Mapping the Human Body at Cellular Resolution -- The NIH Common Fund Human BioMolecular Atlas Program

Short Title: The Human BioMolecular Atlas Program (HuBMAP)

One Sentence Summary: HuBMAP supports technology development, data acquisition, and spatial analyses to generate comprehensive, molecular and cellular 3D tissue maps.

HuBMAP Consortium±

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Transformative technologies are enabling the construction of three dimensional (3D) maps of tissues with unprecedented spatial and molecular resolution. Over the next seven years, the NIH Common Fund Human Biomolecular Atlas Program (HuBMAP) aims to develop a widely accessible framework for comprehensively mapping the human body at single-cell resolution by supporting technology development, data acquisition, and detailed spatial mapping. HuBMAP will integrate its efforts with other funding agencies, programs, and the biomedical research community at large towards the shared vision of a comprehensive, accessible 3D molecular and cellular atlas of the human body, in health and various disease settings.

Introduction

The human body is an incredible machine. Trillions of cells, organized across an array of spatial scales and a multitude of functional states, contribute to a miraculous symphony of physiology. While we broadly understand how cells are organized in most tissues, a comprehensive understanding of the cellular and molecular states and interactive networks resident in the tissues and organs, from organizational and functional perspectives, is lacking. The specific 3D organization of different cell types, together with the effect of cell-cell and cell-matrix interactions in their natural milieu, have a profound impact on the normal function, natural aging, tissue remodeling, and disease progression in different tissues and organs. Recently, new technologies have enabled the molecular characterization of many cell types[1–4] and mapping of their spatial relationships in complex tissues at unprecedented scale and single cell resolution. These advancements create an opportunity to build a high-resolution atlas of 3D maps of human tissues and organs.

HuBMAP (see https://commonfund.nih.gov/hubmap) is a NIH-sponsored program with the goals of developing an open framework and technologies for mapping the human body at cellular resolution as well as generating foundational maps for several tissues obtained from normal individuals across a wide range of ages. To achieve these goals, HuBMAP has been designed as a cohesive and collaborative organization, having a culture of openness and sharing using team science based approaches[5]. The consortium will actively work with other ongoing initiatives including the Human Cell Atlas[6], Human Protein Atlas[7] and related NIH-funded consortia mapping specific healthy organs (including brain[8], lungs[9], kidney[10], and genitourinary[11] regions) and diseased tissue (especially pre-cancer and tumors[12]), as well as other emerging programs.

HuBMAP organization and approaches

HuBMAP is comprised of members having a broad diversity of expertise (e.g., molecular/cellular/developmental/computational biologists, measurement scientists, clinicians, pathologists, anatomists, biomedical/software engineers, and computer/information scientists) and is organized into three components: 1) Tissue Mapping Centers (TMCs), 2) HuBMAP Integration, Visualization & Engagement (HIVE) collaborative components, and 3) Innovative Technologies Groups (TTDs) (**Fig. 1**). Throughout the program, HuBMAP will scale-up the range of tissues and technologies studied through a series of funding opportunities that at their core, have been designed to be synergistic with other NIH and international efforts. In the later stages of HuBMAP, demonstration projects will be added to show the utility of the generated resources and importantly, engage the wider research community to analyze HuBMAP data alongside data from other programs or from their own labs.

Tissue and data generation

The HuBMAP TMCs will collect and analyze a broad range of tissues, representing both sexes and a variety of ages across the adult lifespan. These tissues (**Fig. 2**) include: 1) discrete, complex organs (kidney, ureter, bladder, lung, breast, colon); 2) distributed organ systems (vasculature); and 3) systems comprised of dynamic or motile cell types with distinct microenvironments (lymphatic organs: spleen, thymus, and lymph nodes). Tissue collection will occur at precisely defined anatomical locations (when possible, photographically recorded) according to established protocols that preserve tissue quality and minimize degradation. Beyond meeting standard regulatory requirements, to the greatest extent possible, participants will be consented for open access genomic data sharing to maximize their usage by the biomedical community.

To achieve spatially-resolved, single-cell maps, the TMCs will employ a complementary, iterative, two-step approach (**Fig. 3**). First, ‘omic assays, which are extremely efficient in data acquisition, will be used to generate global genome sequence and gene expression profiles of

dissociated single cells/nuclei in a massively parallel manner. The molecular state of each cell will be revealed by single cell transcriptomic[13] and chromatin accessibility assays[14,15], with the two data types related by imputation of transcription factors to explain the regulation of gene expression[16]. Second, spatial information (abundance, identities, and localization) will be acquired from various biomolecules (RNA[17], protein[18], metabolites, and lipids) in tissue sections or blocks, using imaging methodologies such as fluorescent microscopy (confocal, multiphoton, lightsheet, and expansion), multiplexed error-robust Fluorescence In Situ Hybridization [MERFISH[19]]), imaging mass spectrometry[20], and imaging mass cytometry (IMC[21–24]). The robust single cell/nucleus data obtained will inform *in situ* modalities (e.g., single cell/nucleus RNA-seq will be used to choose probes to RNA or proteins), which provide spatial information for up to hundreds of molecular targets of interest. These data will allow for computational registration of cell-specific epigenomic/transcriptomic profiles to cells on a histologic slide to reveal various microenvironmental states. They will potentially include information about protein localization to cytoplasm, nucleus, or cell surface; phosphorylation; complex assembly; extracellular environment; and cellular phenotype determined by protein marker coexpression. Registration and computational fusion of complex imaging data will provide biological insight beyond any single imaging mode[20,25]. The powerful combination of sequencing and multiplexed *in situ* imaging will provide a pipeline for constructing multi-omics spatial maps for the various human organs and their cellular interactions at a molecular level.

The TMCs will apply complementary methods for data collection with an emphasis on processes to ensure the generation of high quality data and standardized metadata annotations. Benchmarking, quality assurance and control (QA/QC) standards, and standard operating procedures (SOPs), where appropriate, will be developed for each stage of the methodological process and be made available to promote rigor, reproducibility and transparency. It is expected that QA/QC standards for both biospecimens and data will evolve as tissue collection, processing techniques, storage/shipping conditions, assays, and data processing tools change,

as they have for other consortium projects[26–31]. Where possible, metadata related to preanalytical variables and technologies will be harmonized and protocols and standards will be shared with the wider research community.

Computational approaches for building an integrated tissue map across scales

The diversity of data generated by HuBMAP, ranging across macro- and microscopic scales (anatomic, histologic, cellular), modalities (MRI/CT imaging, microscopy, molecular/genomic), and multiple individuals is essential to its core mission. Exploring each of these valuable datasets collectively connects a fragmented view of the human body. Hence, HuBMAP will develop analytical and visualization tools bridging spatial and molecular relationships in order to help generate a high-resolution 3D molecular atlas of the human body.

The volume of data generated and collected by HuBMAP will require the utilization, extension and development of tools and pipelines for data processing. While initial data processing tools will be based on methods developed by consortium members, HuBMAP will also work with and incorporate algorithms developed by other programs and the wider research community to supplement its pipelines. To this end, HuBMAP will provide an extensible open source platform by using recognized standards and harmonizing with the platforms of similar programs, upon which data processing software can be easily added, updated, and used (e.g. as with Dockstore[32] and Toil[33]). This infrastructure will enable external developers to apply their codes, applications, open application programming interfaces (APIs), and data schema in concert with HuBMAP tools and data to facilitate customized processing and analysis. Furthermore, by working with other single cell analysis initiatives, the consortium will seek to reduce the barriers to browsing, searching, aggregating and analyzing data across the programs.

To fully integrate spatial and molecular data across individuals, HuBMAP will create a common coordinate framework (CCF) that defines a 3D spatial representation of many tissues

of the human body across multiple scales (whole body to single cells). This spatial representation will serve as an addressable scaffold for all HuBMAP data, enabling unified interactive exploration and visualization (search, filter, details on demand) and facilitating comparative analysis across individuals, technologies, and labs[34,35]. To achieve these objectives, HuBMAP envisions a strategy inspired by other tissue atlas efforts[36–38] leveraging the identification of "landmark" features including key anatomical structures and canonical components of tissue organization (e.g., epidermal boundaries and normally spatially invariant vasculature) that can be identified in all individuals. These landmarks will enable a "semi-supervised" strategy for aligning and assembling an integrated reference, upon which HuBMAP investigators can impose diverse coordinate systems, including relative representations and zone-based projections. As one example, an open-source, computational histology topography cytometry analysis toolbox (histoCAT[39]) currently facilitates 2D and soon, 3D reconstruction. Ontology-based frameworks will be explored in parallel to effectively categorize, navigate, and name multi-scale data; synergies are expected between these two approaches.

Technology development

Quantitative imaging of different classes of biomolecules in the same tissue sample with high spatial resolution, sensitivity, specificity, and throughput is central to the development of detailed tissue maps. Although no single technique can fully address this challenge at present, the development and subsequent multiplexing of complementary capabilities provides a promising approach for accelerating tissue mapping efforts. The HuBMAP Innovation Technologies groups aim to develop several innovative approaches to address limitations of existing state-of-the-art techniques. For example, transformative technologies such as Signal Amplification by Exchange Reaction (SABER)[40,41], SeqFISH[42,43], and Lumiphore probes[44] will be refined to improve multiplexing, sensitivity, and throughput for imaging RNA and proteins across multiple tissues. Furthermore, new mass spectrometry imaging techniques will enable quantitative mapping of

hundreds of lipids, metabolites, and proteins from the same tissue section with high spatial resolution and sensitivity[45,46]. These efforts will benefit from development of novel computational tools and machine learning algorithms for data integration across modalities.

Challenges

Optimizing collection, preservation, and processing of a wide diversity of tissue types from multiple donors has been approached by previous programs such as GTEx[47]. However, the goal of HuBMAP, to generate comprehensive, interactive high resolution maps using a wide variety of assays, introduces an added level of complexity. Mapping functionally important biomolecules, including some of which we may not even be aware and for which sensitive, specific and high-throughput assays are still lacking, will require devoted attention. Moreover, the volume and diversity of datasets are heretofore unprecedented for comprehensive data capture, management, mining, modelling, and visual exploration and communication. Integration of data from different modalities is necessary to generate robust maps; it will be necessary to develop the corresponding analysis and interactive visualization tools necessary to ensure that the data and atlas are widely accessible to the entire life-sciences community. Finally, given the enormity of a human atlas, HuBMAP faces the challenges of prioritization of tissues and technologies, sampling across tissues and donors, and optimally synergizing its efforts with an increasing number of international efforts..

Resources and Community Engagement

HuBMAP is an important part of the international mission to build a high resolution cellular and spatial map of the human body, and we envision close collaboration with other aforementioned initiatives to build an easy-to-use platform and interoperable datasets that will accelerate realization of a high-resolution human atlas. Shared guiding principles around open data, tools and access will enable collaborative and integrated analyses of data produced across diverse

consortia. One example of the potential for close collaboration is in the study of the colon; multiple projects funded by HuBMAP, the Human Tumor Atlas Network, and the Wellcome Trust will be complemented by projects funded by the Leona M. and Harry B. Helmsley Charitable Trust and Chan-Zuckerberg Initiative later this year. With each project interested in different regions and diseases (e.g., normal tissue, colon cancer, and Crohn's disease) it will be important for all the programs to ensure data is collected and made available in a consistent manner, and we expect that HuBMAP will play an active role in such efforts.

HuBMAP will provide capabilities for data submission, access, and analysis following FAIR (Findable, Accessible, Interoperable, and Reusable) data principles[48]. We will develop policies for prompt and regular data releases in commonly-used formats, consistent with similar initiatives. Robust metadata will be comprised of all aspects of labeling and provenance including de-identified donor information (both demographic and clinical), details of tissue processing and protocols, data levels, and processing pipelines.

Indeed, engagement and outreach to the broader scientific community and other mapping centers is central to ensure that resources generated by HuBMAP will be leveraged broadly for sustained impact. To ensure that browsers and visualization tools from HuBMAP are valuable, the Consortium will work closely with anatomists, pathologists, as well as visualization and user experience experts; such as those having virtual or augmented reality expertise. As described earlier, it is expected that the diversity of healthy samples included in this project will facilitate valuable comparative analyses, pinpointing how cells and tissue structures vary across individuals, throughout the lifespan, and in the emergence of dysfunction and disease. The program will build its resources with these use cases in mind and provide future opportunities, such as the demonstration projects, for close collaboration with domain experts. We also anticipate these data will be highly useful for new biomedical hypothesis generation, tissue engineering, developing robust simulations of spatiotemporal interactions and machine learning of tissue features, as well as for educational purposes.

Conclusions

Analogous to release of the first human genome build, we anticipate the first reference 3D tissue maps will represent the "tip of the iceberg." In these early stages, HuBMAP, working closely with other initiatives, aims to help build a foundation by generating a high resolution atlas of key organs in the normal human body capturing inter-individual differences. The Consortium envisions an easily accessible user-interface where the data can be used to visualize molecular landscapes at the single cell, pathways and networks for molecules of interest, and spatial and temporal changes across a given cell type of interest. Researchers will also be able to browse, search, download, and analyze the data in standard formats with rich metadata, and later will be able to query and analyze datasets across similar programs. As companion and future studies in model systems and within disease contexts deliver results, we believe the technologies and resources discussed herein will generate many new scientific hypotheses, provide insights into the link between organization and function and significantly benefit human health.

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References

1. Svensson, V. *et al.* Power analysis of single-cell RNA-sequencing experiments. *Nat. Methods* **14**, 381–387 (2017).
2. Schwartzman, O. & Tanay, A. Single-cell epigenomics: techniques and emerging

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3. Tanay, A. & Regev, A. Scaling single-cell genomics from phenomenology to mechanism. *Nature* **541**, 331–338 (2017).
4. Norris, J. L. & Caprioli, R. M. Analysis of tissue specimens by matrix-assisted laser desorption/ionization imaging mass spectrometry in biological and clinical research. *Chem. Rev.* **113**, 2309–2342 (2013).
5. National Research Council, Division of Behavioral and Social Sciences and Education, Board on Behavioral, Cognitive, and Sensory Sciences & Committee on the Science of Team Science. *Enhancing the Effectiveness of Team Science*. (National Academies Press, 2015).
6. Regev, A. *et al.* The Human Cell Atlas. *Elife* **6**, (2017).
7. Interactive human protein atlas launches. *Cancer Discov.* **5**, 339 (2015).
8. Ecker, J. R. *et al.* The BRAIN Initiative Cell Census Consortium: Lessons Learned toward Generating a Comprehensive Brain Cell Atlas. *Neuron* **96**, 542–557 (2017).
9. LungMAP - Home. Available at: https://www.lungmap.net/. (Accessed: 20th December 2018)
10. About KPMP - Kidney Precision Medicine Project. *Kidney Precision Medicine Project* Available at: https://kpmp.org/about-kpmp/. (Accessed: 4th January 2019)
11. Welcome to GUDMAP. *GenitoUrinary Development Molecular Anatomy Project (GUDMAP)* (2017). Available at: https://www.gudmap.org/. (Accessed: 24th December 2018)
12. HTA. *National Cancer Institute* (2017). Available at: https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding/upcoming/hta-foa-video. (Accessed: 20th December 2018)
13. Cao, J. *et al.* Comprehensive single-cell transcriptional profiling of a multicellular organism. *Science* **357**, 661–667 (2017).
14. Buenrostro, J. D. *et al.* Single-cell chromatin accessibility reveals principles of regulatory

variation. *Nature* **523**, 486–490 (2015).

15. Cusanovich, D. A. *et al.* Multiplex single cell profiling of chromatin accessibility by combinatorial cellular indexing. *Science* **348**, 910–914 (2015).
16. Cusanovich, D. A. *et al.* A Single-Cell Atlas of In Vivo Mammalian Chromatin Accessibility. *Cell* **174**, 1309–1324.e18 (2018).
17. Shah, S., Lubeck, E., Zhou, W. & Cai, L. In Situ Transcription Profiling of Single Cells Reveals Spatial Organization of Cells in the Mouse Hippocampus. *Neuron* **92**, 342–357 (2016).
18. Goltsev, Y. *et al.* Deep Profiling of Mouse Splenic Architecture with CODEX Multiplexed Imaging. *Cell* **174**, 968–981.e15 (2018).
19. Chen, K. H., Boettiger, A. N., Moffitt, J. R., Wang, S. & Zhuang, X. RNA imaging. Spatially resolved, highly multiplexed RNA profiling in single cells. *Science* **348**, aaa6090 (2015).
20. Van de Plas, R., Yang, J., Spraggins, J. & Caprioli, R. M. Image fusion of mass spectrometry and microscopy: a multimodality paradigm for molecular tissue mapping. *Nat. Methods* **12**, 366–372 (2015).
21. Rapsomaniki, M. A. *et al.* CellCycleTRACER accounts for cell cycle and volume in mass cytometry data. *Nat. Commun.* **9**, 632 (2018).
22. Chevrier, S. *et al.* Compensation of Signal Spillover in Suspension and Imaging Mass Cytometry. *Cell Syst* **6**, 612–620.e5 (2018).
23. Schulz, D. *et al.* Simultaneous Multiplexed Imaging of mRNA and Proteins with Subcellular Resolution in Breast Cancer Tissue Samples by Mass Cytometry. *Cell Syst* **6**, 25–36.e5 (2018).
24. Chevrier, S. *et al.* An Immune Atlas of Clear Cell Renal Cell Carcinoma. *Cell* **169**, 736–749.e18 (2017).
25. Patterson, N. H. *et al.* Next Generation Histology-Directed Imaging Mass Spectrometry Driven by Autofluorescence Microscopy. *Anal. Chem.* **90**, 12404–12413 (2018).

26. Teng, M. *et al.* A benchmark for RNA-seq quantification pipelines. *Genome Biol.* **17**, 74 (2016).
27. Petryszak, R. *et al.* Expression Atlas update--an integrated database of gene and protein expression in humans, animals and plants. *Nucleic Acids Res.* **44**, D746–52 (2016).
28. Hong, E. L. *et al.* Principles of metadata organization at the ENCODE data coordination center. *Database* **2016**, (2016).
29. Campbell-Thompson, M. *et al.* Network for Pancreatic Organ Donors with Diabetes (nPOD): developing a tissue biobank for type 1 diabetes. *Diabetes. Metab. Res. Rev.* **28**, 608–617 (2012).
30. Pugliese, A. *et al.* The Juvenile Diabetes Research Foundation Network for Pancreatic Organ Donors with Diabetes (nPOD) Program: goals, operational model and emerging findings. *Pediatr. Diabetes* **15**, 1–9 (2014).
31. Philips, T. *et al.* Factors That Influence the Quality of RNA From the Pancreas of Organ Donors. *Pancreas* **46**, 252–259 (2017).
32. O'Connor, B. D. *et al.* The Dockstore: enabling modular, community-focused sharing of Docker-based genomics tools and workflows. *F1000Res.* **6**, 52 (2017).
33. Vivian, J. *et al.* Toil enables reproducible, open source, big biomedical data analyses. *Nat. Biotechnol.* **35**, 314–316 (2017).
34. Butler, A., Hoffman, P., Smibert, P., Papalexi, E. & Satija, R. Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nat. Biotechnol.* **36**, 411–420 (2018).
35. Haghverdi, L., Lun, A. T. L., Morgan, M. D. & Marioni, J. C. Batch effects in single-cell RNA-sequencing data are corrected by matching mutual nearest neighbors. *Nat. Biotechnol.* **36**, 421–427 (2018).
36. Mazziotta, J. *et al.* A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos. Trans. R. Soc. Lond. B Biol.*

Sci. **356**, 1293–1322 (2001).

37. Fonseca, C. G. *et al.* The Cardiac Atlas Project--an imaging database for computational modeling and statistical atlases of the heart. *Bioinformatics* **27**, 2288–2295 (2011).
38. Fürth, D. *et al.* An interactive framework for whole-brain maps at cellular resolution. *Nat. Neurosci.* **21**, 139–149 (2018).
39. Schapiro, D. *et al.* histoCAT: analysis of cell phenotypes and interactions in multiplex image cytometry data. *Nat. Methods* **14**, 873–876 (2017).
40. Kishi, J. Y. *et al.* SABER enables highly multiplexed and amplified detection of DNA and RNA in cells and tissues. (2018). doi:10.1101/401810
41. Saka, S. K. *et al.* Highly multiplexed in situ protein imaging with signal amplification by Immuno-SABER. *bioRxiv* 507566 (2018). doi:10.1101/507566
42. Shah, S., Lubeck, E., Zhou, W. & Cai, L. seqFISH Accurately Detects Transcripts in Single Cells and Reveals Robust Spatial Organization in the Hippocampus. *Neuron* **94**, 752–758.e1 (2017).
43. Zhu, Q., Shah, S., Dries, R., Cai, L. & Yuan, G.-C. Identification of spatially associated subpopulations by combining scRNAseq and sequential fluorescence in situ hybridization data. *Nat. Biotechnol.* (2018). doi:10.1038/nbt.4260
44. Cho, U. *et al.* Ultrasensitive optical imaging with lanthanide lumiphores. *Nat. Chem. Biol.* **14**, 15–21 (2018).
45. Yin, R. *et al.* High Spatial Resolution Imaging of Mouse Pancreatic Islets Using Nanospray Desorption Electrospray Ionization Mass Spectrometry. *Anal. Chem.* **90**, 6548–6555 (2018).
46. Zhu, Y. *et al.* Nanodroplet processing platform for deep and quantitative proteome profiling of 10-100 mammalian cells. *Nat. Commun.* **9**, 882 (2018).
47. GTEx Consortium *et al.* Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).

48. Wilkinson, M. D. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* **3**, 160018 (2016).
49. The Human BioMolecular Atlas Program - HuBMAP | NIH Common Fund. Available at: https://commonfund.nih.gov/hubmap. (Accessed: 13th February 2019)
50. Human Cell Atlas. Available at: https://www.humancellatlas.org/. (Accessed: 13th February 2019)
51. Human Cell Atlas: we're funding scientists at six UK research institutes | Wellcome. (2018). Available at: https://wellcome.ac.uk/news/human-cell-atlas-we-are-funding-scientists-six-uk-research-institutes. (Accessed: 13th February 2019)
52. Human Cell Atlas - Chan Zuckerberg Initiative. *Chan Zuckerberg Initiative* Available at: https://chanzuckerberg.com/science/programs-resources/humancellatlas/. (Accessed: 13th February 2019)
53. The Human Protein Atlas. Available at: https://www.proteinatlas.org/.
54. Cell Census Network (BICCN) | Brain Initiative. Available at: https://www.braininitiative.nih.gov/brain-programs/cell-census-network-biccn. (Accessed: 20th December 2018)
55. Funding Opportunity | Helmsley Charitable Trust. Available at: https://helmsleytrust.org/rfa/gut-cell-atlas. (Accessed: 13th February 2019)
56. Generation of Human Tumor Atlases. *National Cancer Institute* (2018). Available at: https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/human-tumor-atlas. (Accessed: 13th February 2019)

Figure Legends

Figure 1. The HubMAP consortium.

The Tissue Mapping Centers (TMC) will collect tissues and generate spatially resolved, single cell data. Groups involved in Transformative Technology Development (TTD) and Rapid Technology Implementation (RTI) initiatives will develop emerging and more developed technologies, respectively, which, in later years, will be implemented at scale. Data from all groups will be rendered useable for the biomedical community by the HIVE. The groups will closely closely collaborate to iteratively refine the atlas it is gradually realized.

Figure 2. Key tissues and organs initially analyzed by the consortium.

Using innovative, production-grade technologies, HuBMAP Tissue Mapping Centers (TMC) will generate data for single cell, 3D maps of various human tissues. In parallel, Transformative Technology Development (TTD) projects, and later Rapid Technology Implementation projects will refine assays and analysis tools on a largely distinct set of human tissues. Samples from individuals of both sexes and across different ages will be studied. The range of tissues will be expanded throughout the program.

Figure 3. Map generation and assembly across cellular and spatial scales.

HuBMAP aims to produce an atlas in which users can refer to a histologic slide from a specific part of an organ and in any given cell understand its contents on multiple 'omic levels--genomic, epigenomic, transcriptomic, proteomic, and/or metabolomic. To achieve these ends, centers will apply a combination of imaging, ‘omics and mass spectrometry techniques to specimens collected in a reproducible manner from specific sites in the body. These data will be then be integrated to arrive at at high-resolution, high-content 3D map for any given tissue. To ensure inter-individual differences will not be confounded with collection heterogeneity, a a robust

common coordinate framework will be developed.

Figure 1

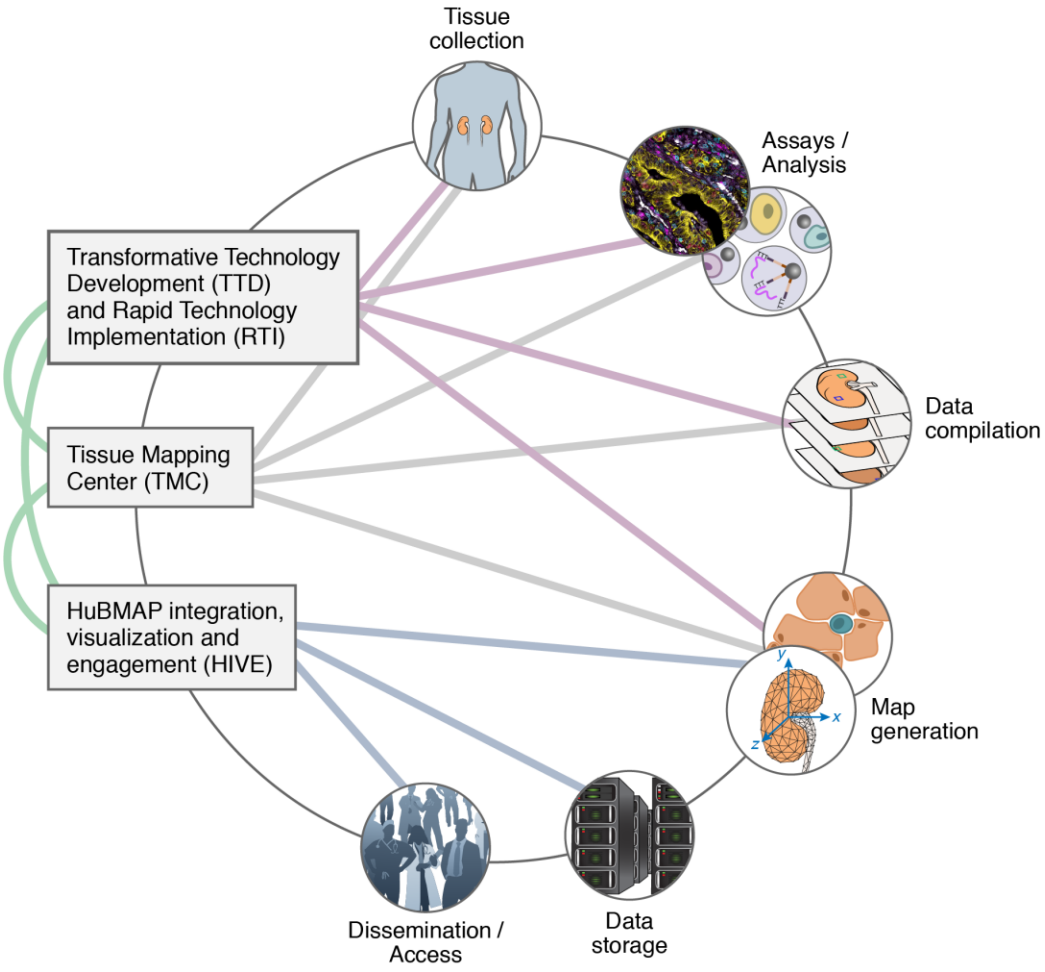


Figure 2

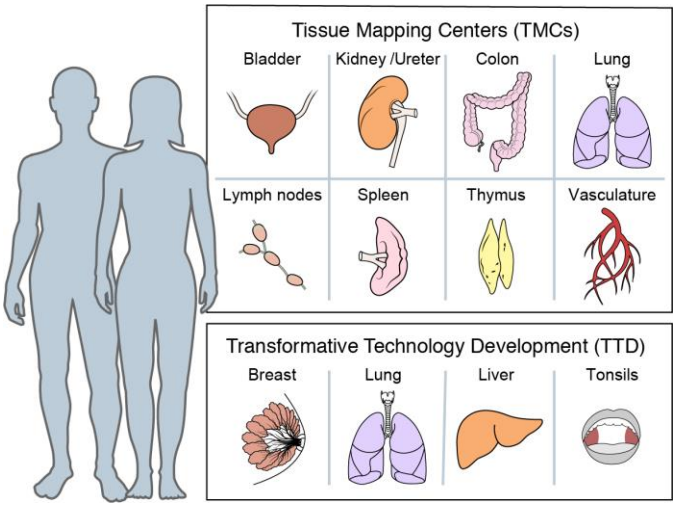
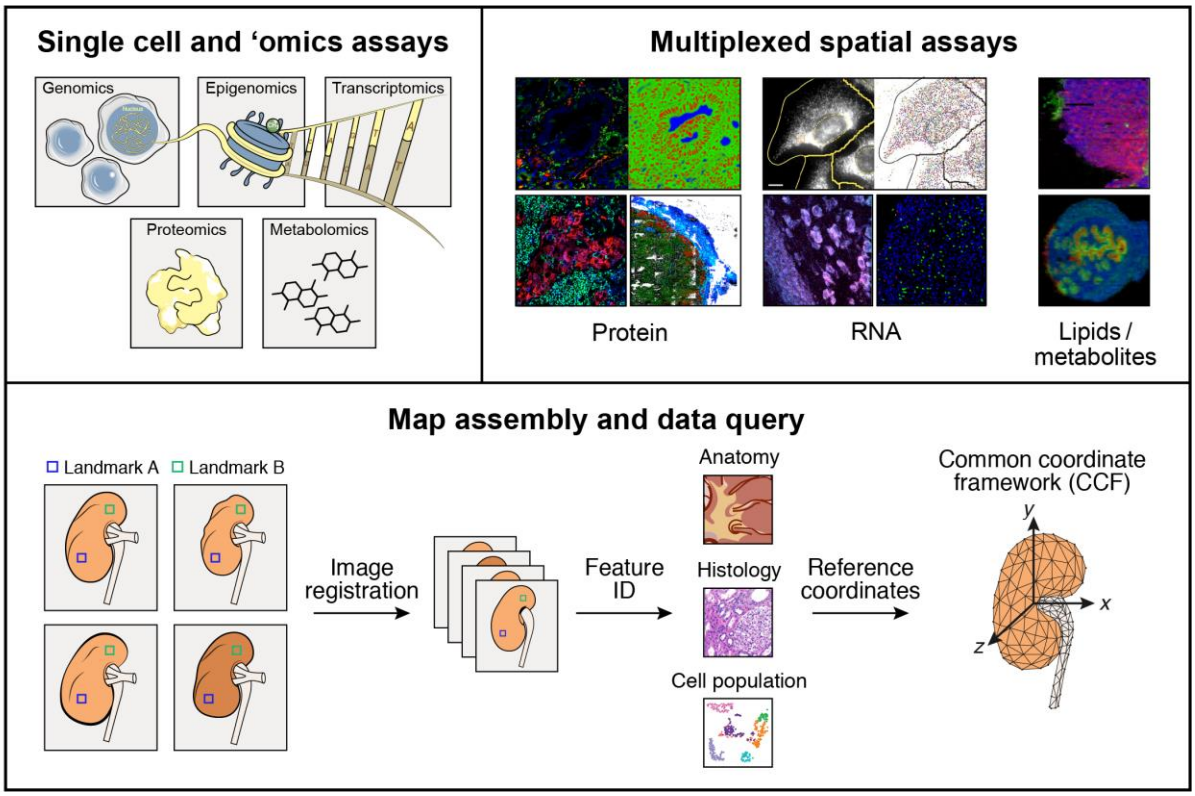


Figure 3


Single cell and 'omics assays
Genomics
Epigenomics
Transcriptomics
Proteomics
Metabolomics
Multiplexed spatial assays
Protein
RNA
Lipids / metabolites
Map assembly and data query
Landmark A
Landmark B
Image registration
Feature ID
Anatomy
Histology
Cell population
Reference coordinates
Common coordinate framework (CCF)
y
x
z