$55M Wellcome Leap Program
Delta Tissue (ΔT): Integrated platforms for predicting changes in tissue state

The pandemic has revealed how much work there is to do in advancing and protecting human health. More than 2.5M people died after infection with SARS-CoV-2 and millions more suffer from its long-term effects. The costs to individuals, families and society are immeasurable.

But the pandemic has also revealed what a difference a scientific breakthrough can make. The scientific and pharmaceutical communities developed revolutionary mRNA vaccines on timescales 10 times faster than was previously thought possible. This advance is saving millions of lives and preventing millions of lost person-years of disability and distress.

We've witnessed a remarkable feat of science, collaboration, and global response that shows what is possible. It's a proud moment for science, but there's so much more to do.

Beyond the millions lost to COVID-19, 2020 and the years before it were tragically normal. In recent years, we have lost:

- 10M people/year to all forms of cancer,
  1.8M people/year to lung cancer, 685K people/year to breast cancer[1]
- 1.4M people/year to tuberculosis (TB)[2]
- 435K people/year to malaria[3]

Without new advances, 2021 and the years that follow will look much the same.

These diseases have something in common. They are all ultimately caused by changes in the molecules and cells that define how a tissue functions and interacts with the other tissues in our bodies. If we could understand the physiological state of a tissue, we could explain the status of a disease in each person and better predict how that disease would progress.

In the case of TB, we know that immune system responses in more than 90% of the 1.7 billion people exposed to *Mycobacterium tuberculosis* (or "Mtb"), the active agent of tuberculosis, will successfully manage or even clear the disease. But, the remaining 10% of the world's infected population propagate a disease that kills more people annually than any other*. The antibiotics we have to fight TB require at least 6 months of regular treatment. Many people don't complete the therapy and this has led to the development of antibiotic-resistant TB, which is cited by the WHO as one of the most significant threats to global health[2]. It is a rapidly growing epidemic in India, China, the Russian Federation and much of Asia. We can't tell who will clear TB on their own and who needs help, so we over-prescribe antibiotics, increase the risk of antibiotic resistance, and make the TB epidemic even worse.

In the case of cancer, we know that ~30% of the population in industrialized countries will be diagnosed with cancer in their lifetimes and 10% of all deaths will be due to the disease[1].

* In 2020, mortality due to TB was exceeded by mortality caused by SARS-CoV-2 infection.

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Diagnosing many forms of cancer earlier in disease progression has improved survival rates, and in some cases, we can intervene successfully. But for a frustratingly large number of patients, our therapies extend life by mere months, instead of providing cures.

We must do better.

We know that infectious and noncommunicable diseases act at the levels of molecules, cells and tissues, so at least part of the solution resides in measuring and understanding their states. Whereas we used to think of cell transitions as one-way and irreversible, we now see that in many cases cells transit between states, sometimes reversing themselves as they respond to changing conditions[4–6]. These cell and tissue dynamics are new territory that we must detect, quantify and ultimately model. Measuring the properties of cells and tissues requires technologies that are expensive to buy and run, and require expert, well-trained staff who are in short supply -- tools should be much more widely accessible to academic centers, start-ups, SMEs, the whole biopharma industry, and ultimately to clinicians and patients for diagnostic use.

Program goals.

We need a new platform – a 'tissue time machine' – that can profile tissue states and predict transitions between states ('Delta Tissue' or 'ΔT'). The platform would provide quantitative, multi-scale, multi-modal information sufficient to build integrated prediction models of key cell and tissue states and transitions. If we are successful, we'll be able to intervene in diseases earlier and with approaches that are targeted to the individual. We'll also have an improved understanding of the mechanisms that drive disease, which in turn will provide more opportunities for intervention. If we succeed, we'll begin to eradicate the stubbornly challenging diseases that cause so much suffering around the world.

Such a platform is now possible if we combine the latest cell and tissue profiling technologies with recent advances in machine learning and other computational methods. With this foundation, we can now imagine the tissue time machine, which assembles a rational set of profiling modalities, integrates their outputs and builds predictive models of tissue states and transitions.

To build this new platform, we will need to overcome key limitations and achieve three main goals:

1. Develop and optimize method(s) to select modalities that accurately profile tissue in a given state.
    - The method(s) should quantitatively assess the value of a set of integrated modalities for predicting different tissue and disease states.
    - The method should be demonstrably better than expert human judgement with respect to time, cost, resource requirements, and predictive value.
    - As an example, the approach might involve an initial survey of tissue composition (e.g., scRNA-Seq) that is combined with publicly available data and resources to produce a defined set of modalities required for profiling and prediction of tissue state.

2. Develop new or improve existing individual molecular and structural profiling capabilities, with respect to spatial and/or temporal resolution, number of markers, volume of tissue

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and/or other assay properties, so as to reveal the states and transitions for the exemplar diseases described in the Platform Demonstration Areas.
    - New or enhanced profiling methods should improve one or all of the following in the context of a sample volume of at least 1 mm^3:
        - Number of molecular markers or features routinely detected by 10-100x;
        - Spatial resolution by 5-10x over what is achievable by conventional light microscopy;
        - Sample processing time by 5-10x.
    - A key goal is the expansion and linkage of markers and structures, e.g., establishing the relative value and linkage of molecular markers and features derived from an organelle or cell/tissue structure.
    - Rather than build or acquire all the required tissue profiling technologies within the program, where appropriate, performers are expected to leverage research infrastructure resources that have come on-line and that provide access to the global scientific community.

3. Develop a platform that integrates multi-scale, multi-modal data from different states and builds models that predict states and transitions. Inclusion of explainable models in the platform is of interest. Performers working in this goal will:
    - Identify and implement methods to integrate models or knowledge of state gained in Goal 1, ultimately improving the prediction of profiling methods.
    - Test the platform against the Platform Demonstration Areas at least annually.
    - Construct an open data resource to share models and datasets, providing a route to integrate contributions from others.

Call for abstracts and proposals.

We are soliciting abstracts and proposals for work over 3 years (with a potential additional one-year option). Proposers should clearly relate their work to one or more Program Goals and indicate which of the Platform Demonstration Areas (PDAs) they will participate in. Additional PDAs can be proposed, but all performers must validate their work against at least one of the specified PDAs.

Wellcome Leap accepts project proposals from any legal entity, based in any legal jurisdiction, including academic, non-profit and for-profit organizations. Applicants are encouraged to contact Wellcome Leap about joining its Health Breakthrough Network by executing its MARFA (or CORFA for commercial entities) agreement. Full execution of the Wellcome Leap MARFA is not required for application submission but is required for any award.

Platform Demonstration Areas. We rarely consider infectious diseases, cancer and many others as related, but all exert their effects on molecules, cells and tissues. We have identified three distinct biological systems where we aim to demonstrate the platform. The demonstrations may be executed on human tissues, for example from biopsies, human organoids or assembloids, or where justified, non-human models that have been demonstrated to faithfully model human biology and/or disease. Proposals that include one or more

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demonstrations in other systems are permitted, but must also demonstrate successful operation in one or more systems described below. Program performers will have the opportunity to work with other performers to run these demonstrations. Synergies and integrated system demonstrations will be facilitated by Wellcome Leap on at least an annual basis as we make progress together towards the Program Goals.

For each of these platforms we will deliver a functioning model that defines tissue states and state transitions. Evaluation of the models will involve standard iterative train-test splits and seek to achieve at least 80% prediction accuracy. We will evaluate and potentially revise this target upwards as we learn more about weighing and integrating different cell and tissue markers and features.

1. Tuberculosis (TB): TB is the leading single cause of death globally[2,7]. MTb infects cells of the upper airway of an individual. Macrophages internalize MTb cells by phagocytosis, and through a poorly understood process construct a granuloma around the infection site in an attempt to isolate the infection and/or eliminate MTb cells entirely. In a minority of cases, the integrity of the granuloma is compromised and MTb cells infect other parts of the lung and/or enter the lymph system and reach other organs or systems. We know that cytokine, TGF-beta and other signaling systems are involved in the establishment and maintenance of the TB granuloma[8], but we don't yet have a sufficient view of the factors that control its state or a way to predict how its integrity and function will evolve over time.

   Goal of demonstration: Establish a method for defining and profiling the states of the TB granuloma, and predict whether the integrity will be maintained or compromised. Demonstration test will involve achieving >80% accuracy in the prediction of the maintenance or loss of integrity of a granuloma in a preclinical model.

2. Triple Negative Breast Cancer (TNBC): TNBC is a subtype of breast cancer that accounts for 15-20% of all breast cancers and is characterized by loss of progesterone receptor, estrogen receptor, and epidermal growth factor receptor (HER2). Patients diagnosed with TNBC have the highest risk of metastasis of any breast cancer and have 40-80% risk of recurrence after therapy. TNBCs are highly heterogeneous and there is evidence that suggests this heterogeneity contributes to resistance to chemotherapy and relapse[9]. Development of resistance to chemotherapy appears to occur through epigenetic changes that modify the activity of key regulators of cell state and produce “persister” cells that can survive prolonged treatment with chemotherapy[4,5].

   Goal of demonstration: Establish a method for differentiating TNBC states and predicting state switches in response to chemotherapeutic treatment. Demonstration test will involve achieving >80% accuracy in the prediction of the cell states and transitions in response to chemotherapeutic agents, e.g, doxorubicin combined with cyclophosphamide.

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3. Glioblastoma multiforme (GBM): GBM is an extremely aggressive brain tumor and one of the most deadly forms of cancer, with a two year survival rate of less than 1 in 3[10]. Classification of GBM based on specific gene mutations (isocitrate dehydrogenase-1) or DNA methylation (promoter region of the MGMT DNA repair enzyme) provides an accurate prognosis but has yielded limited clinical improvement in patient outcomes. Defining features of GBM include infiltration of activated microglia and an abundant variety of immune cells not normally found in the brain, e.g., monocyte-derived macrophages, neutrophils, and T-cells[11]. Single cell profiling of RNA and protein in patient biopsies have recently revealed as many as 14 distinct transcriptional states of microglia within the tissue and tumor microenvironment[6]. The fact that intratumor cell heterogeneity is strongly correlated with patient survival underscores the dire need to determine how tumor and healthy cell function are coordinated at the tissue level, and how the tumor microenvironment responds to therapeutic intervention[12]. A major obstacle to treating GBM is recurrence after tumor resection. The ability to accurately define and predict tissue state transitions after removal of the tumor would pave the way for novel therapeutics with greater efficacy and reduced toxicity. State definition based on properties of tissue resident and infiltrating leukocytes are of particular interest.

   Goal of demonstration: Discover quantitatively distinct tissue states within the GBM tumor microenvironment and indicators that can accurately predict tissue state transitions. Demonstration test will involve achieving >80% accuracy in the prediction of state transitions in the context of tumor progression and/or response to standard or novel therapeutic interventions.

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