BIOSCIENCES *Scientific Research Initiative*

Single Cell Spatial Analysis Program

Lead PI: Evan Keller; Co-PIs: Justin Colacino, Jun Li, Sunitha Nagrath, Arvind Rao, Tom Wilson
Urology, Environmental Health Sci, Human Genetics, Chem Engineering, Comp Med and Bioinf; Pathology

<u>Executive Summary</u>

Vision Develop UM into a global leader in applying high-resolution spatially-resolved multi-omic analysis of cells within tissues to drive next-generation solutions in biology and human health

Scope, Significance and Challenges

Understanding human biology and disease requires insights into how cells assemble into tissues and organs, and how, in the case of pathology, these functions are altered. Recently there has been an explosion in technologies that allow researchers to probe genomic and other data on a single cell basis at great sensitivity and throughput. Current leading-edge methods utilize cell suspensions and describe the attributes of individual cells (e.g. how they cluster into groups, differentiation trajectories, rare cell identification), which is providing unprecedented, often novel, views of cellular diversity. What is missing is how this highly granular cellular information can be related to the physical structure of tissues and used to inform an increasingly higher resolution understanding of tissue (dys)function that reveals hidden therapeutic and preventive strategies.

The major present challenge in single cell biology is thus to establish at single cell resolution how rigorously defined cell types localize, interact and signal within intact tissues and subsequently lead to emergent tissue (dys)function over time. The field is poised to answer these questions using high throughput techniques that integrate imaging, concurrent measurements (RNA, DNA, protein, etc.), lineage tracing, and/or genetic perturbations (e.g. CRISPR) in individual cells *in situ* or *in vivo*, with retention of 2D or 3D information, a conceptual approach we term “single cell spatial analysis”, or simply “spatial analysis”. Mature spatial analysis technologies will be required to (i) acquire high-throughput data from intact tissue samples, (ii) permit direct comparison of multiple data types (DNA, RNA, protein, etc.), (iii) use state-of-the-art imaging to correlate signals to tissue architecture, (iv) use advanced information processing to integrate data into predictions of tissue assembly and function, and (v) reveal the high-dimensional impact of gene or environmental perturbations. Examples of early technologies that meet some needs are tissue CyTOF (proteins), and sequential FISH (RNA). However, no platform achieves all goals (e.g. multi-modality); thus, improved strategies are critically needed.

Progress meeting these challenges will be a boon to both basic and clinical sciences. We will learn with remarkable resolution and depth how biological molecules allow cells to communicate to create and function in tissues, which will create opportunities for entirely new ways of thinking about how tissue biology can be exploited to devise novel health interventions. Outcomes will be applicable to a great many biomedical disciplines and applications. Examples include enhanced tissue regeneration, therapeutics targeted to specific tissue microenvironments (e.g. stem cells), immunotherapy, prevention of disease-causing tissue alterations in inflammation, aging and oncogenesis, and many others.

Opportunities for Impact

Achieving global status in spatial analysis at Michigan will be challenging but will be greatly enabled by our many existing strengths in dissociated single cell analysis, engineering and computation. Michigan has an extensive group of investigators aggressively pursuing both the theory and the application of single cell analysis techniques. At a 2018 internal retreat, we had over 150 registrants with 50 UM faculty attending and many presenting on wide-ranging applications. The Michigan Institute for Data Science (MIDAS) has a thriving program in single cell data analytics. We have several relevant and busy core facilities, including the Cancer Center Single Cell, Advanced Genomics and Immunology Cores.

Our benchmarking identified multiple programs in single cell analysis of single cell suspensions, including the Broad Institute and multiple single cell cores at many academic institutions, with grant support by the NIH HuBMAP, Chan Zuckerberg Initiative and others. However, most of these are only beginning to focus on tissues and lack multidisciplinary programs. Technical advances in achieving spatial analysis have mainly come from individual laboratories at other institutions. It is thus an ideal time for Michigan to aggressively pursue an integrative program in spatial analysis, when the field has established its feasibility but is nevertheless in its infancy with many conceptual and practical advances yet to be realized.

Single Cell Spatial Analysis Program

Michigan is ideally positioned to help lead the required advances in spatial analysis technology (e.g. physical sciences expertise in the Colleges of Engineering and Literature, Sciences and Arts) and data analysis (e.g. world-leading skills in the Departments of Biostatistics and Computational Medicine and Bioinformatics). We are equally well equipped to aggressively pursue applications of this critical enabling "next wave" in imaging and genomics in preventive interventions (e.g. established teams in the School of Public Health) and translational medicine (e.g. active Medical School Centers in Cancer, Organogenesis, Allergy, Aging and more). Investigators throughout these diverse units are making extensive use of dissociated single cell technologies who are eager to make the transition to spatial analysis. We will respond to this imperative and exploit our campus-wide strengths by creating the cross-cutting *Michigan Single Cell Spatial Analysis Program* to stimulate growth and collaborations across critical Michigan units.

Aim 1: Recruit new faculty experts. Consistent with the purpose of Biosciences Scientific Research Initiatives, we will identify and recruit outstanding new faculty researchers to bring missing expertise in spatial analysis to our campus. We request resources to support three new faculty recruits to be chosen on a basis of established excellence and because they offer transdisciplinary expertise complementary to each other and to current Michigan strengths, resulting in convergent approaches to the common challenge. We will be open to all possibilities as best candidates emerge but will target new hires in engineering technology, data analysis and creative biomedical application. Many of our participating departments already share this vision and are recruiting toward these goals; we will integrate these search processes to leverage resources and provide an institutional gain beyond the current scope of Biosciences funding.

Aim 2: Establish required infrastructure. Growth in spatial analysis at Michigan must also come from within. Given our strengths in single cell biology it is natural for our institution to make the transition to excellence in spatial analysis, but organized effort and investment are required. Our ability to recruit missing expertise will also depend on Michigan having a fertile environment in which new faculty candidates will be confident their programs can grow. We will first transition existing high-functioning single cell core facilities into viable spatial technology resources for all Michigan investigators to use. We will staff these facilities with people able to help investigators with project development, sample handling and data analysis. Resources are requested to support seed equipment and staffing, with the recognition that future investments will also be required.

Aim 3: Build a vibrant research community. Spatial analysis is the epitome of a challenge that requires a multidisciplinary approach harnessing convergent expertise in technology, computation and health sciences. We will build a community at Michigan capable of working together to respond to this challenge. We will host events to help researchers create collaborative partnerships in spatial analysis. We will establish pilot project funding to help these new research partners become proficient and competitive; this mechanism will be built with partner funding to further leverage Biosciences resources. The Program will be the research community's portal that links academia, industry, government and philanthropy to continuously reassess institutional needs in a rapidly evolving field. These and all Program endeavors will be strongly informed by our new faculty recruits.

Project Team / Michigan and Industry Partners

We have convened a multidisciplinary team that will organize and implement our strategies. We as applicants are leaders of campus groups that serve the single cell community, including core facilities and MIDAS, so we are ideally positioned to see the needs of the field and implement our plan. We have commitments from an array of departments across four units with expertise in technology development, data sciences and applications. Units already recognized the importance of recruiting in spatial analysis (see letters). To broaden our base and further leverage Biosciences funding we obtained over $1.6 million in matching support from partners including Departments/Schools, Rogel Cancer Center, Biointerfaces Institute, Forbes Institute and 10x Genomics. Together we are poised to implement our vision for the Michigan Spatial Analysis Program.