

Application of Systems Biology for Pharmaceutical Drug Development: Improving “Translational Research”

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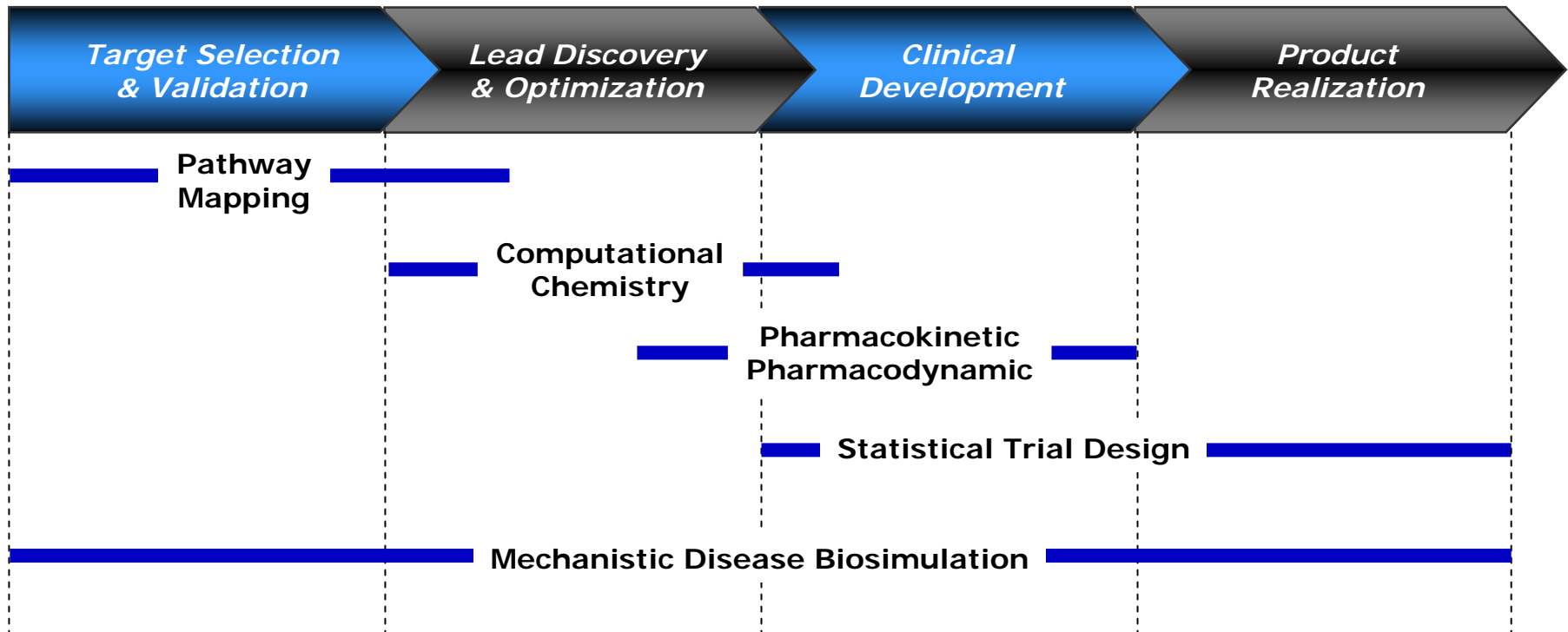


Agenda

- Computational models in drug development
- Improving translational research in Type 1 Diabetes (T1D)
 - Introduction and Methodology
 - Results: key pathways mediating efficacy of anti-CD3 mAbs



Alternate Forms of Computational Modeling Inform Different Steps in the R&D Process



What is Mechanistic Disease Modeling?

What are the Challenges?

- Explicit mathematical representation of a clinically relevant biologic process and the underlying mechanisms believed to control that process

Challenge	Solution
Biologic processes are complex, networked, and dynamic	Focus on key clinical outcome(s) and core underlying mechanisms
Life scientists and engineers do not traditionally speak the same language	Develop organizations and tools that facilitate communication and insight
Patient responses to therapy vary	Change model parameters to reflect variability and assess the clinical implications
Knowledge gaps exist in our understanding of biologic processes	Use know clinical and lab data to guide simulations of alternative hypotheses to identify experiments that fill the gap

Agenda

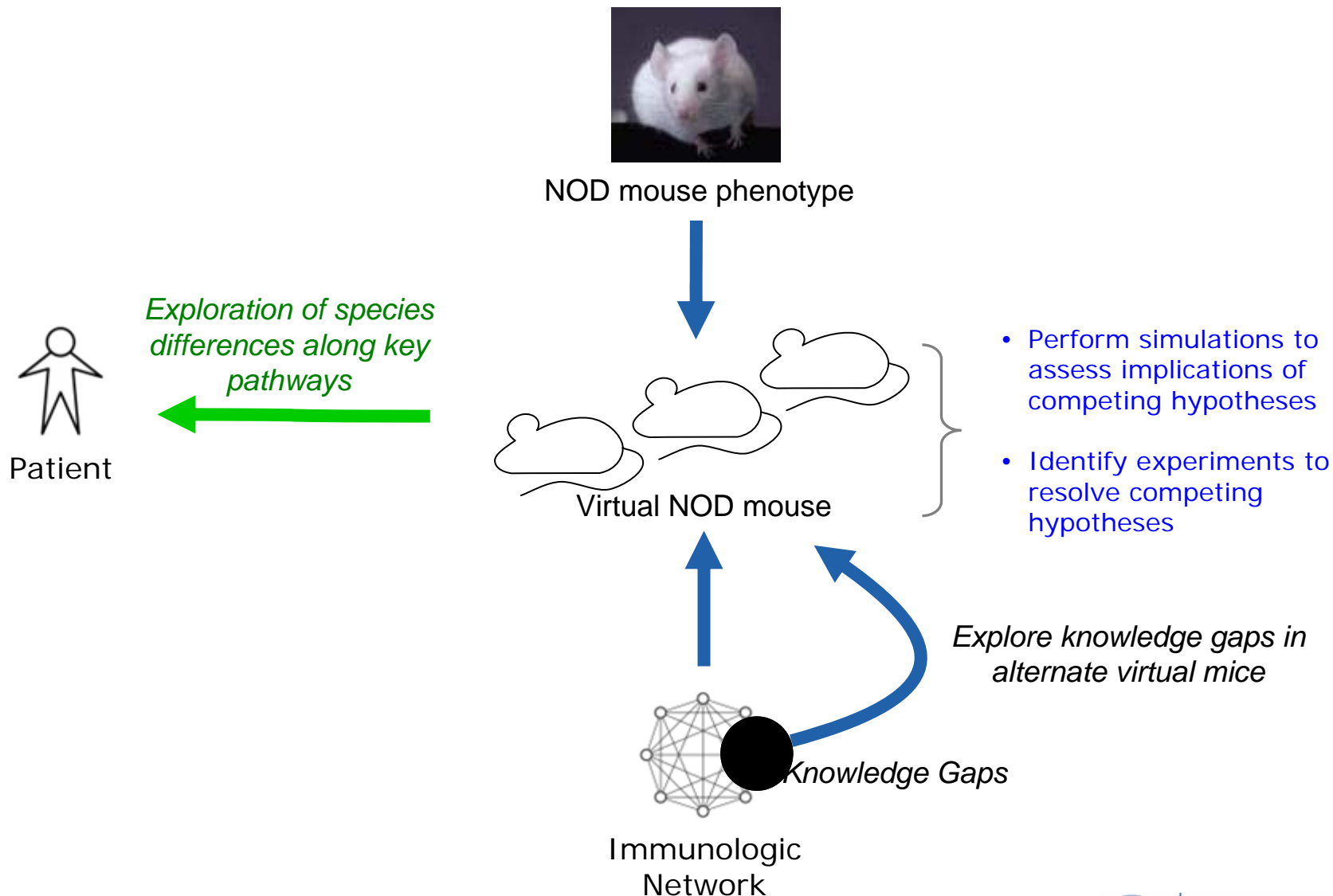
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There is an Unmet Need for Treatment of Type 1 Diabetes

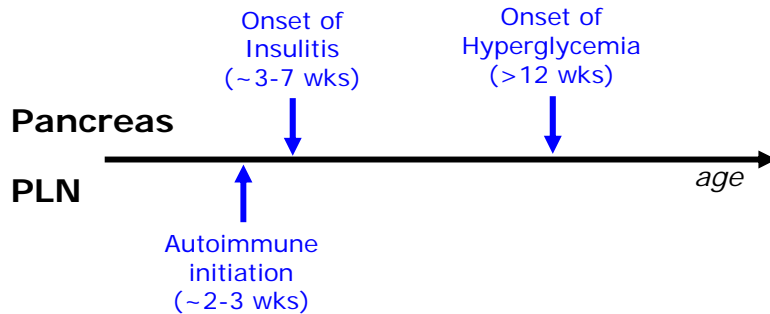
- **Problem:** 1 million T1D patients in US alone; no cure
 - Therapies which show promise in preclinical animal models of T1D have not demonstrated sustained clinical efficacy
- **Research Goals:**
 - Improve understanding of disease pathogenesis through mechanistic mathematical modeling, starting in the non-obese diabetic (NOD) mouse
 - Improve the rationale for advancing potential therapeutic agents to human clinical trials
 - Over 200 different agents can protect NOD mice from developing diabetes; identifying key mechanisms of action in NOD mice is the first step to assessing their applicability to human patients

Virtual NOD Mice Provide a Research Tool for Investigation of Preclinical Efficacy

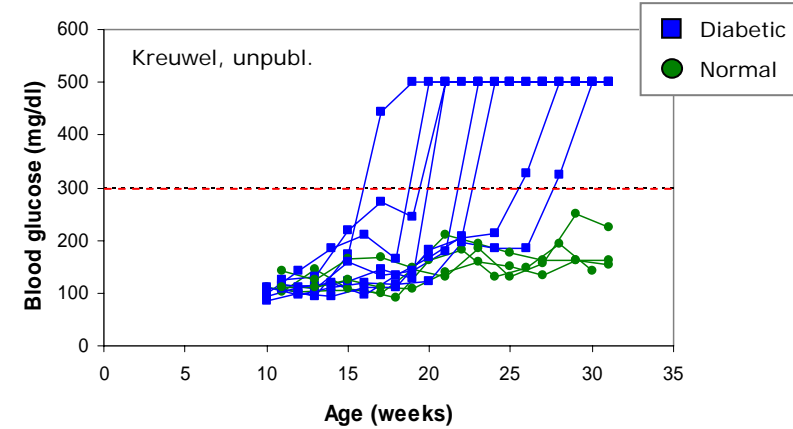


Key Characteristics of the Pathophysiology of Type 1 Diabetes in the NOD Mouse

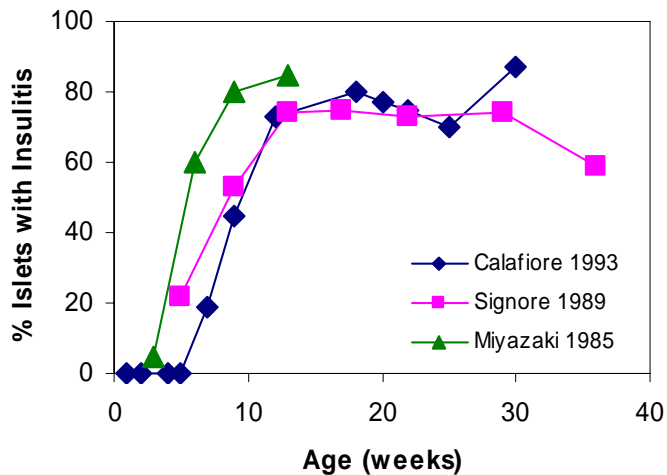
The pancreas and pancreatic lymph node (PLN) are the sites of key events in the pathogenesis of type 1 diabetes.



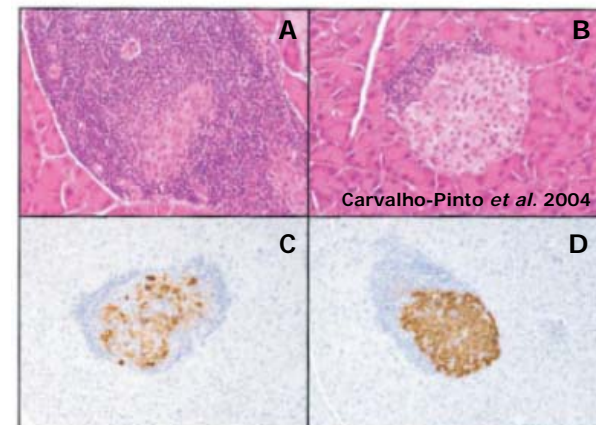
Diabetes onset (defined by loss of blood glucose control) is a rapid and heterogeneous event.



Islets become progressively infiltrated by leukocytes.

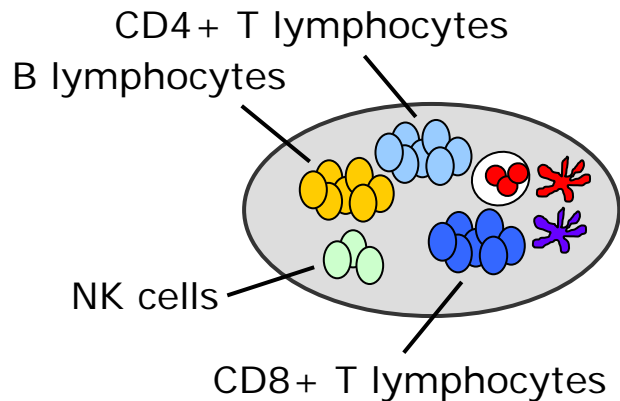


There is significant heterogeneity in islet infiltration at all stages of disease.

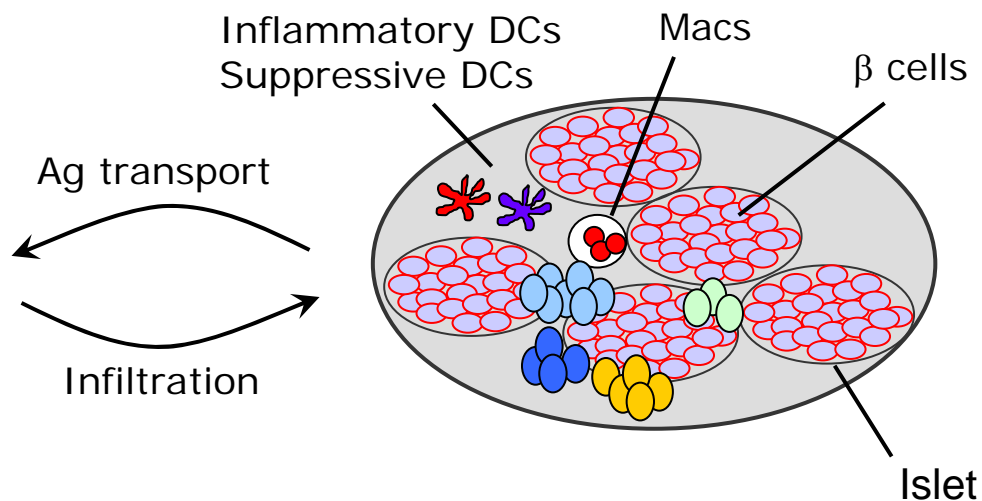


Multiple Tissues and Cell Types Were Modeled to Reproduce Pathophysiology of NOD Mouse

Pancreatic Lymph Nodes

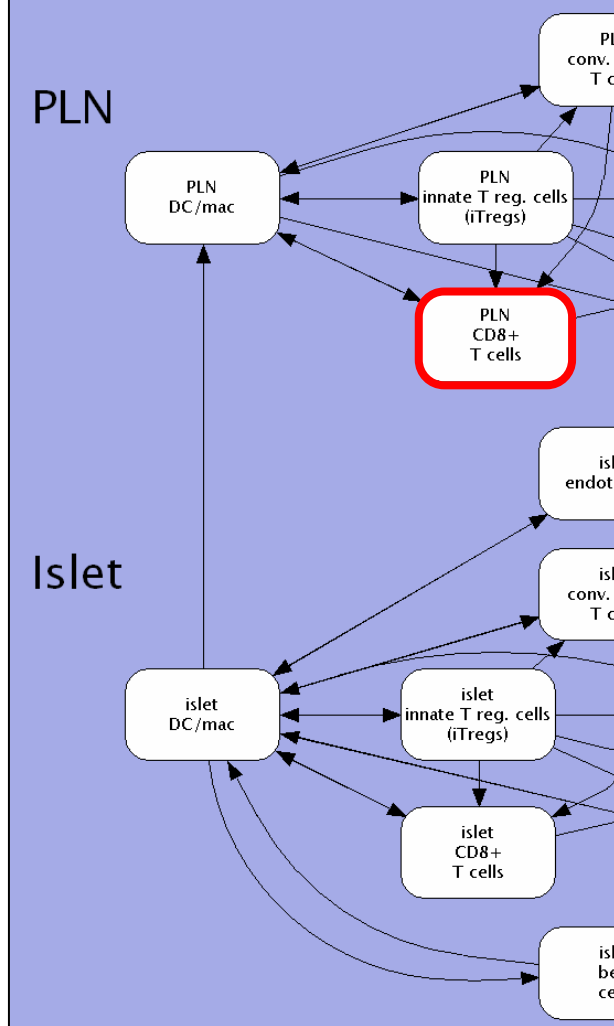


Pancreas

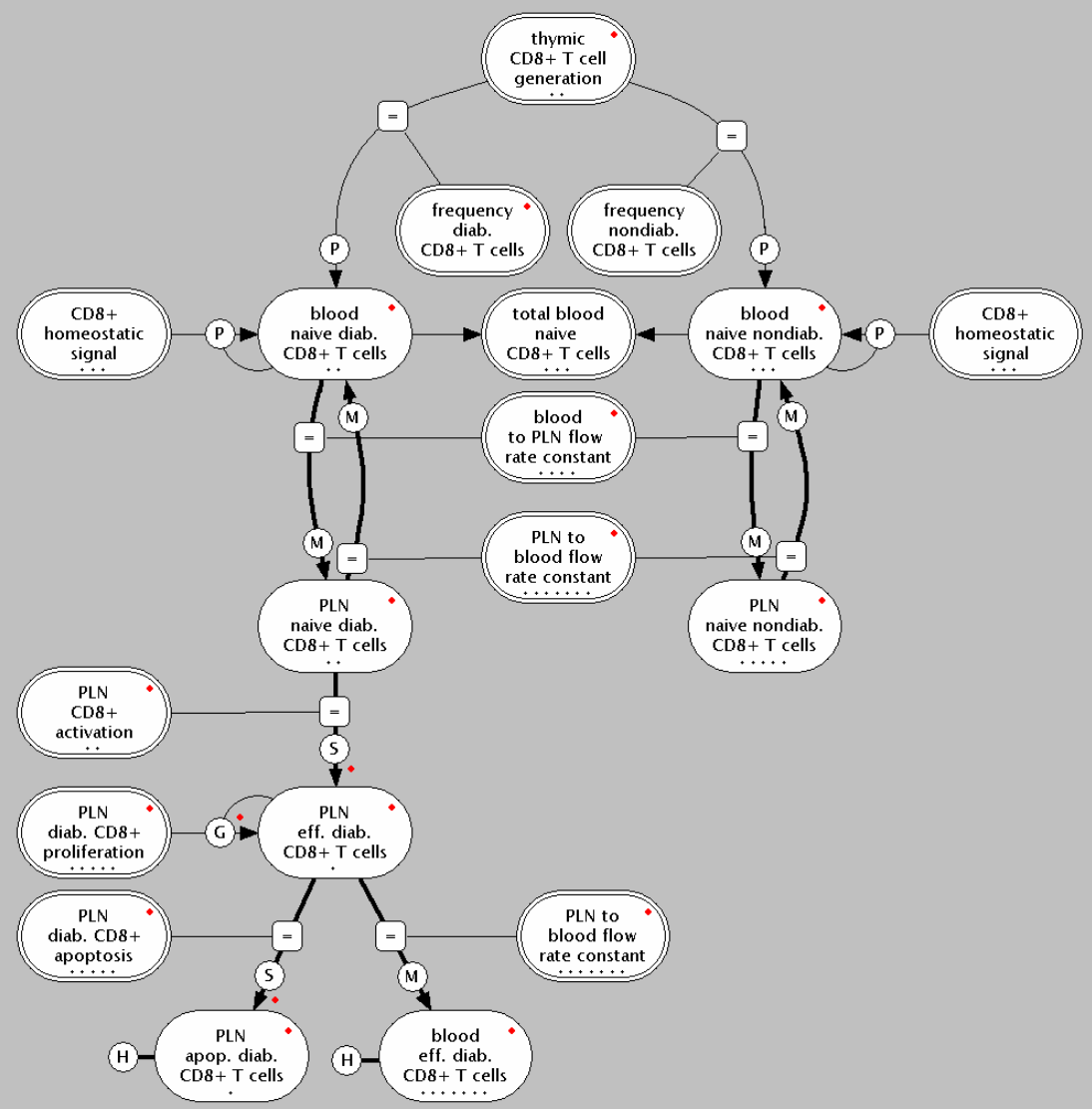


Mechanistic Model was Developed to Improve Translational Approach

Summary Diagram

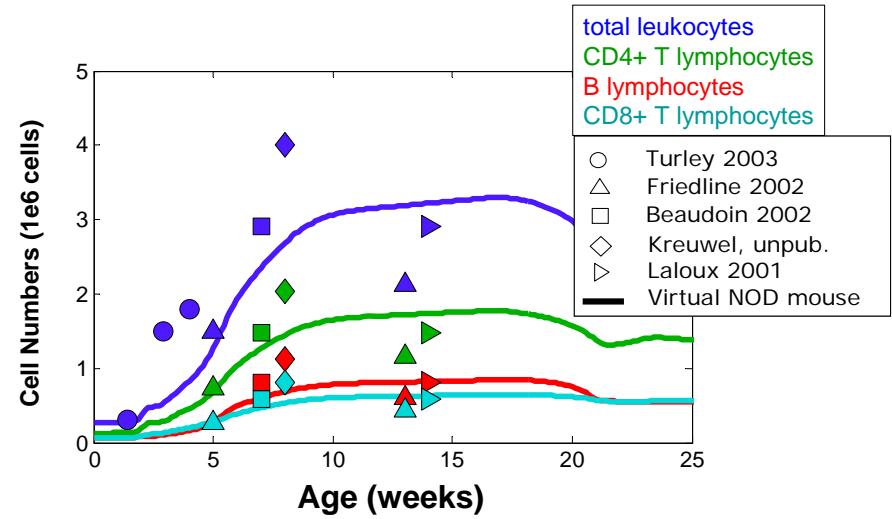


PLN: CD8+ T cell Recruitment & Life Cycle



Virtual NOD Mouse Reproduces Quantitative Dynamics of Type 1 Diabetes Onset and Pathogenesis

(a) Leukocytes in PLN

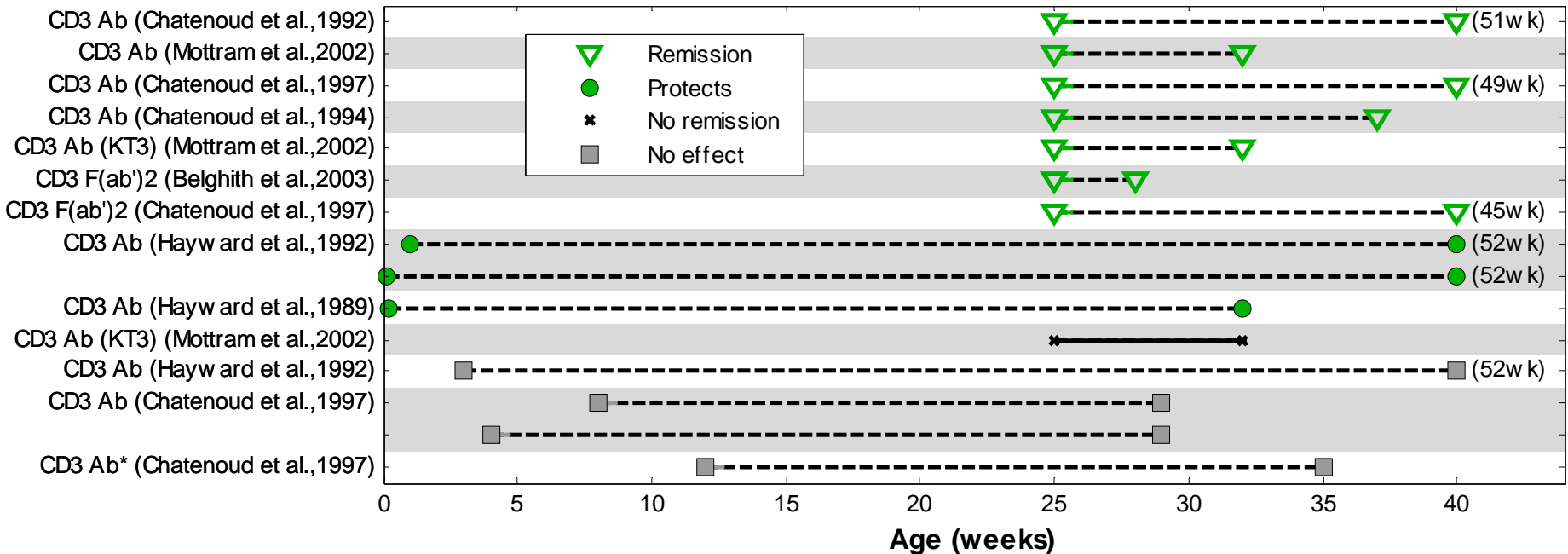


Model Calibration and Validation Ensure System/Subsystem Behaviors Reproduce Known Data

Untreated Phenotype & Underlying Biology	Calibration Therapies	Validation Therapies
Normoglycemia until diabetes onset	anti-CD8 Ab	anti-CD40L Ab
Diabetes onset between 12-35 wks	anti-CD3 Ab	TGF-beta
Rapid onset of hyperglycemia	IL-10	Exendin-4
Age-dependent increase in β cell mass	anti-B7-1 + anti-B7-2 Abs	Rapamycin
Age-dependent thymic output	LipCl ₂ MDP	anti-IL-2
PLN expansion dynamics	No diab. CD4+ T cells	
Islet infiltration dynamics	No diab. CD8+ T cells	
Multiple modes of β cell death	No diab. iTregs	
	No diab. B cells	
	No maternal autoAb	
	No endog. autoAb	

Anti-CD3 Antibody Efficacy in NOD Mice Differs with Treatment Start Times

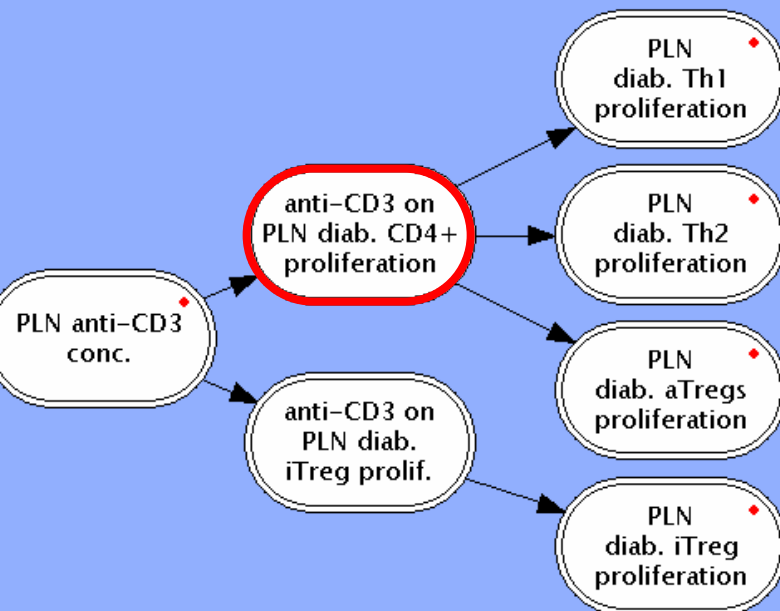
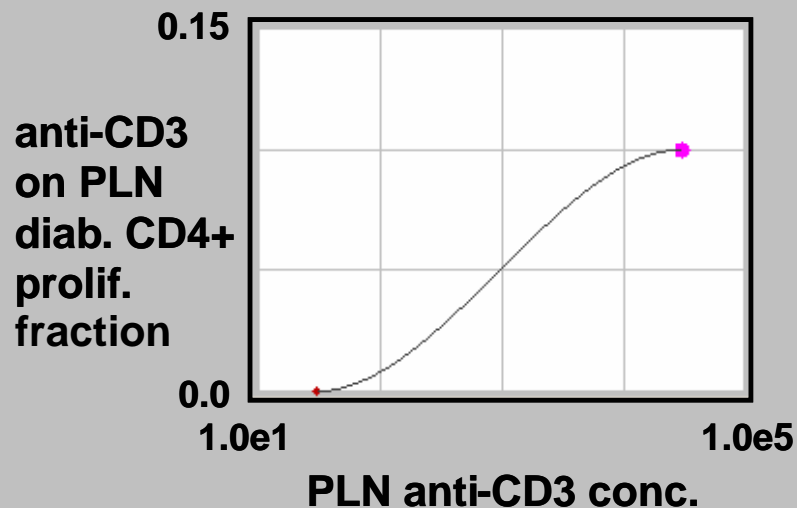
- Early and later protocols yield protection and remission, respectively
- Intermediate protocols have no effect on disease outcome



Known Effects of Anti-CD3 Ab Treatment Implemented in the Virtual NOD Mouse

- Direct effects of anti-CD3 Ab on activation, proliferation, and apoptosis of T cell subsets in blood, PLN, and islets
- Differential effects for conventional T cells vs. iTregs (innate regulatory CD4+ T cells) and naïve vs. activated T cells
- Pharmacokinetics for routes of administration (i.p. or i.v.) and reported functional antibody half life

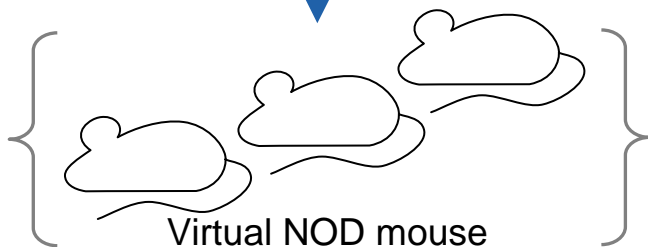
Effect of anti-CD3 Ab on the Proliferation of CD4+ T cells in the Pancreatic Lymph Node



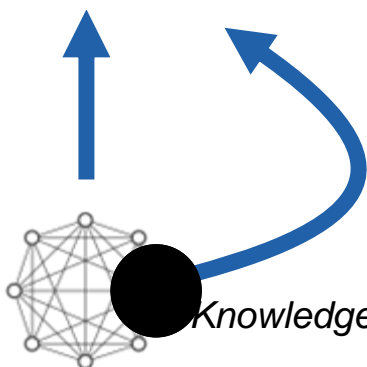
Knowledge Gaps in the Function of iTregs Were Represented in Three Virtual NOD Mice



NOD mouse phenotype



Virtual NOD mouse



Immunologic
Network

- iTregs are known to be important for the efficacy of anti-CD3 Ab therapy.
- Knowledge gaps in the functions of iTregs during pathogenesis were represented in three virtual NOD mice.
- The impact on the efficacy of anti-CD3 Ab therapy was examined.

	iTreg Functional Pathways
Virtual NOD 1	<i>iTreg colocalization with T cells in PLN</i>
Virtual NOD 2	<i>iTreg colocalization with activated T cells in PLN</i>
Virtual NOD 3	<i>iTreg colocalization with T cells in PLN 30% increase in iTreg activation</i>

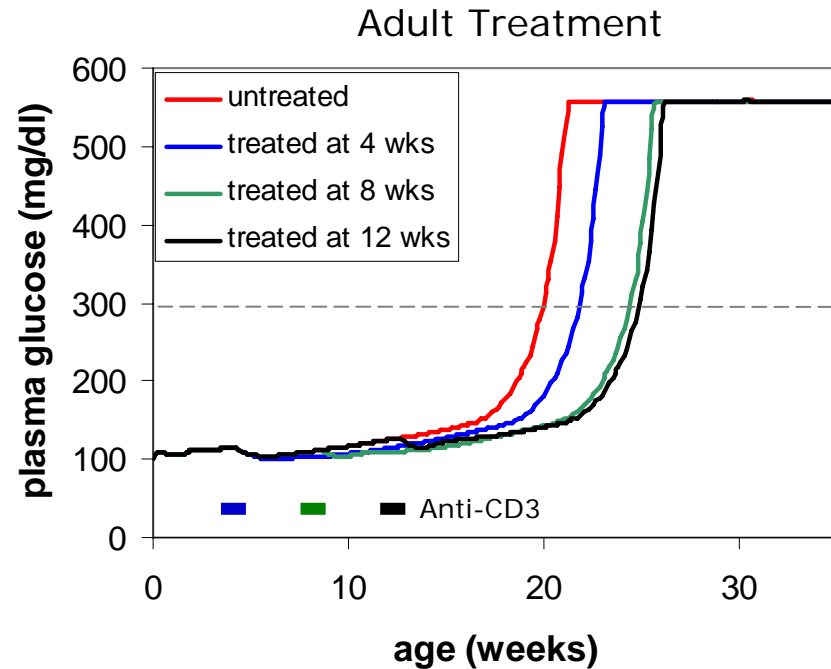
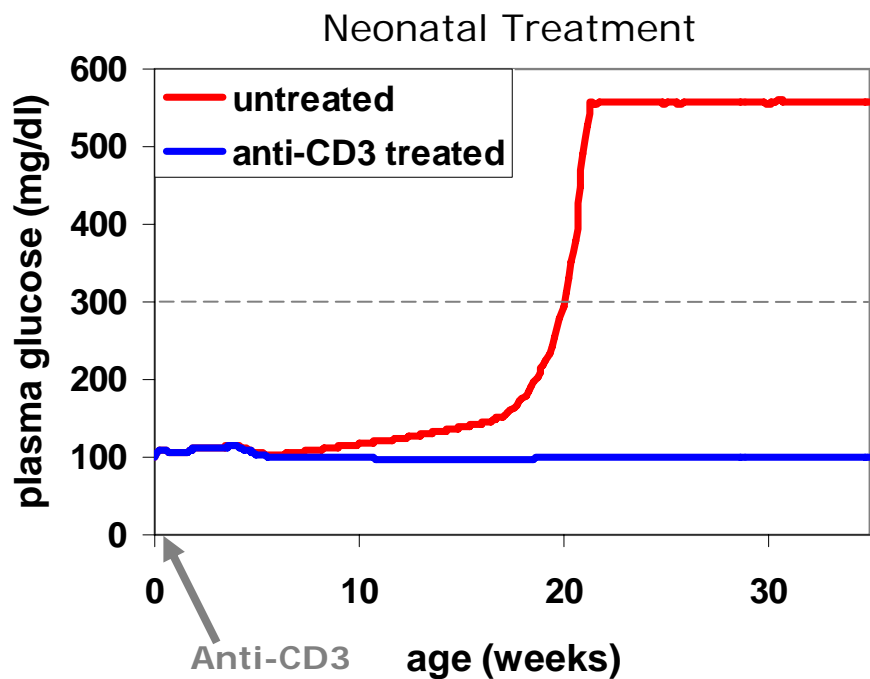
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Published Anti-CD3 Ab Treatment Protocols for NOD Mice Were Tested in the Virtual Mice

- Treatment of prediabetic mice:
 - Disease progression in all three virtual NOD mice matched that reported for NOD mice.

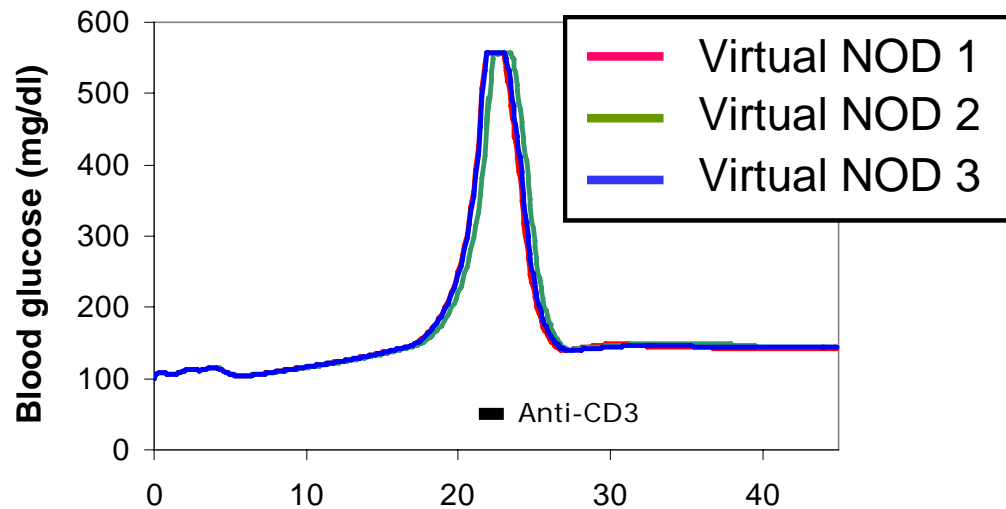


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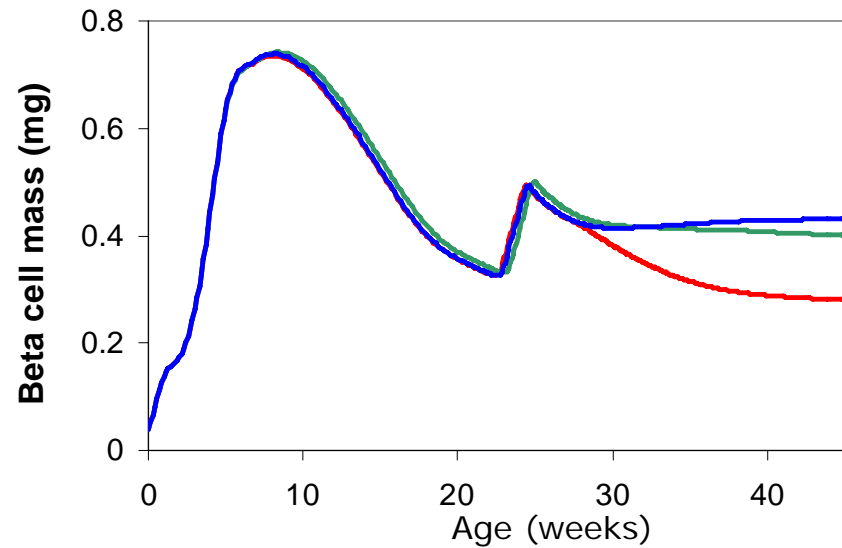
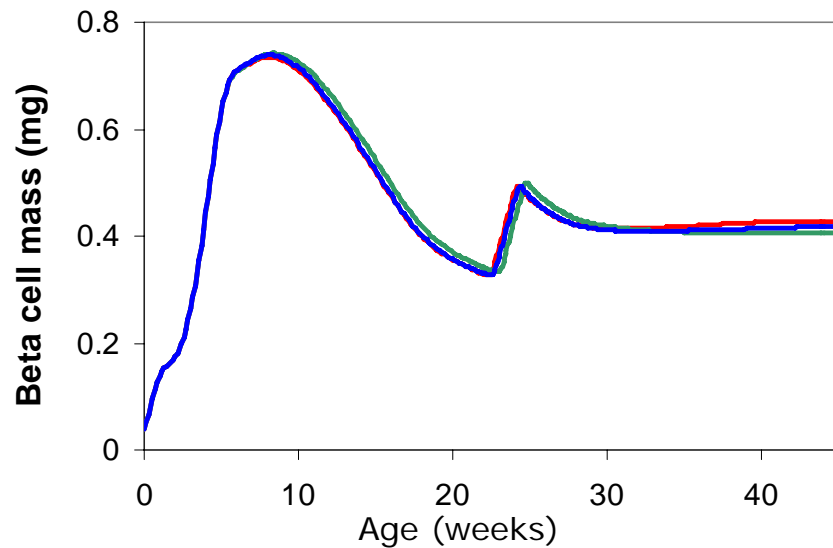
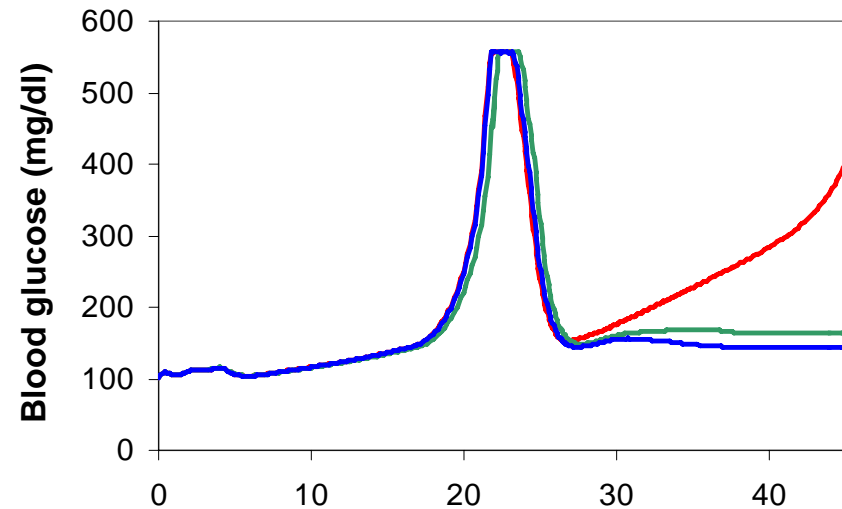
- Treatment of prediabetic mice:
 - Disease progression in all three virtual NOD mice matched that reported for NOD mice
- Treatment of diabetic mice:
 - Novel insights into mechanism of remission were gained beyond the direct T cell effects previously reported
 - Rapid β cell recovery (*e.g.*, 1.25-fold normal proliferation level) enabled by clearance of inflammation was required for remission in all virtual NOD mice
 - Virtual mice with suppressed iTreg activity required an altered pancreatic infiltrate (*e.g.*, predominately suppressive antigen presenting cells) to induce remission

Sustained Remission Depends on Balance of iTreg Activity and Infiltrate Condition

With Altered Pancreatic Infiltrate



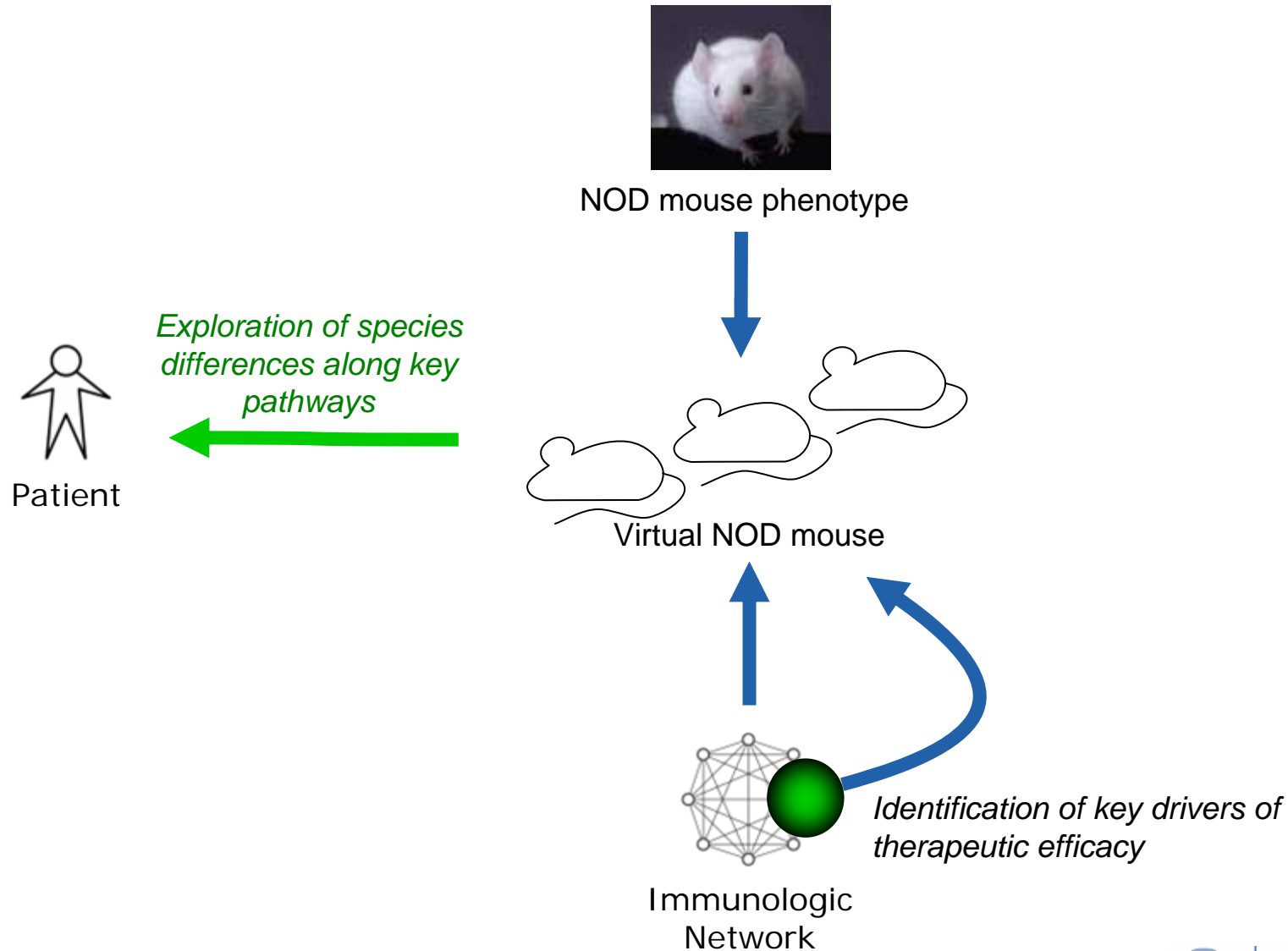
Without Altered Pancreatic Infiltrate



Novel Insights From the Virtual NOD Mouse Suggest Experiments to Confirm Disease Mechanisms

- Experimental confirmation:
 - Characterization of enhanced β -cell health (*e.g.*, increased proliferation) following anti-CD3 treatment could help verify that this mechanism is critical for remission
 - Laboratory assessment of iTreg activity and its impact on infiltrate could elucidate which mechanism(s) identified here mediate suppressed infiltration and remission
- A full understanding of the mechanism of anti-CD3 Ab-mediated remission in NOD mice will help to validate critical target pathways for new clinical therapies.

Understanding Species Differences in Key Disease Pathways Will Allow Better Translation of Efficacy Predictions From Mouse to Man



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