Highlighting Human Diversity in *In Vitro* Preclinical Models

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Significant failure rates in drug development have stimulated a paradigm shift in current approaches to preclinical disease models. Drug attrition reached an unprecedented high of 95% in 2021. Only 50% of the drugs in Clinical Phase I progressed to Phase II; only 36% of those in Phase II succeeded to Phase III; and only 59% of the Phase III attained regulatory approval and market entry[1]. These high failure rates have been attributed to lack of animal model translatability to fully represent the human condition. In particular, animals are inbred and maintained in standardized conditions and therefore, do not account for genetic and ethnic diversity of the human population at large[1]. These challenges often lead to unnoticed drug safety and efficacy issues in certain subpopulations.

To address these challenges, our attention has been directed to the advancement of microphysiological systems (MPS), a subtype of *in vitro* preclinical models that strive to replicate human biology by culturing patient-derived cells, tissues, and organoids in a physiologically relevant and anatomically accurate manner[2, 3]. This methodology could facilitate the technology's gradual progression toward a precision medicine approach in disease modeling and drug discovery. Precision medicine not only accounts for the individual variability in genes, environment, and lifestyle of each person, but when combined with technology and medicine, can identify individual patient's responses to disease and treatments[4, 5]. This initiative is further supported by the FDA Modernization Act 2.0, a bill that was introduced to authorize alternatives to animal testing and permit usage of human preclinical models in the initial stages of drug screenings[1].

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Despite the monumental strides that the scientific community has achieved in developing more clinically relevant and predictive *in vitro* preclinical models, we have yet to fully represent the population at large. For this, we must be cognizant of interindividual differences and disparities in disease onset, progression, and treatment response correlated with patient demographics including age, race/ethnicity, sex, and body mass index.

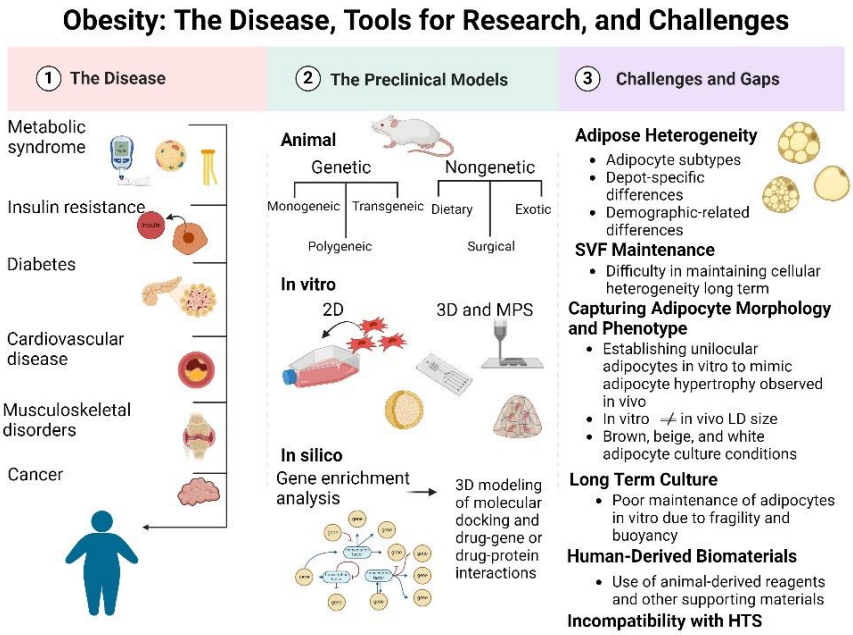

Figure 1. Current preclinical models and challenges associated with the development of clinically relevant obesity *in vitro* model for disease modeling and drug discovery. Created with Biorender.com.

In the context of metabolic diseases, and with predictions of obesity impacting approximately 50% of the Untied States' adult population in 2023, there is a dire need to establish more humanized, predictive models that account for interspecies variability and a three-dimensional (3D) microenvironment [3, 6, 7] (**Figure 1**). Addressing this issue proves to be quite complex, as it is well documented that individuals differ in adipose tissue functionality on the basis of age, race/ethnicity, sex, and BMI. Aging results in drastic changes in adipose morphology, which is reflected in changes in the quantity and distribution of adipose tissue throughout the body[8-10]. Zhang et al. demonstrated that abdominal obesity was the most important risk factor for metabolic syndrome for non-Hispanic whites and persisted in most of the age categories. In Mexican Americans and Chinese, increased triglyceride levels in the blood was the most associated component with metabolic disorder. In contrast, non-Hispanic blacks 50-70 years old presented elevated blood glucose levels after fasting [10]. These examples reiterate the need to generate more comprehensive, physiologically relevant models that capture the adipose heterogeneity.

Obatala Sciences' is poised to address these challenges. **Obatala Sciences'** donor inventory is composed of around 10,000 cryopreserved vials of the stromal vascular fraction (SVF) and adipose-derived stromal/stem cells (ASCs) from consenting, deidentified patients. The generation of large biobanks and repositories of patient-derived samples, and subsequent integration of these samples into preclinical models, enhances the validity and predictive power. As presented in **Figure 2**, our inventory addresses the needs of the precision medicine goalpost as we continue to collect and make patient-derived cells readily available to the scientific community. An extensive overview of Obatala Sciences' products and services can be found at [Obatala Sciences | Organ-on-a-Chip for Research](#).

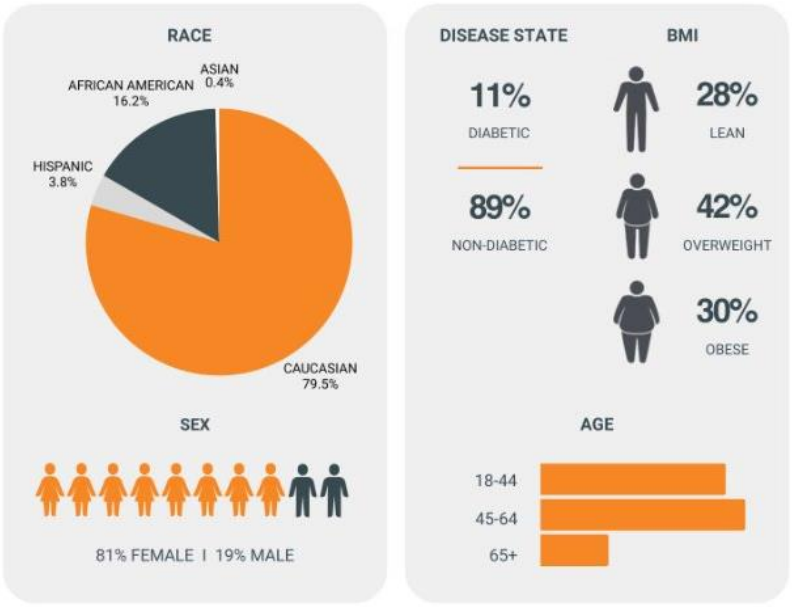

Figure 2. Obatala Sciences' donor inventory highlights diversity in patient race and ethnicity, sex, age, body mass index, and diabetic comorbidity.

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