anticipated due to known and unknown risks, uncertainties and other factors, including but not limited to the risks, uncertainties and other factors described in the "Risk Factors" sections of our Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 25, 2016 and our subsequent Quarterly Reports on Form 10-Q filed with the SEC. Prothena undertakes no obligation to update publicly any forward-looking statements contained in this presentation as a result of new information, future events or changes in Prothena's expectations.

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Dr. Gene Kinney
Chief Operating Officer

Introduction

Vision: Deliver novel protein immunotherapies to transform patients' lives

Deep scientific expertise in protein misfolding and cell adhesion, applied toward diseases that lack effective therapies

Executive team with a proven track record of R&D and Commercial innovation

Three mAb programs in clinical development, one in preclinical development, and a discovery engine generating new therapeutic candidates

Strong cash position of $447 million* at end of 2Q16

Establishing a fully-integrated organization

* Includes cash, cash equivalents and restricted cash

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R&D Pipeline for Lead Programs

Protein Immunotherapy

	PROGRAM	Preclinical	Phase 1	Phase 2	Phase 3	COMMERCIALIZATION RIGHTS
Protein Misfolding	**NEOD001** ***AL Amyloidosis*** *Fast Track Designation*	The VITAL Amyloidosis Study (Phase 3) PRONTO (Phase 2b)				prothena
Protein Misfolding	**PRX002** ***Parkinson's Disease***	Phase 1b MAD				prothena Roche
Protein Misfolding	**PRX004** ***ATTR Amyloidosis***	Preclinical				prothena
Cell Adhesion	**PRX003** ***Psoriasis***	Phase 1b MAD				prothena

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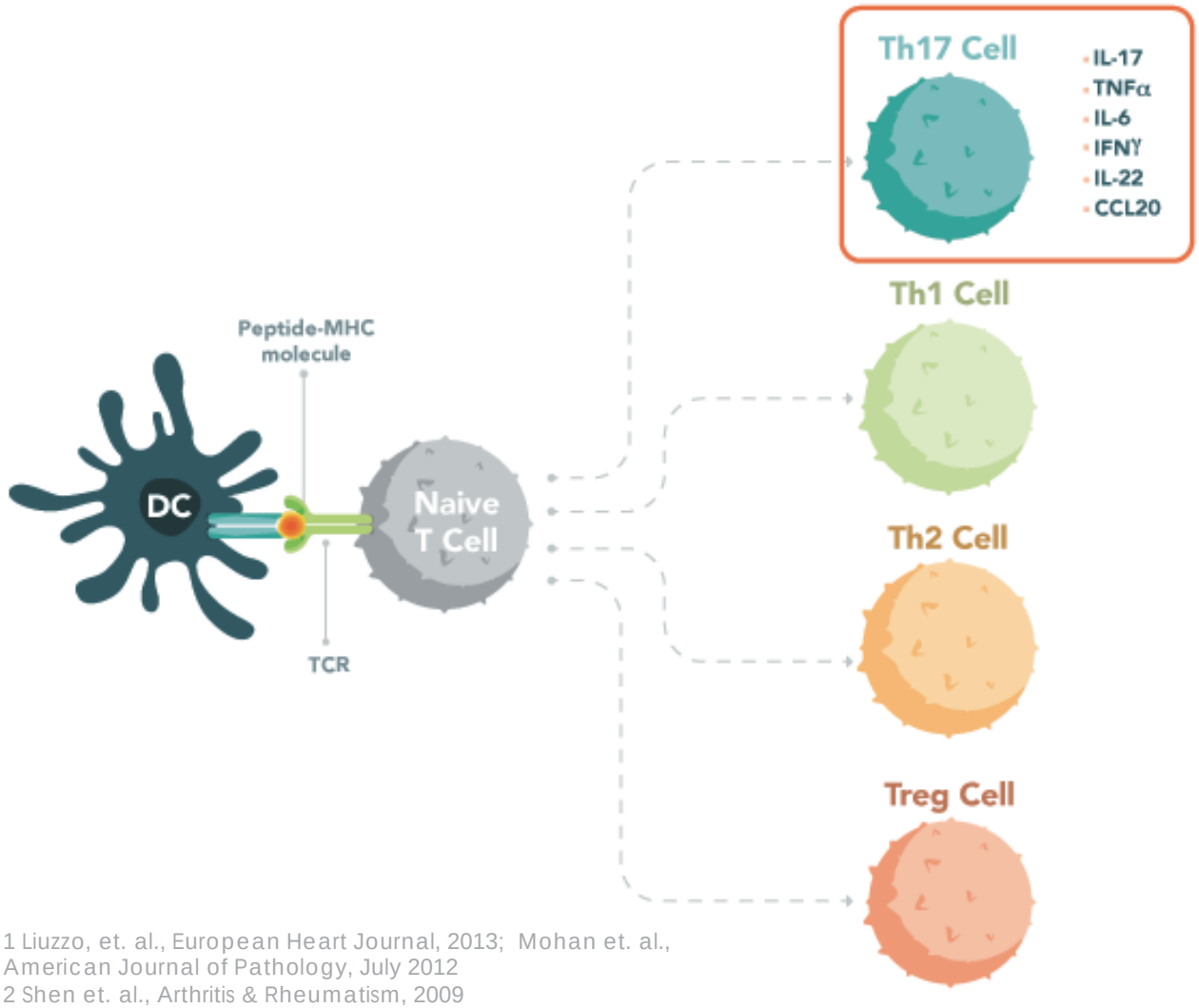
Dr. Ken Flanagan
Senior Scientist

Th17 and Inflammatory Disease

Pro-inflammatory Th17 Cells Produce Multiple Potentially Pathogenic Cytokines[1]



- A new approach for potentially treating Th17 mediated diseases where multiple cytokines contribute to pathology
- Th17 cells represent less than 5% of T cells[2]

1 Liuzzo, et. al., European Heart Journal, 2013; Mohan et. al., American Journal of Pathology, July 2012
2 Shen et. al., Arthritis & Rheumatism, 2009

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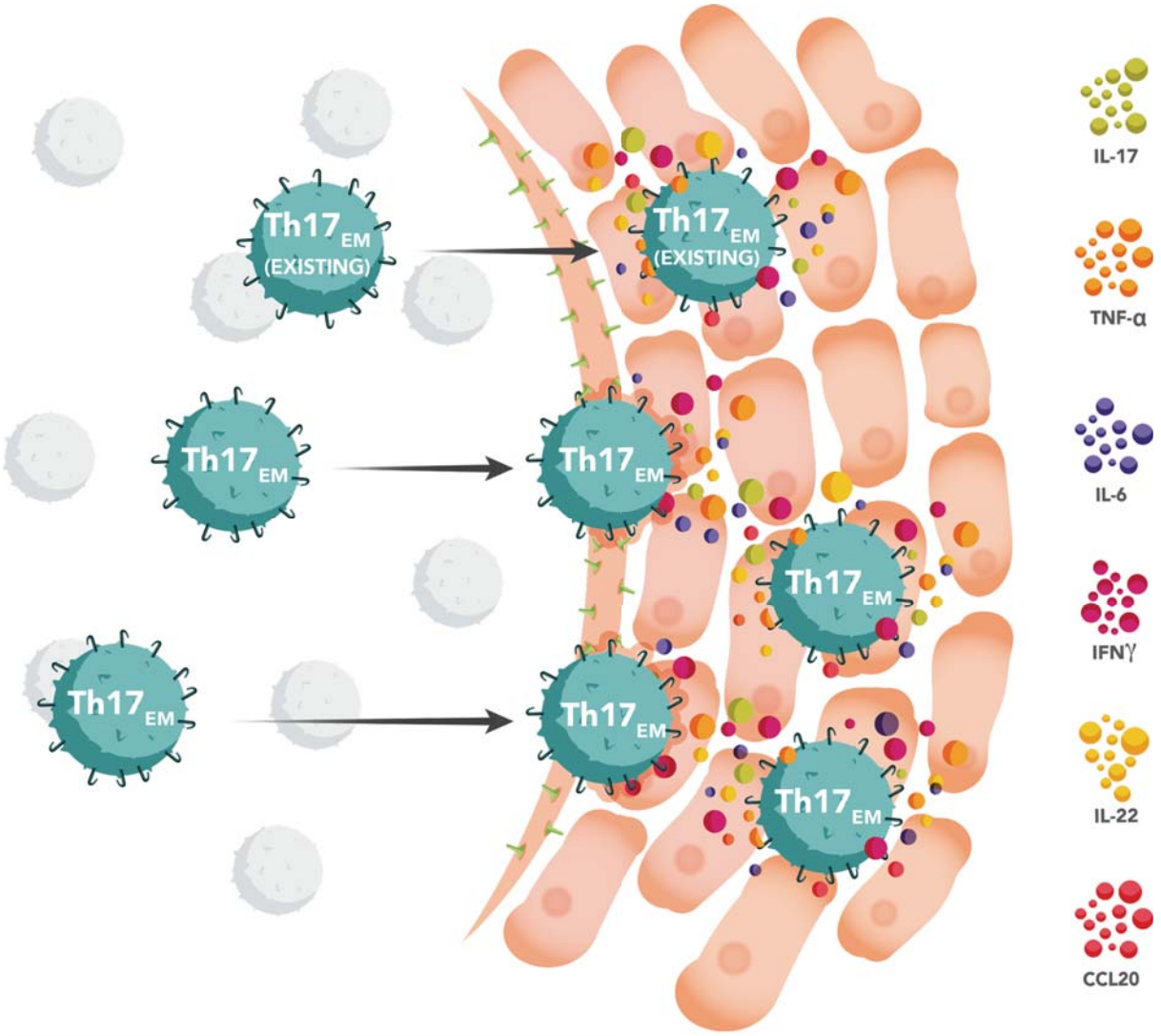
Th17 Cells Migrate Into Tissue, Releasing Multiple Pathogenic Cytokines



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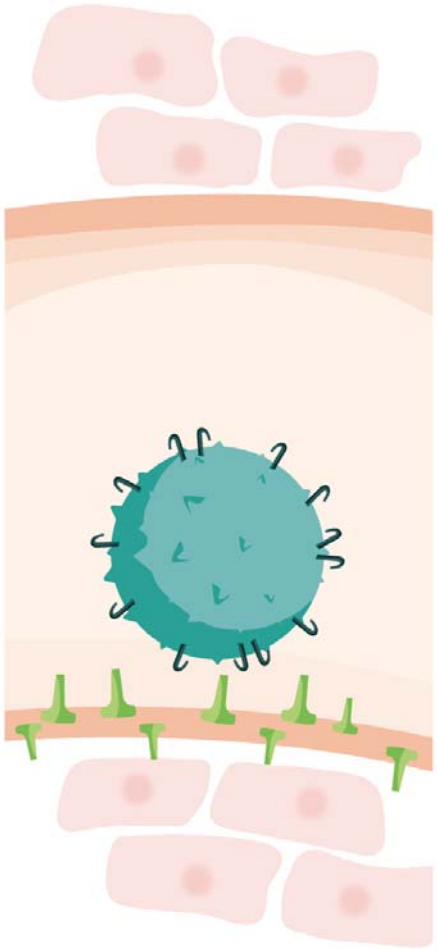
Laminin α4 is the Binding Partner for CD146 (MCAM)

CD146

Th17 T CELL

LAMININ ALPHA 4



- CD146 or Melanoma Cell Adhesion Molecule (MCAM), is expressed on the surface of Th17 cells

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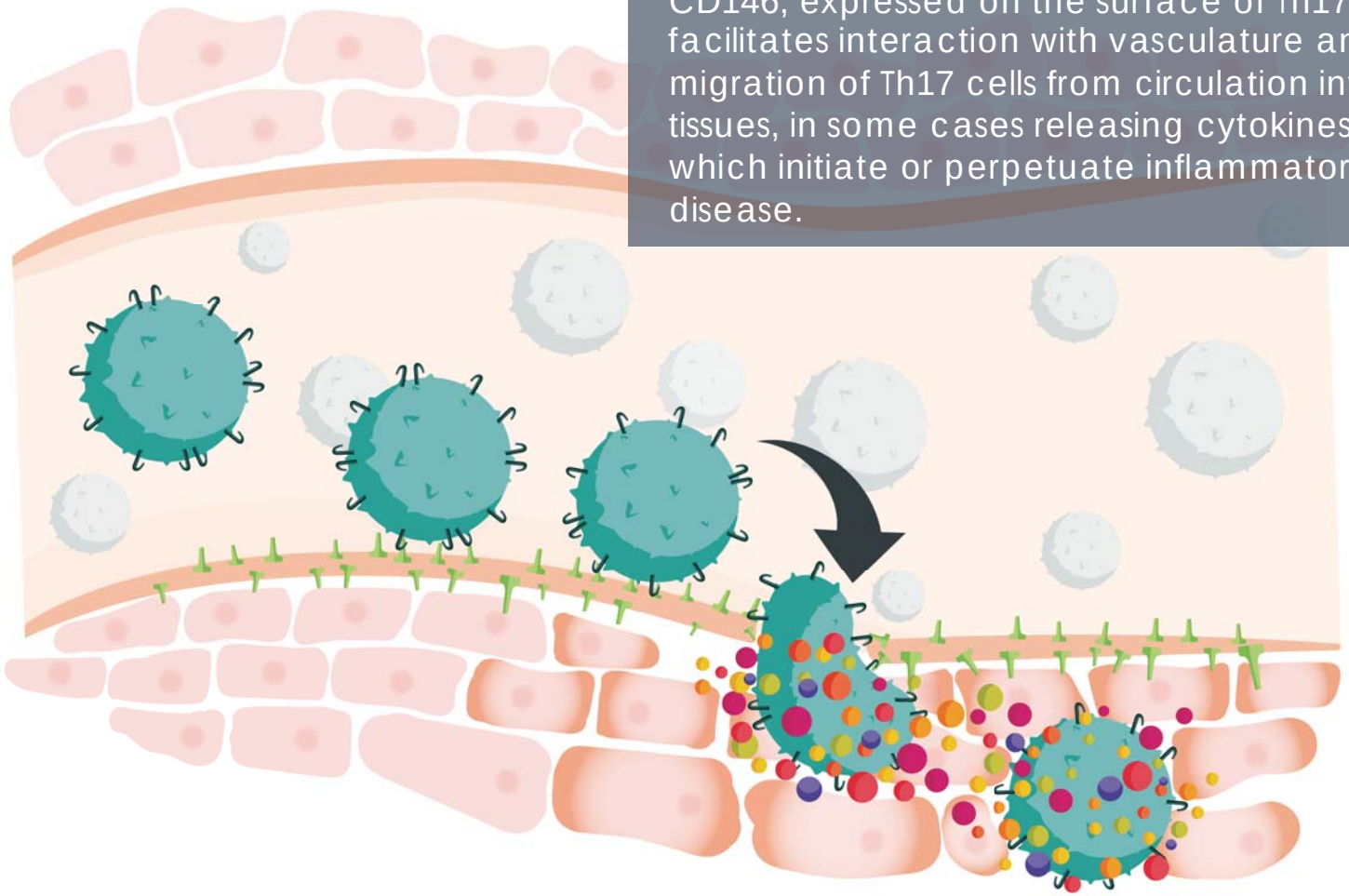
Th17 Driven Inflammation Process

CD146, expressed on the surface of Th17 cells, facilitates interaction with vasculature and the migration of Th17 cells from circulation into tissues, in some cases releasing cytokines which initiate or perpetuate inflammatory disease.



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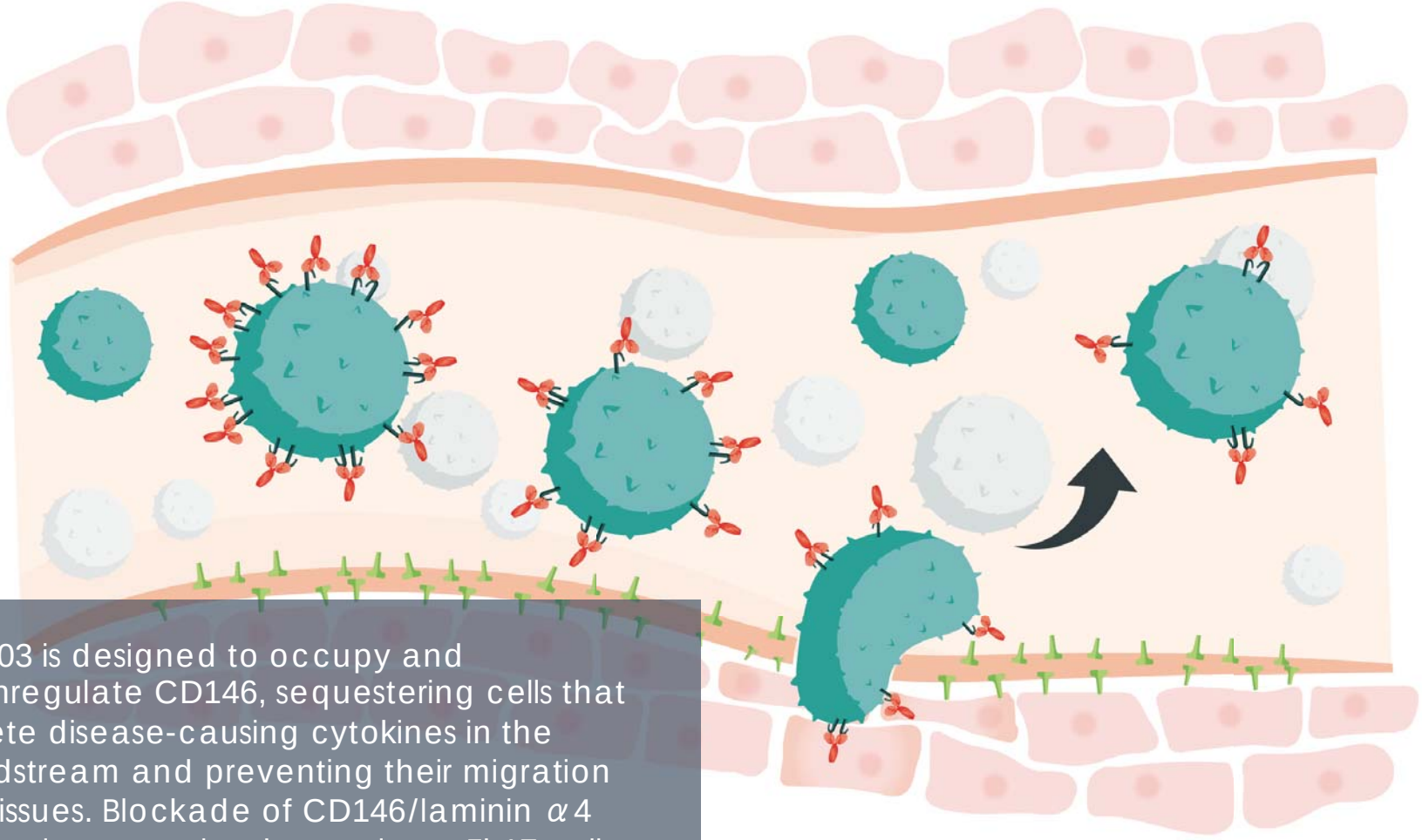
PRX003 Proposed Mechanism of Action



PRX003 is designed to occupy and downregulate CD146, sequestering cells that secrete disease-causing cytokines in the bloodstream and preventing their migration into tissues. Blockade of CD146/laminin $\alpha 4$ interaction may also demarginate Th17 cells.

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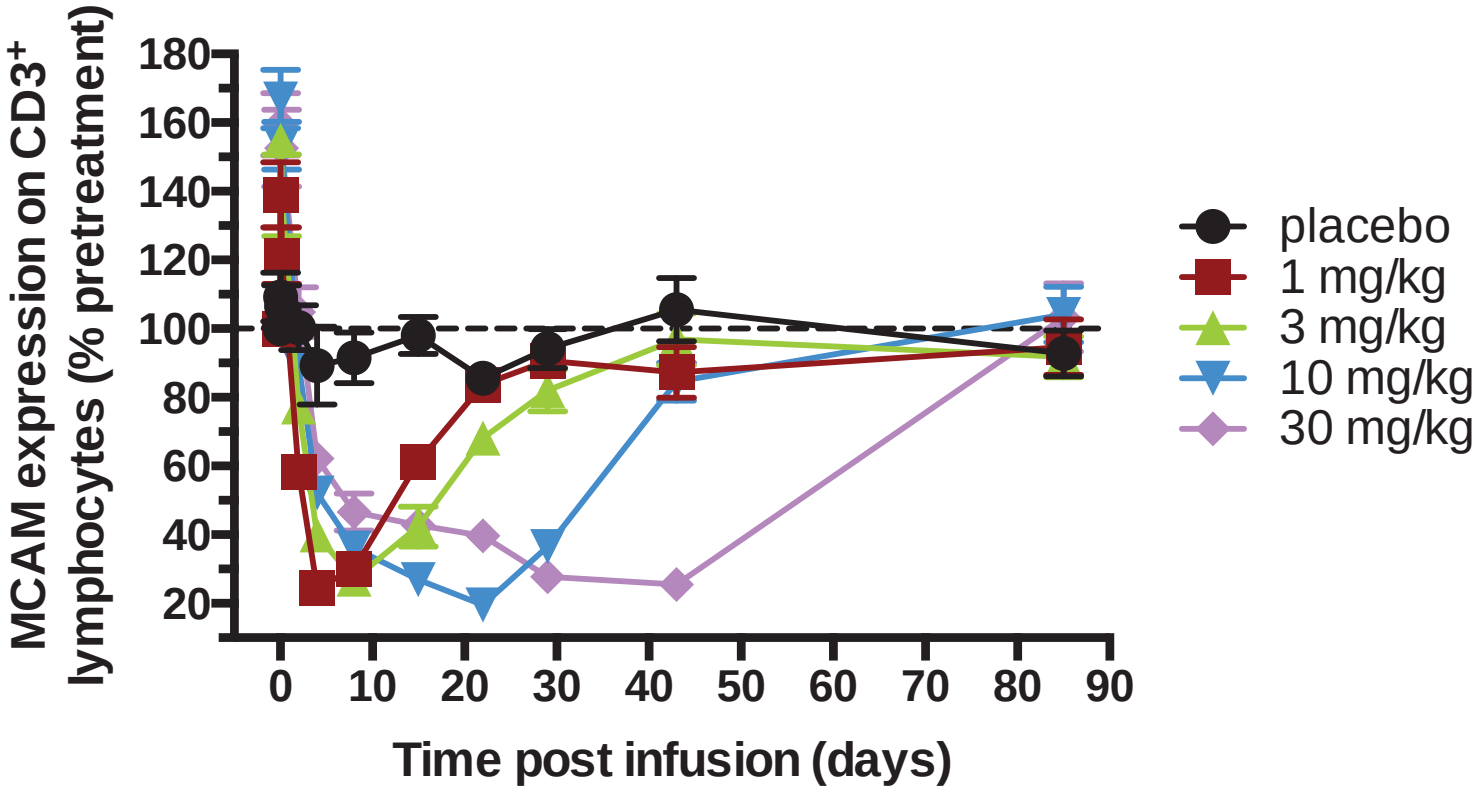
PRX003 Phase 1 SAD: Pharmacodynamic Activity



- **Evidence of rapid down-regulation of CD146 (MCAM) expression**
- **Dose-dependent duration of effect**
- **>95% neutralization achieved when occupancy was assessed with down-regulation**

Data presented in oral session at EULAR, June 10, 2016

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Dr. Gene Kinney
Chief Operating Officer

Planned PRX003 Phase 2
Development Strategy

Ongoing PRX003 Phase 1b MAD Proof-of-biology Study in Psoriasis

- Psoriasis is mediated by Th17 pathology and is strongly driven by IL-17 cytokine pathology
- Visually defined nature of psoriasis provides rapid path to proof-of-biology for PRX003
- Well-defined development pathway with PASI endpoints as clinical benchmarks
- However, a high bar to differentiate from existing therapies

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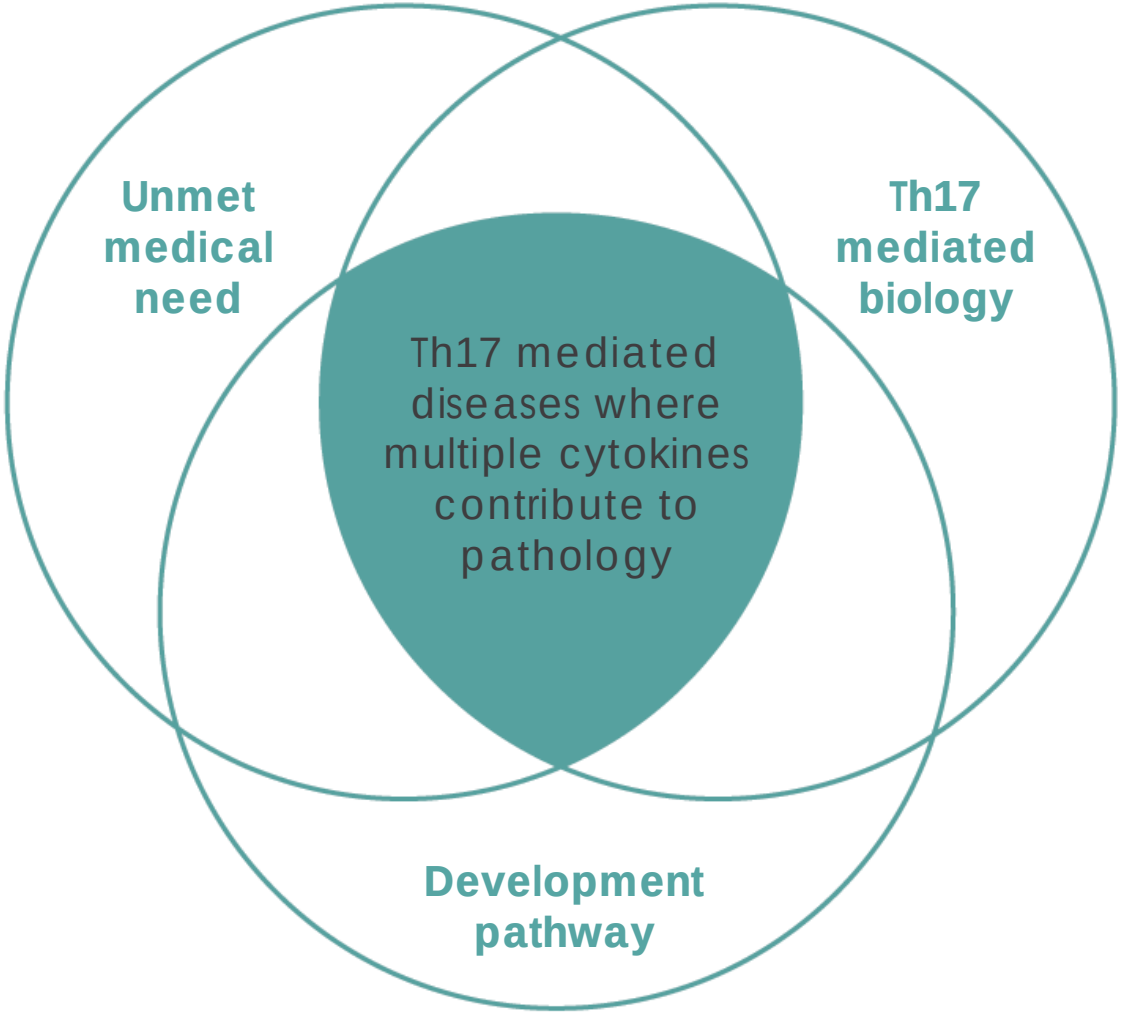
Beyond Psoriasis:
Assessing PRX003 Indication Options



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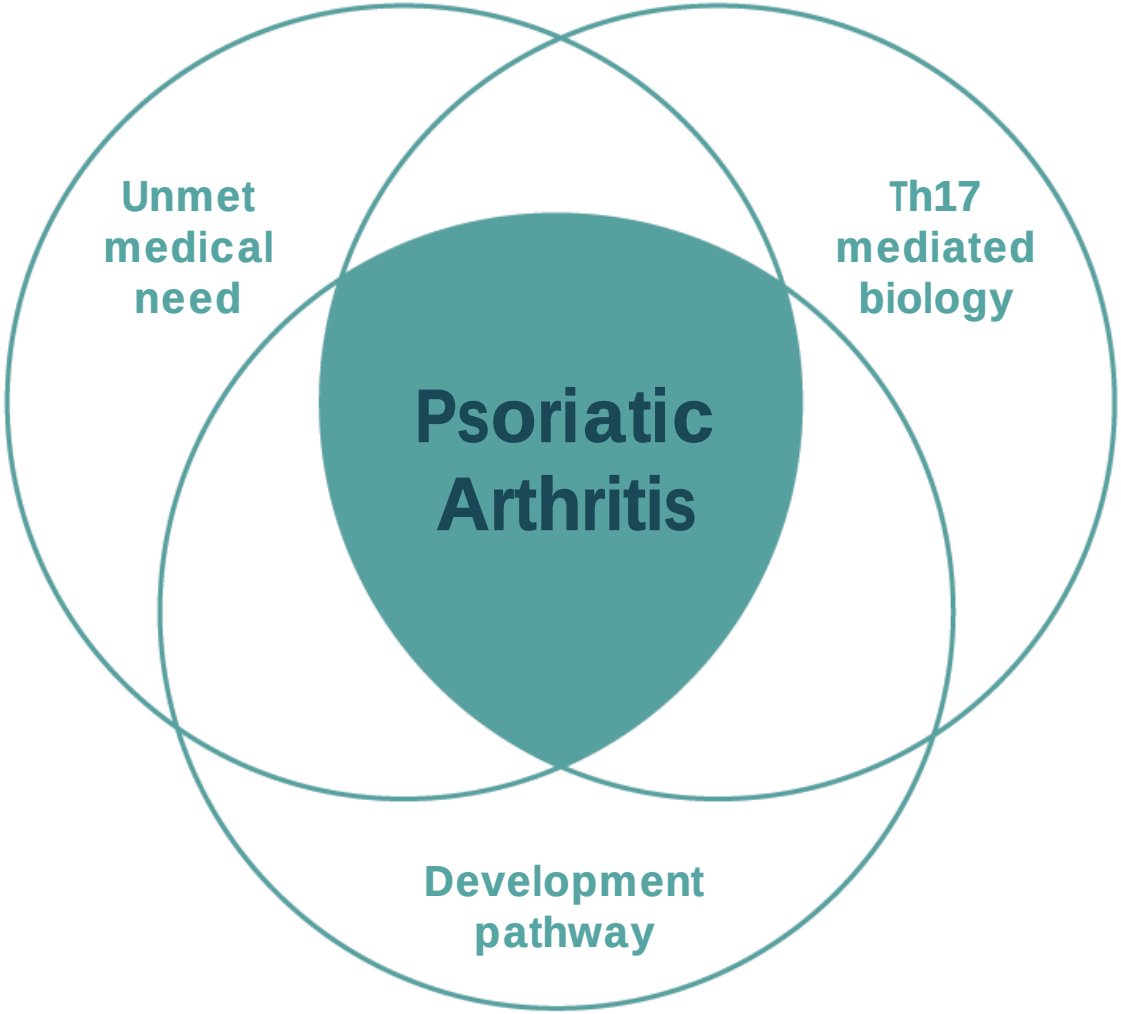
Looking Ahead:
Planned Phase 2 in **Psoriatic Arthritis**



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Psoriatic Arthritis, an Inflammatory Form of Arthritis with Unmet Medical Need

- Psoriatic arthritis (PsA) is an inflammatory autoimmune disorder characterized by pain, stiffness and inflammation in the joints and surrounding ligaments and tendons
  - Patients are at risk of comorbidities and severe joint damage
- Up to 42% of patients with psoriasis will eventually develop psoriatic arthritis 5 to 12 years after their initial diagnosis[1]
- ~1 million patients with PsA in US, EU5, and Japan[2]
- Approximately 45% of patients with PsA are dissatisfied with their current treatment[3]
  - Not reaching sufficient level of control of symptoms
  - Unresponsive or intolerant to therapy

1 National Psoriasis Foundation, 2015; AAD, 2015; Gottlieb et al., 2008
2 Datamonitor, 2013 report
3 Armstrong AW, et al. Findings from the National Psoriasis Fdn surveys, 2003-2011. Oct. 2013

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Current Approaches in Psoriasis and Psoriatic Arthritis

- Implications in Psoriatic Arthritis:
  - Suggests multiple cytokines contribute to pathology
  - Opportunity for improved efficacy

	Psoriasis PASI75	Psoriatic Arthritis ACR20	Psoriatic Arthritis ACR50
Anti TNF	46-78%[1]	50-57%[1]	37-39%[1]
Anti IL-17	75-90%[2]	54%[3]	35%[3]

1 Full prescribing information for etanercept and adalimumab
2 Full prescribing information for secukinumab and ixekizumab
3 Full prescribing information for secukinumab

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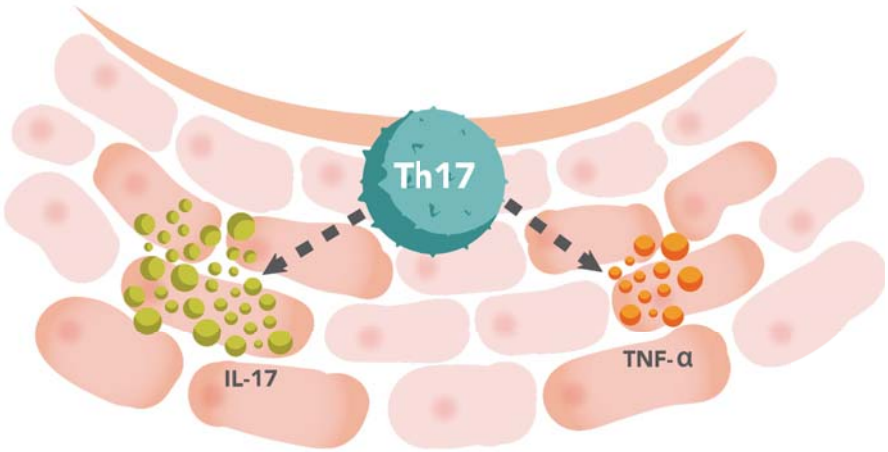
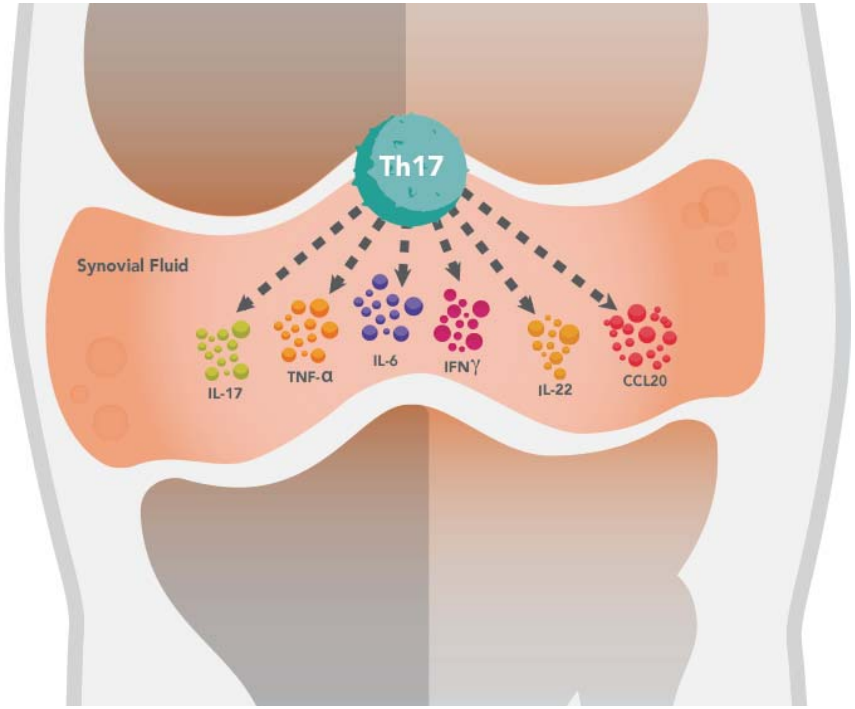
Th17 Mediated Biology: Cytokines May Play Different Roles in Skin vs. Joint Pathology





Adapted from Lubberts, Nature, July 2015, Volume 11

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Planning for PRX003 Phase 2 Development

- Phase 1b MAD: Double blind, placebo controlled, multiple ascending dose study in 56 patients with psoriasis is ongoing (ClinicalTrials.gov NCT02630901)
  - Interim expected by mid-2017
  - Full results expected by 2H17
- If results meet certain pre-specified criteria, we expect to begin preparation for a Phase 2 study in psoriatic arthritis

Summary

- Pro-inflammatory Th17 cells release multiple cytokines that contribute to inflammatory disease pathology
- PRX003 was designed to target CD146, a cell adhesion molecule expressed on Th17 cells, and reverse the disease process by acting upstream of the release of multiple pathogenic cytokines
- Should the PRX003 Phase 1b MAD study meet certain pre-specified criteria, we plan to advance PRX003 into Phase 2 development for psoriatic arthritis:
  - PsA is a Th17 mediated disease where multiple cytokines contribute to pathology
  - There is an unmet medical need for therapies with improved efficacy in psoriatic arthritis

Q&A