The CWRU Psoriasis Center of Research Translation (CORT) is focused on a Central Research Project (CRP) that is supported by an Administrative Core (AC) and two scientific Cores, the Applied Meta 'Omics Core (AMC) and the Preclinical Modeling Core (PMC). The abstracts for the CRP and supporting cores are summarized below:

Central Research Project (CRP) Abstract:

The overall goal of the CWRU Psoriasis Center of Research Translation (CORT) is to combine new bioinformatic methodologies with advanced murine and human experimental approaches to translate scientific findings into clinical applications that more nimbly advance therapy for psoriasis and related inflammatory comorbidities. Our highly innovative, synergistic and cross-disciplinary CORT will use a collaborative research project (CRP) as a central hub with bi-directional input from 2 highly interactive research cores, to refine and test hypotheses, identify and test repurposed drug leads and advance understanding of psoriasis and related inflammatory comorbidities. To do so, the CRP will integrate input from the: 1) Preclinical Modeling Core (PMC), that will provide and customize our many validated, unique transgenic psoriasiform animal models and translatable human xenograft approaches, essential to translating new mediator/pathway roles and drug leads; and the 2) Applied Meta-'Omics Core (AMC), that will apply multi-platform (transcriptome, metabolome, micro/mycobiome) bioinformatics to individual patient and murine samples to identify novel pathway-specific targets. Iterative experimental testing of these targets and feedback from the PMC and CRP will identify novel pathways in psoriasis pathogenesis that are likely to benefit from intervention by new or repurposed drugs that will translate to psoriasis therapy. Our overarching hypothesis is that we can powerfully combine existing and developing psoriasis basic science datasets, patient records, bioinformatics and computational systems biology with bi-directional mouse and human studies to identify new therapeutic targets and repurposed drugs that can be expeditiously moved to clinical trials, improving psoriasis treatment and patient care. To test and refine this hypothesis, the Specific Aims are: (1) Identify new pathways central to psoriasis pathogenesis and new psoriasis drug candidates by analyzing psoriasis patients' EMR data, tissue and blood samples and; (2) Evaluate AMC-identified gene targets and efficacy of pathway-specific drug candidates using preclinical molecular genetic psoriasis mouse models. The concentrated interactions between the CRP and Cores will provide value-added research output, far beyond any incremental advances that a given Core or specific project could provide. Our novel, highly integrated and synergistic CORT design, powered by exceptional resources and expertise of our interdisciplinary translational investigative team, will exert a transformative and sustainable impact on the psoriasis field and patient care.

Administrative Core (AC) Abstract:

The mission of the CORT is to advance therapy for psoriasis and related comorbidities by leveraging new bioinformatic methodologies with well-developed murine and human experimentation capabilities. This technology concatenation is expected to more nimbly translate new scientific opportunities into clinical applications. The CORT Administrative Core (AC) proposes to manage an innovative model wherein a collaborative research project (CRP) will serve as the central hub that will iterate significant bi-directional work from 2 highly interactive research cores to experimentally test hypotheses and newly identified pathway specific and repurposed FDA drug leads. The AC will accomplish this goal through its Aims to: 1. Convene an Internal Advisory Committee and an External Advisory Board which a) develops and applies accountability metrics for the CRP, each Core, and the P&F projects, b) manages a Go-NoGo iterative algorithmic decision-making process regarding CORT resource utilization and c) coordinates patient cohort assets and regulatory compliance; 2. Provide fiscal management of the CORT; 3. Branch out exciting new developments deriving from CORT findings through a robust Pilot & Feasibility (P&F) program; 4. Organize and advertise Enrichment Activities that bring CORT and Community researchers together in scientific venues to exchange ideas and new technologies. The AC leadership will work closely not only with lab scientists, but also with the leadership and programmers of the CLEveland Area Research Platform for Advancing Translational Healthcare (CLEARPATH), a comprehensive research database with Limited Data Set contribution from all 3 major Cleveland healthcare systems. CLEARPATH will create connected data (e.g., Biospecimen results, EMR clinical phenotype, `Omics data) as well as a Single person record across the system, enabling research cohort discovery and validation across the aggregate dataset. This approach will allow us to preliminarily validate psoriasis cohort subsets, mix `omic pathways and drug leads identified by the Cores and CRP. In addition to its roles as an information conduit and facilitator for research, the AC also promotes the cutaneous research environment for psoriasis and its comorbid and related conditions through enrichment programs. As such, the AC is instrumental in the design and planning of research symposia, and recruiting potential P&F program recipients with innovative technologies and/or complementary research expertise to the CORT. The cross-disciplinary approach of combining a Preclinical Modeling Core (PMC) with an Applied Meta `Omics Core (AMC) that takes advantage of artificial intelligence, data mining, network techniques and machine learning to query available interaction networks and highly annotated integrated electronic medical records (EMRi) is highly innovative. The active engagement of the AC will be instrumental for the successful achievement of the broader goal of identifying new psoriasis pathways and repurposed approved drugs.

Applied Meta'Omics Core (AMC) Abstract:

To date, most existing cellular or immunological evaluations of psoriasis inflammation have been limited by the low-resolution data used for analysis and often rely on gross clinical endpoints. The overall goal of the CORT is to combine new bioinformatic methodologies with advanced murine and human experimental approaches to translate scientific findings into clinical applications that more nimbly advance therapy for psoriasis and related inflammatory comorbidities. Systems biology provides an unbiased approach to generating a comprehensive assessment of the host responses involved in psoriasis-mediated inflammation that may lead to new therapy targets for psoriasis and ideally, those tailored for the specific patient. This evolving investigative paradigm driven by modern high-throughput technologies that generate enormous datasets ("Big Data") has engendered the need for a centralized 'omics core service and analysis platforms that the CORT Applied Meta'Omics Core (AMC) will provide. The AMC is designed to serve as an innovative collaborative resource with bidirectional experimental ties to the Collaborative Research Project (CRP) and Preclinical Modeling Core (PMC). The AMC will receive samples from the CRP and PMC, generate transcriptomic, metabolomic, microbiome and mycobiome datasets, and provide the bioinformatic pipelines to analyze those datasets in conjunction with clinical outcomes and/or other data types, including incorporation of artificial intelligence, data mining, network techniques and machine learning to enable identification of novel pathways and differentially-expressed gene targets that will allow for identification of new and/or re-purposed drugs. The AMC supports the CORT CRP's overall objectives via the following aims: (1) perform SOP-driven sample acquisition, sample preparation, and 'omic assays for the PMC and CRP; (2) identify differential metabolomic, gene and pathway expression signatures, as well as changes in the micro/mycobiome, between psoriatic involved, uninvolved and control skin from human and psoriasiform murine models for the CRP; (3) (i) identify systems biology donor profiles (endotypes) and candidate biomarkers that may define the pathogenesis of psoriasis in humans and mouse models and (ii) identify FDA-approved drugs that are predicted to target the biomarkers and/or pathways associated with psoriasis. Highly interactive Cores synergistically interacting with the central CRP, the AMC team's expertise, innovation and extensive resources will drive the CORT's transforming and sustainable impact on psoriasis understanding and clinical care. The AMC will shed deeper insight into the pathological events in psoriasis, which can be translated into targeted diagnostic and therapeutic strategies to manage psoriasis at the individual level. By combining myco/microbiome, metabolomic, and transcriptomic analyses to identify pathological or protective correlates that are perturbed in disease, as well as their predicted drug targets, the AMC is envisioned to be critical in supporting the PMC and CRP in their goals of targeted therapeutics and precision, individualized treatments.

Preclinical Modeling Core (PMC) Abstract:

The CORT Preclinical Modeling Core (PMC) will serve as a resource for the Collaborative Research Project (CRP), providing enabling technology and model systems that will be used to specifically test targets identified by the Applied Meta-Omics Core (AMC). The broad goal of the CWRU CORT is to combine new bioinformatic methodologies with advanced murine and human experimental approaches to translate scientific findings into clinical applications that more nimbly advance therapy for psoriasis and related inflammatory comorbidities. This goal requires a rich array of readily-deployable and flexible/adaptable psoriasis-relevant and innovative in vivo systems that permit testing of a wide range of novel concepts, roles of specific mediator/pathways, and efficacies of specific repurposed and anti-psoriasis drugs. The PMC will meet this need, by working closely with the AMC and CRP to provide all needed transgenic and psoriasiform mouse models and isolated tissues, blood and cells for analyses and bioinformatic-derived biomarker and target generation. The PMC will enable generation and testing by the CRP of hypotheses generated as a result of human and mouse bioinformatics data. The goals of the PMC include providing enabling materials, technology and expertise in psoriasis mouse models and mouse molecular genetics that will allow and enhance successful completion of the CRP Aims and Objectives. To support the CRP's objectives, the PMC will: A. Provide genetically modified existing mouse models of psoriasiform skin inflammation; B. Engineer new innovative genetic mouse models based upon novel genes/proteins identified by the AMC; C. Provide primary cells isolated from genetically manipulated mice for ex vivo hypothesis testing; D. Identify the most appropriate psoriasis mouse model(s) to test efficacy of pathway-specific drugs identified by the AMC, and generate and provide mice to the CRP for preclinical testing and evaluation; and E. Generate germ-free mice and re- introduce bacteriome/mycobiome species identified by the AMC and provide animals to the CRP for analysis and hypothesis testing. The PMC will also provide reiterative data generation for additional "omics" data analyses and identification by the AMC of novel pathways, biomarkers, micro/mycobiome species, and cellular mediators, contributing new insight into psoriasis pathogenesis, enabling validation in clinical psoriasis patient samples. The PMC provides a coordinated center of excellence enabling the creation of new, and utilization of existing, animal models of psoriasis to better test the cellular and molecular mechanisms hypothesized to mediate psoriasis. Within the novel CORT structure of highly interactive Cores synergistically interacting with the central CRP, the PMC team's expertise, innovation and extensive resources will drive the CORT's transforming and sustainable impact on psoriasis understanding and clinical care.