

The Commitment of the Human Cell Atlas to Humanity

Human life is diverse. We are made of trillions of cells and share a basic body plan, but each of us is unique because of our own genetic endowment, environmental exposures and life-experiences. We know that some of these factors can impact our cells and are important to consider when we get sick, but we don't always know which are critical, how they make us vulnerable to specific diseases, or what the best course of treatment might be. The impact on our cells may also influence our wellness, without actually making us sick; we need to understand these factors as well.

The Human Cell Atlas (HCA) is a global partnership of scientists who are actively working to create an exhaustive guidebook of the types and properties of all human cells. This guidebook, although only partially complete now, is already beginning to help us understand, diagnose, monitor, and treat health and disease. The HCA seeks to understand how the cells in our bodies work together to form our organs and carry out specific physiological functions essential to life. HCA scientists are creating a view of healthy cells and their behaviours in individuals, representing various ages, genders and life-styles, from as many populations as possible from a diversity of environments. A view obtained from a diverse set of people will help us better understand human biology, as well as the contributions of our environments and genetics to the ways in which our cells work to keep us well.

Far too much of our healthcare research has been conducted without considering the impacts of variations in our genetic make-up, environmental exposures or life-experiences. This has led to medical breakthroughs that are seldom equally beneficial to all. Some previous scientific studies have been extractive and exploitative, failing to sufficiently consider the priorities of, or benefits to, contributing communities. We are striving to make the HCA socially and scientifically distinctive by open participation: through commitment to global engagement; by creating an active outreach and education programme to build local capability; and by forging and fostering local collaborative partnerships so that we can all benefit from diverse community perspectives and shared approaches to facing complex challenges in human biology. To us, this is mission critical. We need your help in our attempt to get it right.

We hope that the efforts of the HCA will eventually allow us to understand whether every person afflicted with a disease – for example, liver cancer – has common biological or cellular changes in the affected organ. We believe that the understanding being gained from this work will result in better management and care of individual patients. To achieve this ultimate goal of understanding both health and disease, it is important to catalogue how much biological and cellular variation is present in an organ among healthy individuals from diverse backgrounds. Unless we understand the nature and extent of variation among healthy

persons, it will not be possible to detect changes that may lead to the disease being studied. For example, blood and urine tests could be misleading if they are not calibrated to the natural range of variation of the relevant population group. This is the reason why we are focusing on healthy variation in HCA. The guidebook that we are creating in the HCA will be the first step to accomplishing the ultimate goal of providing better care to individual patients, which we believe is immensely beneficial to all of humanity.

Until recently, because of technical limitations, it has not been possible to assess comprehensively our fundamental building blocks – individual cells – in health and disease. With the technologies that were available earlier, we have obtained comprehensive information on the properties of only aggregates of cells, but not on individual cells. Recent scientific and technological advances have enabled us to obtain information on single cells. However, we do not yet have an adequate understanding of the cell types that make up the different tissues of our body and how their relative abundance varies among a diverse set of individuals. We hope that the single-cell information that HCA is generating will continue to yield conclusions that provide better management of health to enhance quality of life by pinpointing precisely where things go wrong and how.

What are we studying in the Human Cell Atlas?

We are studying cellular variation in healthy individuals. There are many different cell types in the human body. We do not know all of the cell types that compose each organ and their relative proportions. And, even in the same organ, the proportions of cell types can vary between, for example, males and females, children and adults, non-smokers and smokers, Bantu speakers of Africa and Austro-Asiatic speakers of India, etc. We need to understand when and how genetic, environmental, and experiential factors of healthy persons contribute to their cellular variation. This requires collecting cells from various organs from diverse cohorts of people. The HCA has started to collect cells and study the biological characteristics of each collected cell, for example, which genes are expressed and at what level. This information is enabling us to identify the types of cells and their proportions in various organs of the human body. We are also able to estimate the nature and extent of variation that exists across individuals at a very high resolution, at the level of single cells. Examination of the variation in relation to ethnicity, demographic parameters and environmental exposures is enabling us to infer the possible causes of variation. HCA investigators are reaching out globally to various communities to undertake projects driven by local scientists. HCA hopes that this global information will enable us to better understand the circumstances that are unique to a community, or commonly seen around the world. Information generated from local projects driven by local priorities and local scientists, and assisted by the information provided by the global collective, will generate conclusions that will be beneficial to local communities.

How do we recruit individuals who self-identify with a specific community/ethnicity into this study?

The HCA will not perform 'helicopter science.' HCA membership is open to scientists globally who are committed to adhere to its values. We are reaching out far and wide to scientists in a community/ethnicity – a group of people who share a common cultural and/or biological background – to become active, contributing members of the HCA. HCA leadership is committed to supporting, and working with, local scientists to help facilitate this work; for example, helping to provide adequate information about HCA to the general members of the community to gain their confidence, to train local scientists in methods of single-cell analyses so they can lead research in this area, and to obtain approvals from the local research ethics committees to undertake HCA studies.

To facilitate engagement of local communities, the HCA encourages local scientists to become members of the HCA and get actively involved in HCA activities. Together, the HCA consortium reaches out to community leaders, persons engaged in scientific research, community medical practitioners, teachers, and other similar groups of people. We help explain the intent of the HCA in detail. In doing so, we emphasize the purpose of HCA and the information that the HCA hopes to collect from persons in the community. We work with local scientists to plan sample collection and discuss what analyses to carry out and how. We make sure that each participant, whether engaged scientifically or as a sample donor, and the community, understands how any information generated will be used and shared, what safeguards exist to maintain privacy, and how results will be communicated back to individual participants and summarized to the community.

To be clear, we believe that the HCA research should be led by local scientists or individuals who wish to be part of the HCA and should include members of the specific communities and ethnic groups on whom studies are undertaken. The HCA leadership is committed to the success of these individuals through active partnership. The nature of biological material to be collected is determined by the local scientific partners and in consultation with the community. The nature of information to be generated, stored, analysed and shared with the community, and the modalities of conduct of these activities are also determined in consultation with local scientists, members of the community, ethics committees and other similar groups of the community. Moreover, we obtain a written consent to participate from each participant, but only after the participant is completely satisfied with our explanations and with our answers to their and the community's questions about the study. We wholeheartedly believe that it is essential to do so. The HCA is committed to working with members of each community to make sure that information is collected and shared in an appropriate manner with participating individuals and/or the groups that comprise their identity.

Sample collection

The nature of samples collected in a HCA project depends on the specific objectives of the project. For example, HCA investigators who are studying the process of infection by SARS-CoV-2 coronavirus are collecting nasal and throat swabs. Those who are studying the cellular processes associated with childbirth are collecting cord blood and placenta. Those who are studying chronic liver disease are collecting liver tissues. Those who study the colon would collect colonic biopsies and materials from surgery. After obtaining written informed consent, samples are collected from a study participant by experts with adequate safeguards in place, making sure to minimize risks and pain associated with sample collection. Collected samples are stored in vials labeled with numbers, but with no personal identifiers.

Sample analysis

The collected samples are processed so that information can be collected from single cells. This process is performed under the strict supervision of a well-trained scientist and with great care to minimize wastage of collected samples. At this time, all identifying information is removed prior to DNA/RNA analysis of each cell. HCA recommends that, to the extent possible, sample analysis be done in a laboratory close to the community collection site by local scientists. The HCA helps facilitate training to support this. Efforts are made to keep the sample-processing laboratories open to visits by study participants or community members. Scientists provide explanations to such visitors of the various stages of sample analysis.

Data storage, analysis and sharing of results

Data generated from the experiments are stored in databases of principal investigators of the study and in publicly-accessible global databases for advancement of science, following strict legal and ethical standards. No personal identifying information is kept in these databases. The data comprise those that are collected from each participant, such as age at the time of collection, gender, information on how the cells were collected, and the primary data generated in the laboratory, such as levels of expression of genes in single cells. Depending on the study, some general information about the study participant's health (e.g., whether the participant has high blood pressure or has ever been infected with malaria) and environment (e.g., whether the participant lives in a city or near a humid, forested area, or whether the participant typically cooks with gas, charcoal, wood, or another fuel source) might also be recorded. Altogether, such ancillary information helps us understand the different factors that might influence the behaviour of genes in our cells. Although some genetic information collected in the RNA and DNA sequences could be used to predict family relationships between donors, best privacy and security practices are used by HCA investigators to maintain the security of the databases and the responsible use of the data by investigators. These data are analysed using statistical and other bioinformatic methods. HCA encourages and supports training and engagement of local HCA investigators or other persons from the community to participate equitably in data analysis. After appropriate analyses are completed and

conclusions drawn, the conclusions are conveyed to each study participant if the participant wishes to know, or shared with the community in a summary form through local scientists. The HCA strongly advocates that community meetings be organized by local researchers and summary results be explained to the participating communities. Subsequently, the ~~summary~~ data, stripped of all personal identifiers, are placed on a globally-accessible, public-domain database for the advancement of science.

Use of data and the potential for discrimination

Some biological characteristics are observed to be similar within family groups, and among communities with similar ancestries. Regrettably, these similarities and differences have sometimes been grossly abused for racial profiling and discrimination. Race is a social construct, not a biological one. HCA strongly opposes the use of biological differences for social discrimination. Instead, all efforts are made in HCA to explain the scientific meaning of the data and to answer questions from individuals and communities on how information related to genetic differences might be used to improve health and well-being of the community. Being perceived and treated differently based on actual or presumed genomic makeup violates fundamental human rights and freedoms. The HCA is aware that misinterpretation of observed genetic patterns could lead to genetic discrimination – a source of exclusion and stigmatization. The HCA considers racial profiling or any form of discrimination to be against the spirit of the consortium, the purpose of the data collection, and the ethical conduct expected to be followed by the consortium members.