CHEMICAL ENGINEERING
UNIVERSITY *of* WASHINGTON

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Sentinel Biomaterials Remotely Identify Alloimmunity: Predicting Transplant Rejection and Prenatal Complications

Monday July 24th
Lecture 4:00-5:00 p.m. | Physics/Astronomy Auditorium (PAA) A118
Reception 5:00-6:00 p.m. | Benson Hall Lobby

Bio

Dr. Russell R. Urie is a postdoctoral fellow at the University of Michigan with Professor Lonnie Shea, developing tissue engineering scaffolds for immunosurveillance of transplant rejection and prenatal complications. Prior to his postdoc, he obtained his PhD in Chemical Engineering from Arizona State University, where his research centered on the creation of laser-activated nanomaterials for tissue repair. His innovative work resulted in the development of rapid sealing nanomaterials to prevent wound complications. Russell received his B.S from Brigham Young University. Throughout his academic journey, Russell has received several accolades for his research and teaching contributions. Moreover, he has demonstrated a strong commitment to mentoring undergraduate and graduate students in their research pursuits.

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Abstract

Introduction: As there is no assay to predict alloimmunity in transplant or fetal rejection, clinicians rely on invasive tissue biopsy and aggressive immunosuppression. Immunosuppression protects transplants but increases systemic toxicities. Also, nearly half of all cases of prenatal complication have an undefined immune basis. This immune cascade inhibits placenta development, yet the clinic focuses on later disease stages. Primary tissue histology is a flawed standard for alloimmunity surveillance and diagnostics, as histological evidence of rejection inherently lags behind molecular biomarkers and suffers from variability. Noninvasive alternatives, including gene profiling and cell-free DNA, also measure lagging indicators of rejection. A minimally invasive surveillance method is urgently needed to identify early risk of rejection for minimizing invasive procedures and personalizing interventions.

I have developed porous biomaterial implants ("scaffolds") for minimally-invasive sampling. These scaffolds amass immune cells producing biomarkers of disease as an engineered immunological niche, and gene expression in biopsied scaffolds predicts disease onset. In this work, I employ microporous scaffolds as a synthetic immunological niche to capture the longitudinal immune domain of healthy and rejecting transplants and healthy and miscarriageprone rodent pregnancies without needing to disrupt the primary tissue and with greater specificity than blood.

Methods: Biomaterial scaffolds accumulate immune cells producing biomarkers of rejection as an engineered immunological niche. We implanted subcutaneous poly-caprolactone scaffolds in murine heart transplant recipients and miscarriage-prone pregnancies. Scaffolds were biopsied and analyzed for differential gene expression by RNA sequencing using elastic net regularization for differential expression across mice, tissue, and day to generate a biomarker signature of rejection. We performed singular value decomposition and supervised machine learning (Random Forest) to derive single-metric scores and a predictive model for graft or fetus rejection.

Results and Conclusions: Gene expression in the cell-capture scaffold identified biomarker signatures of early rejection in heart transplant (Fig 1) and miscarriage prone pregnancies (Fig 2), without invasive biopsy. This implantable scaffold enables minimally invasive histological evaluation and molecular calculation of the early risk of rejection (Fig 1B-E) to reduce the frequency of invasive biopsy and personalize treatment to prevent alloinjury. In healthy and preeclampticlike pregnancies, the scaffold implant recapitulates the immune microenvironment of the placenta with greater tissue specificity than blood (Fig 2B). Gene expression in the scaffold can distinguish between gestation at different stages and immunological states (Fig 2C). We identified 8 genes that differentiate between allogeneic and syngeneic pregnancies at embryonic day 5, prior to fetal or placental organogenesis.
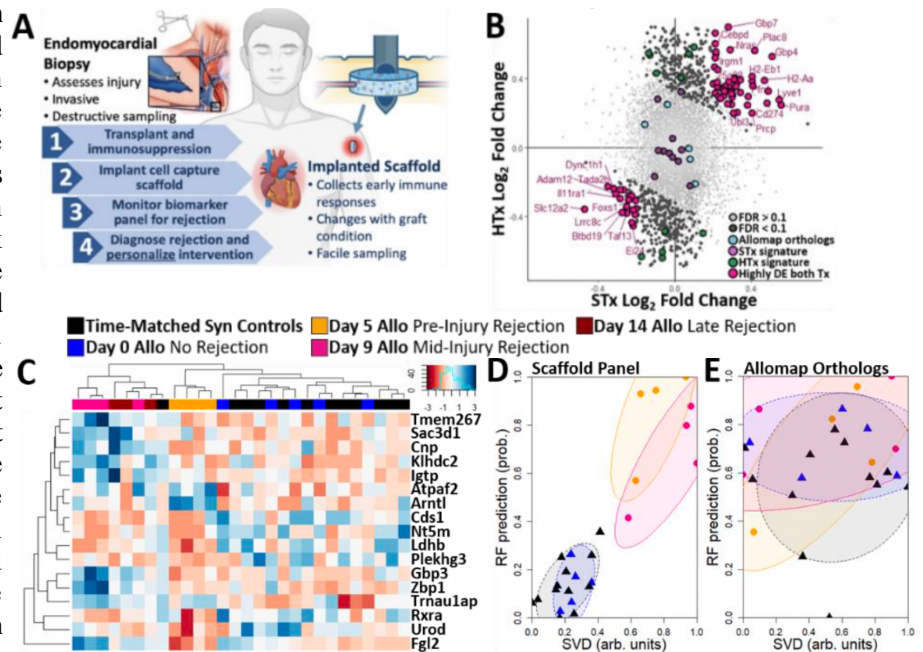
Fig 1. (A) Scaffolds in solid organ transplant. (B-E) In murine skin and heart transplants, subcutaneous scaffold implants identify (B) 43 conserved genes for acute allograft rejection. A sparse 17-gene signature of stages of rejection at the scaffold (D) identifies pre-injury rejection, (E) whereas the blood-based Allomap genes cannot.
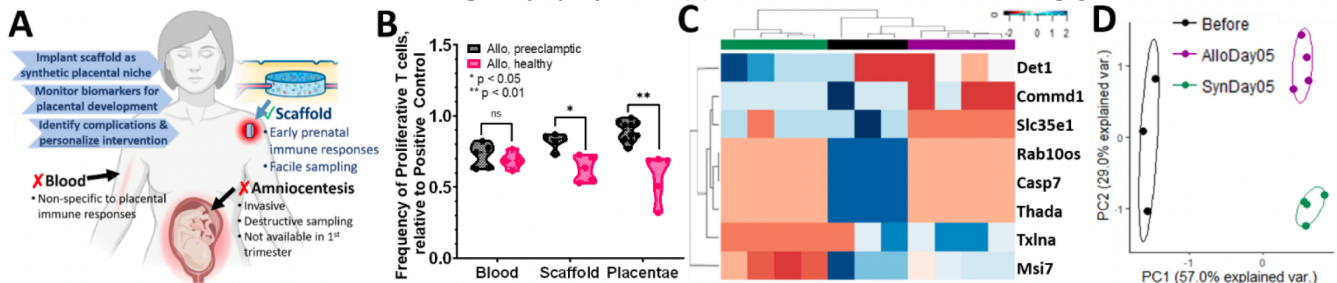

Fig 1. (A) Scaffolds in gestation. (B-D) Scaffold implants capture (B) immune responses of the placenta and (C) identify novel biomarkers of prenatal immune state in healthy and preeclamptic rodent pregnancies at the (D) early stage of embryonic day 5.

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We have developed an implant to remotely monitor immunological markers of alloimmunity in transplantation and pregnancy. Scaffold gene expression can differentiate immune state across time and disease progression prior to the onset of symptoms, creating an early, novel therapeutic window to prevent transplant or fetal injury.

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