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iPSCs for personalized medicine: what will it take for Africa?

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Induced pluripotent stem cells (iPSCs) are cutting edge biotechnology that may revolutionize medicine, and creating iPSCs from ethnically diverse individuals would generate valuable therapeutic and drug development tools. However, challenges must be overcome in creating the infrastructure and scientific capacity needed to pursue innovative, leapfrogging strategies to make iPSCs available in Africa.

Why iPSCs and Africa?

While participating in a recent workshop on 'Personalized Stem Cell Medicine', I was struck by the potential of the field to impact human health by providing a renewable resource of cells that can potentially be used for drug discovery and regenerative therapies. I was left asking the question 'What would it take to have this technology widely available in Africa?' The workshop discussion was focused on applying stem cells to the practice of medicine in the United States, but the differences in research culture and resources makes it difficult to simply apply the same methods to the African continent. In this article, I discuss the factors that make iPSCs a particularly attractive technology for medical applications in Africa and lay out many of the fundamental changes that need to occur before iPSC technology can be widely available (Box 1). Not only are there social considerations for research design and community outreach but also practical issues of laboratory and protocol design that need to be addressed.

Genetic diversity in African populations: implications for disease and drug response

Sub-Saharan Africa (SSA) has the highest burden in the world for infectious diseases, and chronic diseases have rapidly taken hold. Consequently, health status in Africa is in dire straits. SSA has the highest prevalence of HIV/AIDS on the planet, where at least 22.9 million people live with the disease [1]. The World Health Organization (WHO) predicts that in the next decade SSA will have the greatest increase in death rate from cardiovascular disease, cancer, respiratory diseases, and type 2 diabetes mellitus [1]. Moreover, many African countries will be unable to meet the Millennium Development Goal (MDG) targets for infant and maternal mortality; currently, 1 in 8 children die before age five [1]. To further complicate these dire statistics, social factors such as brain drain, poor scientific capacity, and poor infrastructure make it challenging for the continent to address its own scientific and medical problems [2].

As the birthplace of modern humans, the population of Africa has a very rich cultural, linguistic, ethnic, and genetic diversity, exemplified by the presence of more than 2000 ethno-linguistic groups [3]. As a result of the age and demographic history of the population, the genetic structure of African populations is unique compared with other populations worldwide. Africans have more haplotypes, shorter linkage disequilibrium (LD) blocks, and more varied patterns of LD [3]. Understanding these features are essential for reconstructing human evolution, comprehending the expansion of populations out of Africa, as well as fine mapping complex disease [3]. SSA has the greatest structural genetic diversity, including single nucleotide polymorphisms (SNPs), when compared with non-African populations, as well the highest within population genetic diversity [3,4]. For example, a comparison of sequencing data between two Bushmen from South Africa showed more differences between those two genomes than the average number of differences between genomes from individuals of Asian and European (Caucasian) origin [4].

Genetic variation worldwide has very practical implications for personalized medicine. Information such as individual genetic variation, family history, and environmental and lifestyle factors are used to personalize medical approaches for preventing, diagnosing, or treating disease. Despite the wealth of information African genomes have to offer, these populations remain understudied. Only a few African populations, such as the Yoruba, have genome information included in projects such as HapMap or 1000 genomes. A Yoruba genome has been fully sequenced [5] and is used to represent the 'African' genome; however, a recent study shows that the extent of genetic diversity among African genomes, even those within close geographic proximity, implies that there is no representative African genome [4].

African genomic diversity has important implications for dissecting the genetic risk of both complex and infectious diseases. Different populations have varied risk and disease prevalence, and genetic factors contribute to both [3]. For example, sickle cell disease is largely limited to populations of African heritage [3], and the CCR5-Δ32 deletion mutation, which protects against HIV infection when homozygous in an individual genome and delays

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Box 1. What it will take for Africa

- Widespread collection of suitable biospecimens, including blood, hair, and skin.
- Leapfrogging innovations in laboratory technology – such as room temperature storage and low volume microfluidic technologies – to reduce the resources required for implementation.
- Cooperation between nations to establish public-oriented biorepositories with representation of diverse genetic backgrounds.
- Strong collaborations should be fostered on both sides of the ocean between Africa and other continents to aid capacity building, technology transfer, and advocacy for African biomedical research needs.

death from AIDS when heterozygous, is prevalent in Caucasian, but not African, populations [3,5].

iPSCs for dissecting complex disease mechanisms and studying genetics

Current models for dissecting the genetics underlying complex diseases rely on genome wide association studies (GWAS) performed on human samples from populations with or without the disease of interest [3,6]. Typically, these GWAS involve sample collections of blood, from which DNA is extracted for SNP genotyping analysis. Although numerous risk variants have been determined using such samples, DNA alone is static and finite in nature and does not allow phenotypic or functional studies, such as gene expression profiling. However, a renewable source of DNA for future studies can be created by Epstein–Barr virus (EBV) transformation of the blood lymphocytes to generate renewable lymphoblastoid cell lines (LCLs) that can continuously undergo mitotic cell divisions. LCLs allow phenotypic studies on the genetic backgrounds of individuals or populations from which the primary blood source was obtained [6]. Despite the utility of LCLs for numerous genetic studies, there are several limitations, including the fact that they do not represent a natural cell type in the body. Furthermore, LCLs cannot be differentiated into other tissue types and are not useful for future therapeutic purposes. iPSCs could be a more powerful, dynamic, and renewable tool for dissecting complex diseases and accelerating translational research and personalized medicine. iPSCs are generally derived by reprogramming somatic cells to pluripotency by forced expression of transcription factors involved in embryonic development [7]. iPSCs are uniquely capable of both self-renewal and pluripotency. Self-renewal is the ability to proliferate indefinitely in culture by mitosis while retaining normal properties, whereas pluripotency is the ability to be converted into all types of specialized cells within the body while maintaining normal properties. This technology has opened up new avenues to study human development, disease risk, and pharmacogenomics and has the potential to be used for transplantation and to treat debilitating diseases such as neurological diseases and HIV/AIDS. In addition, iPSCs can be created from diverse sample types, including, but not limited to, blood [8], skin [7,9], and the outer root sheath of hair [10]. In fact, even LCLs can be reprogrammed into EBV-free cell lines that have the normal properties of iPSCs, potentially expanding the current utility of LCLs [6]. LCLs as a source of iPSCs is of great interest because well-characterized LCL biorepository samples are available from genetically diverse populations, such as the HapMap collections in which African populations are represented, providing a potentially comprehensive catalog of cells lines representing human genetic variation [3,6].

The ability to generate iPSCs from adult somatic tissues circumvents many of the ethical concerns involved in deriving human embryonic stem cells (hESCs), which involves the destruction of embryos. We propose that innovative iPSCs techniques should be implemented in Africa within the larger context of existing disease priorities and emerging science and development initiatives on the continent [2] (Table 1). Furthermore, studies using iPSCs should focus on translation towards personalized medicine and therapy development. The first iPSCs have been generated from an African individual, of Yoruba ethnicity [11], thus leading the way for larger studies on the iPSC-based genomics of African populations.

Creating large-scale biorepositories on the African continent will enable personalized medicine

New initiatives are underway on the African continent to create large-scale biorepositories that can function to collect, process, store, and catalog biological samples, all of which will be an important part of building greater scientific capacity [2]. These facilities will harmonize sample collection efforts, support large-scale genomic studies, and be a centralized point for disseminating samples for collaborative research. African biorepositories will be a critical piece of infrastructure that will enable high-throughput approaches for biomarker discovery, drug development, and personalized medicine, as well as provide potential samples for regenerative therapies. We suggest that the generation of renewable cell lines via iPSCs should be included in the agenda for biorepositories on the continent. Moreover, sample collection efforts should include cell types from which iPSCs can be generated, such as the outer root sheath of hair, skin, adult blood, as well as umbilical cord blood (UCB) and associated tissue. Samples such as outer root sheath of hair are especially desirable because they can be easily obtained by non-medical personnel, which facilitates collection in low-resource settings. Sources such as UCB are typically disposed of at birth as medical waste but can be easily obtained without risk to the donors and are a rich source of cell types for reprogramming [12]. In addition, there are many current applications of UCB for regenerative therapy that do not require reprogramming, including treatments for leukemia and thalassemia. Furthermore, UCB collection efforts could stimulate further access to patients for interventions that support maternal, fetal, and infant health. Given that Africa is falling behind on MDG targets, innovative interventions are desirable [1].

There are currently only three UCB banks in Africa, all of which are private cord blood banks located in South Africa. There is a need for other African countries to create UCB banks and save these valuable specimens that not only represent African genomes but could also be useful for both prospective cohort studies and therapeutic purposes. Public UCB banks that are for community benefit rather