BIOSCIENCES ntific Research Initiative

Engineering Cell Programmable Biomaterials for Dental and Musculoskeletal Health

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EXECUTIVE SUMMARY

Major Unsolved Problem This SRI Will Address: Musculoskeletal and oral tissues, including bone, cartilage, muscle, ligaments, teeth and skin, are comprised of multiple cell populations that are precisely organized to fulfill functional requirements. The guidance of cells to form tissues has been recapitulated *in-vitro,* however the signals driving 3D functional tissue neogenesis in a spatial-temporal sequence *in-vivo* remain largely unknown. Limitations in material design to reconstruct complex musculoskeletal structures have led to failed attempts at using cellular therapeutics for tissue engineering. Targeted delivery and homing of host cells is a major deficiency in the clinical implementation of cell therapies. **A critical gap in developing biomaterials is understanding what signals should be designed into materials to direct cell differentiation in time and space, and tissue formation across length scales.** Our goal of creating cell programmable, niche-mimicking biomaterials integrates research strengths in a wide variety of fields from across the University. Our approach spans dimensional scale, but also spans from fundamental science to applied science to clinical translation.

Engineering technologies can provide the tools to organize cells in 3D and at the appropriate times, which will provide an enabling means for studying tissue development and, ultimately, be translated therapeutically. Basic insights into factors that influence tissue development and function, including biochemical, mechanical and structural function, can be used as design criteria for new biomaterials. Most biomaterials are imported from other industries into medicine/dentistry, serve only an inert space-filling role, not a biologically instructive role, and/or are able to reproduce only a fraction of the organizational framework of native tissue. Even the most advanced biomaterials do not have sensory capabilities to provide feedback on whether they are fulfilling their intended biological function. **Our goal is to develop advanced materials that control the programming of cells and the resulting development and spatio-temporal organization of tissue, while also providing feedback on the function of the tissue.** One component of this unmet need is the demand for biologically-driven material design criteria. Another component is the need for more robust computational tools to connect cell and matrix signals to material design across dimensional scale. In this regard, there are gaps in instrumentation and expertise at UM, specifically the ability to understand cell-matrix, cell-cell and cell-material interactions in 4D (in space and time) via imaging, utilizing this information to design materials using computational/artificial intelligence (AI) approaches, and development of preclinical models to investigate the *in-vivo* function of materials.

Strategies for Addressing Problem: Our vision is to bring a new approach: identification of complex patterns and signatures in musculoskeletal and oral tissues in time and space, and incorporating this information into materials design. A second component of this vision is designing sensors into materials that can report on the status of tissue development. This vision is achieved through a combination of **(1)** strategic new faculty hires, **(2)** new instrumentation, **(3)** the development of a biomaterials collaborative laboratory – a "collaboratory", and **(4)** convergence of faculty from engineering, life science and clinical backgrounds. We also build upon existing expertise in biomaterials and tissue engineering, as well as the translational infrastructure of the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center in Dentistry, the Bioengineered Cell-Based Therapies cluster in Engineering, and our formal NIH-funded training program in tissue engineering (TEAM) **(Fig. 1).** These strengths make our SRI well-suited to target the clinical implementation of novel bioinspired biomaterials for patient care. We focus on tissues that provide structural and mechanical roles - tissues in the musculoskeletal and dental/oral/craniofacial (DOC) spaces. We utilize the expertise and infrastructure of our Resource Center and bring this approach to the University to solve problems not under the purview of our Center. Using biomaterial-based reprogramming along with sensors is substantially different from developing approaches that use genetic (CRISPR) approaches and is more translatable to real-world clinical application.

How This SRI Will Make UM a Global Leader in Cell Programmable Biomaterials: This SRI leverages existing expertise in biomaterials and musculoskeletal tissue engineering with the goal of filling critical gaps at UM in imaging, computational design of materials and ex vivo/in vivo preclinical models for materials evaluation. This SRI will elevate UM to pre-eminent status in biomaterials and tissue engineering via 4 mechanisms: 1) recruiting experts to fill in these gaps, 2) incorporating a unique perspective of how to envision tissue engineering, 3) incorporating sensing into biomaterials and 4) leveraging our strengths in biomaterials and tissue engineering. Catalyzing interactions between engineers, life scientists and clinicians will provide a multi-disciplinary approach to answer critical questions about how materials can program cells.

While there are few formal programs in biomaterials or tissue engineering nationally, these sub-fields are central to many dental schools, BME and orthopaedics departments. **However, only UM has national top 10 Colleges/Schools of Engineering, Dentistry and Medicine**. While peer institutions have institutes focused on tissue engineering, these institutions are generally categorized into 2 groups: 1) life science and clinical units promoting basic research primarily on stem cells and 2) STEM units focusing on technology. Many life science units are at institutions without top-tier engineering programs and do not utilize materials (or any engineering tools) to compliment stem cell research. While some STEM-based initiatives have a biomaterials focus, many leading programs are at institutions without a clinical arm. UM is unique in having strengths in both, along with ability to translate technologies into the clinic to advance patient health care.

Resources Required to Make UM Pre-eminent in Biomaterials: To elevate UM to preeminence in biomaterials, there are 4 critical needs: 1) additional expertise, 2) instrumentation, 3) a centralized collaboratory for disseminating advances in biomaterials design, and 4) mechanisms to promote and enable collaborations across campus. Critical gaps in expertise in UM will be filled by recruitment of faculty with expertise in: 1) imaging, particularly tissue imaging via mass spec (to obtain information about tissues), 2) computational (bio)materials/AI (to help design next-generation materials); and 3) development of relevant pre-clinical models (to validate biomaterials on the path to translation). These targets are well aligned with recruiting in the departments of Biologic & Materials Sciences (BMS), Periodontics & Oral Medicine (POM), Biomedical Engineering (BME) and Orthopaedic Surgery. The Dental School has long been a campus hub for biomaterials research and tissue engineering. The School is an international leader in dental regenerative medicine, however this SRI will propel the school and key collaborators in BME and Orthopaedics to transform UM's leadership role in cell programmable biomaterials. Recruiting in BMS and POM target FTEs who fit the department scopes of oral regeneration at the genomic, molecular, cell, tissue or systems levels. BME has a track in biomaterials and regenerative medicine and seeks applications from individuals in all areas of BME that will complement and expand upon current areas of strength. Orthopaedics seeks faculty with expertise in structure-function relations in musculoskeletal tissues. Faculty will be hired by integrating members of this SRI within departmental search committees. Convergence science will be promoted as indicated in **Fig. 1** – via specific technologies new FTEs will employ, which extend well beyond the boundaries of our SRI, and via the "glue" that this SRI will provide.

A critical unmet equipment need is the ability to perform tissue imaging by MALDI-TOF. Coupling desorption electrospray ionization (DESI), an ambient ionization technique that can be coupled to mass spectrometry, allows for chemical imaging of samples in-situ. This technology can map the spatial distribution of endogenous proteins, lipids or metabolites, or exogenous drugs in sectioned tissue. Having such instrumentation would enhance our capabilities to understand tissue structure at the nanoscale, relate these findings to macro-scale function, and use this information to inform the rational design of biomaterials. We will also organize a collaboratory, or hub of expertise in biomaterials design, processing and characterization. This organization will enable faculty to connect with technologies and expertise to enhance research. While a collaboratory has elements of a core, it is also an intellectual hub geared toward providing enabling technologies related to materials to investigators (e.g. a stem cell biologist in need of a delivery system for a particular in-vivo experiment).

Figure 1 - Biomaterials and tissue engineering ecosystem at UM Existing infrastructure and expertise to be leveraged are depicted on the perimeter to bridge gaps in expertise (blue boxes) and tangible needs to fill these gaps (maize boxes)