Rheumatoid Arthritis Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES	GADINA, MASSIMO	Translational Immunology research: a support for clinical immunological research	**Research Question:**
			• The abstract describes various research projects undertaken by the TIS, but doesn't focus on a single specific question.
			Stage:
			• The research involves a mix of in vitro (experiments conducted in the lab using cells or molecules) and in vivo (experiments conducted with live animals) studies.
			Methods:
			• The TIS utilizes various methods including:
			  ○ Measuring cytokine levels to assess immune function.
			  ○ Genetic analysis to identify polymorphisms associated with autoimmune diseases.
			  ○ Deep immunophenotyping to analyze immune cell composition.
			Drug Development:
			• The TIS is involved in characterizing biomarkers for autoimmune diseases and evaluating the effects of existing drugs like tocilizumab and JAK inhibitors on immune cells.
			Focus Areas:
			• The abstract highlights several areas of research including:
			  ○ VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome.
			  ○ Relapsing polychondritis (RP).
			  ○ Giant cell arteritis.
			  ○ COVID-19 and its effects on patients with systemic autoimmunity.
			  ○ Systemic Juvenile Idiopathic Arthritis (sJIA).
			  ○ SHARPIN deficiency and its associated symptoms.
			  ○ Innate Lymphoid Cells (ILCs) and their role in autoimmune diseases.
			Collaborations:

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			• The TIS collaborates with various internal and external researchers on different projects. **Overall, the TIS is involved in diverse research efforts to improve our understanding of autoimmune diseases and develop new therapeutic strategies.**
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	HIRSCH, RAPHAEL	Role of FSTL-1 in Arthritis	**Research Question:** • Does FSTL-1 play a central role in arthritis, and can its neutralization be a novel therapeutic approach? **Stage:** • This research involves a mix of in vitro (experiments conducted in the lab using cells) and in vivo (experiments conducted with live animals) studies. **Methods:** • DNA microarray gene expression analysis in mice with collagen-induced arthritis (CIA) • Overexpression and neutralization of FSTL-1 in mice • Analysis of FSTL-1 expression in human rheumatoid arthritis tissues • Studying how FSTL-1 induces Th17 cells (immune cells involved in autoimmunity) **Drug Development:** • This research focuses on investigating FSTL-1 as a potential therapeutic target for arthritis by neutralizing it with antibodies. **Findings:** • FSTL-1 is highly overexpressed in arthritic joints of mice and humans. • Overexpressing FSTL-1 worsens arthritis in mice, while neutralization improves it. • FSTL-1 can induce the development of Th17 cells, which are important for autoimmune diseases like arthritis. **Future Directions:**

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			• Understand how FSTL-1 promotes inflammation and Th17 cell development. • Identify the factors regulating FSTL-1 expression. • Develop and test FSTL-1 neutralizing antibodies for arthritis treatment. **Public Health Relevance:** • This research may lead to a better understanding of arthritis and potentially novel therapeutic strategies targeting FSTL-1.
UNIVERSITY OF ALABAMA AT BIRMINGHAM	MOUNTZ, JOHN D	Suppression of pathogenic autoantibodies in lupus by inhibition of AID	**Research Question:** • Does IL-17 promote the formation of germinal centers (GCs) leading to pathogenic autoantibodies in autoimmune diseases like rheumatoid arthritis? **Stage:** • This research proposes in vitro (experiments conducted in the lab using cells) and in vivo (experiments conducted with live animals) studies. **Methods:** • Analyze the effects of IL-17 on B cell migration, activation-induced cytidine deaminase (AID) expression, and autoantibody production. • Use techniques like confocal microscopy, flow cytometry, transwell chambers, and live imaging to study cell behavior. • Utilize shRNA technology and targeted knockout mice to modulate IL-17 signaling and RGS proteins. • Employ a newly developed collagen-induced arthritis (CII) model in BXD2 mice. **Drug Development:** • This research doesn't directly focus on drug development, but explores mechanisms to potentially block GC formation and autoantibody production as a novel therapeutic approach for autoimmune diseases. **Focus:**

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			• The study investigates the role of IL-17 in promoting the interaction between B and T cells, leading to the formation of GCs where autoreactive B cells are generated. • It explores the involvement of regulators of G-protein signaling (RGS) proteins in this process. • The research aims to distinguish the contribution of autoantibodies versus inflammatory responses in rheumatoid arthritis development. **Significance:** • Blocking GC formation could be a novel therapeutic strategy to prevent the generation of pathogenic autoantibodies in autoimmune diseases. • Understanding the mechanisms of IL-17 driven autoimmunity can lead to new therapeutic targets. **Overall, this research investigates a potential pathway for IL-17 driven autoantibody production in GCs and its role in rheumatoid arthritis, aiming to identify novel therapeutic targets.**
JESSE BROWN VA MEDICAL CENTER	SHAHRARA, SHIVA	Discovering a novel therapy for RA patients	**Research Question:** • Can targeting Toll-like receptor 5 (TLR5) with a specific antibody be an effective treatment strategy for RA patients who don't respond to existing therapies? **Stage:** • This research proposes in vitro (experiments conducted in the lab using cells) and in vivo (experiments conducted with live animals) studies. **Methods:** • Analyze TLR5 expression in macrophages from RA patients and its correlation with disease activity. • Investigate how TLR5 ligands present in RA synovial fluid activate macrophages and T cells. • Evaluate the effects of a novel TLR5 antibody on macrophage and T cell function.

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			• Use pre-clinical models to compare the efficacy of TLR5 antibody therapy with existing RA treatments. **Drug Development:** • This research focuses on developing a novel therapeutic approach - a TLR5 antibody - for RA patients who are unresponsive to current treatments like anti-TNF drugs. **Focus:** • The study investigates the role of TLR5 in activating macrophages and Th17 cells, which contribute to the inflammatory process in RA. • It explores the potential of a TLR5 antibody to block the interaction between macrophages and T cells, thereby halting the inflammatory cascade. • The research aims to establish a new treatment option for RA patients who don't respond to existing therapies. **Significance:** • A successful TLR5 antibody therapy could benefit veterans and civilians with RA by improving their quality of life and reducing healthcare costs. • This research may lead to a novel therapeutic strategy for a subset of RA patients who have limited treatment options. **Overall, this research investigates a potential new target, TLR5, and its role in RA progression. It proposes a novel antibody-based therapy for RA patients who are unresponsive to current treatments.**
UNIVERSITY OF CALIFORNIA, SAN DIEGO	FIRESTEIN, GARY S	Pathogenic role of ILC2 in rheumatoid arthritis	**Research Question:** • Do ILC2s play a pathogenic role in RA by promoting joint inflammation and destruction through the production of amphiregulin (AREG)? **Stage:** • This research proposes in vitro (experiments conducted in the lab using cells) and in vivo (experiments conducted with live animals) studies.

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			Methods: • Analyze AREG levels in the joints of arthritic mice and its cellular source. • Investigate the effects of AREG on fibroblast-like synoviocytes (FLS) function in vitro. • Use mouse models to assess the impact of ILC2-derived AREG on arthritis development. **Drug Development:** • This research doesn't directly focus on drug development, but explores a novel pathway involving ILC2 and AREG as potential therapeutic targets for RA. **Focus:** • The study investigates a potentially counterintuitive concept - whether ILC2s, usually considered anti-inflammatory, can promote RA through AREG production. • It explores the role of AREG in activating FLS, which contribute to joint destruction in RA. • The research aims to understand the ILC2-AREG-FLS axis and its contribution to RA pathogenesis. **Significance:** • Validating this concept could open doors for novel therapeutic strategies targeting the ILC2-AREG pathway in RA. **Overall, this research investigates a novel mechanism by which ILC2s might contribute to RA and explores a potential new target for therapeutic intervention.**
ABWIZ BIO, INC.	MARUYAMA, TOSHI	Engineering a unique antibody for patients with RA	**Research Question:** • Can a high-affinity humanized anti-TLR5 antibody be developed as a novel therapy for RA patients who are unresponsive to existing treatments? **Stage:** • This research involves a combination of in vitro (experiments conducted in the lab using cells) and in vivo (experiments

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			conducted with live animals) studies, with an emphasis on antibody development. **Methods:** • Phage display library screening to identify high-affinity TLR5 binding human Fab fragments. • Analysis of Fab clones for TLR5 neutralization capacity in human and murine cells. • Site-directed mutagenesis to enhance the affinity of the most promising Fab clones. • Testing the ability of anti-TLR5 antibody candidates to block the inflammatory response induced by RA synovial fluid in humanized RA mouse models. **Drug Development:** • This research directly focuses on developing a novel therapeutic drug - a high-affinity humanized anti-TLR5 antibody - for RA patients who don't respond to current therapies like anti-TNF drugs. **Focus:** • The study builds upon previous findings that TLR5 activation contributes to RA by promoting M1 macrophage and Th17 cell activity. • It aims to develop a specific antibody that neutralizes TLR5, thereby disrupting the pro-inflammatory pathway in these patients. • The research emphasizes improving the affinity of the antibody candidate for optimal therapeutic efficacy. **Significance:** • A successful anti-TLR5 antibody could provide a new treatment option for a subset of RA patients who have limited treatment options.

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			Overall, this research focuses on the development of a humanized anti-TLR5 antibody as a potential therapeutic strategy for RA patients who are unresponsive to current therapies.
MAYO CLINIC ROCHESTER	WEYAND, CORNELIA M.	Oligoclonal T Cell Expansion and Rheumatoid Arthritis	**Research Question:** • How do metabolic abnormalities in T cells contribute to the development and progression of RA, and can these abnormalities be targeted for therapeutic intervention? **Stage:** • This research proposes in vitro (experiments conducted in the lab using cells) studies with the potential for future in vivo studies. **Methods:** • Analyze metabolic profiles of T cells from RA patients compared to healthy controls. • Investigate the effects of manipulating T cell metabolism on their differentiation, survival, and function. • Explore how metabolic changes influence T cell interactions with other immune cells and tissues relevant to RA. • Identify potential small molecule drugs that can restore normal T cell metabolism and function. **Drug Development:** • This research focuses on identifying potential therapeutic targets based on metabolic abnormalities in RA T cells. • The project proposes the development of small molecule drugs that can modulate T cell metabolism and function. **Focus:** • The study investigates how altered glucose metabolism in RA T cells leads to increased production of proinflammatory cytokines and a shift towards T helper 17 (Th17) and T follicular helper (Tfh) cell development. • It explores the role of redox signaling pathways and key enzymes like PFKFB3 and G6PD in T cell function.

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			• The research aims to identify how metabolic reprogramming affects T cell interactions with other immune cells and tissues involved in RA pathogenesis. **Significance:** • Understanding the link between metabolism and T cell function in RA could lead to novel therapeutic strategies targeting metabolic pathways to prevent or treat the disease. **Overall, this research investigates the role of metabolic abnormalities in RA T cells and explores the potential for metabolic intervention as a novel therapeutic approach for RA.**
VANDERBILT UNIVERSITY MEDICAL CENTER	MAJOR, AMY S	Targeting the T cell immune synapse in autoimmunity	**Research Question:** • Can specific inhibition of the immune synapse between T cells and antigen-presenting cells (APCs) be a therapeutic approach for SLE? **Stage:** • This research proposes in vitro (experiments conducted in the lab using cells) studies with the potential for future in vivo studies. **Methods:** • Develop CD4-targeted nanoparticles loaded with a small molecule, eggmanone (Egm), that disrupts the immune synapse. • Investigate the effects of Egm-loaded nanoparticles on T cell interaction with APCs. • Analyze the impact of disrupting the immune synapse on T cell help for B cells and autoantibody production. **Drug Development:** • This research focuses on developing a novel therapeutic approach using CD4-targeted nanoparticles loaded with Egm to specifically target the immune synapse and T cell activation in SLE. **Focus:** • The study explores a new strategy to target the communication between T and B cells by disrupting their physical interaction at the immune synapse.

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			• It utilizes a small molecule, Egm, delivered by nanoparticles conjugated with an anti-CD4 antibody fragment to specifically target CD4+ T cells. • The research aims to prevent T cell help for B cells and ultimately reduce autoantibody production in SLE. **Significance:** • A successful approach targeting the immune synapse could lead to a novel and specific therapy for SLE with fewer side effects compared to broad immunosuppression. **Overall, this research investigates a new therapeutic strategy for SLE by targeting the immune synapse between T and B cells using CD4-targeted nanoparticles loaded with an immune synapse disrupting molecule.**

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	LENARDO, MICHAEL J	Molecular Mechanisms Of The Autoimmune Lymphoproliferative Syndrome	**Research Question:**
			• This research focuses on identifying genetic mutations that cause various immune disorders and developing targeted therapies based on these discoveries.
			Stage:
			• This research involves a combination of clinical studies with patients (observational), in vitro (experiments conducted in the lab using cells), and potentially in vivo (experiments conducted with live animals) studies.
			Drug Development:
			• This research project actively explores targeted therapies for several immune disorders based on identified gene mutations:
			  ○ Hydroxychloroquine for LRBA deficiency (LATAIE)
			  ○ Abatacept for LRBA deficiency and potentially CHAI disease
			  ○ Eculizumab for CD55 deficiency (CHAPLE) disease
			Focus:
			• The study investigates the role of specific genes (CTLA4, LRBA, STAT5B, CD55) in immune regulation and their mutations in

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			causing various disorders like ALPS, CHAI, LATAIE, RALD, and CHAPLE. • It explores the mechanisms by which these mutations lead to immune dysregulation and proposes targeted therapies to address the underlying causes. • The research emphasizes the importance of clinical observations, genetic analysis, and functional studies in understanding immune disorders and developing personalized treatments. **Significance:** • Identifying specific gene mutations allows for a more precise diagnosis of immune disorders and the development of targeted therapies with potentially fewer side effects compared to broad immunosuppression. **Overall, this research contributes to precision medicine for immunological diseases by linking genetic variations to specific disorders and proposing targeted therapeutic approaches.**
Kobe University	TBA	Regulation of neddylation system as a novel therapeutic target of rheumatoid arthritis and rheumatoid lung	**Research Question:** • Can targeting the neddylation pathway be a novel therapeutic approach for rheumatoid arthritis (RA) and its associated interstitial pneumonia (IP)? **Stage:** • This research proposal is likely in the early stages and hasn't specified the methods in detail. **Drug Development:** • This research focuses on developing a new treatment for RA and its lung complication, IP, by targeting the neddylation pathway. **Focus:** • The study explores the role of neddylation, a cellular process involving the NEDD8 protein, in RA and associated lung disease. • Given neddylation's involvement in cell survival, proliferation, and inflammation, the research suggests it might be a target for therapeutic intervention.

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			Significance: • If successful, this research could lead to a novel treatment for RA and its associated lung complications. **Overall, this research proposes targeting the neddylation pathway as a potential therapeutic strategy for RA and interstitial pneumonia, but more information is needed on the specific methods and approaches.**
Nagoya City University	Yoko Miura	Characterization of neovascular cells in pannus leads to novel therapeutic strategies for rheumatoid arthritis.	**Research Question:** • What are the characteristics of the newly identified neovascular cell population in RA, and can they be targeted therapeutically to suppress disease progression? **Stage:** • This research proposes in vitro (experiments conducted in the lab using cells) and potentially in vivo (experiments conducted with live animals) studies based on analysis from an existing arthritis model. **Drug Development:** • This research focuses on identifying the characteristics of novel neovascular cells in RA with the goal of developing therapies that target these cells to prevent disease progression. • The project suggests that blocking new blood vessel formation (neovascularization) could be a therapeutic target for RA and potentially other diseases like cancer. **Focus:** • The study investigates a specific population of neovascular cells found in the pannus tissue of RA joints. • It aims to understand the characteristics of these cells and their role in supplying nutrients and oxygen to the affected joint. • The research explores the potential of targeting these cells to inhibit neovascularization and suppress RA progression. **Significance:**

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			• Identifying and targeting these novel neovascular cells could lead to a new therapeutic approach for RA by cutting off nutrient and oxygen supply to inflamed joints. • The findings might also be applicable to other diseases characterized by neovascularization. **Overall, this research investigates a specific type of neovascular cell in RA and explores its potential as a therapeutic target to prevent disease progression.**