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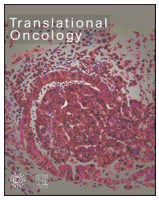

A new dawn: Vitalising translational oncology research in Africa with the help of advanced cell culture models

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ABSTRACT

The advent of in vitro models such as induced pluripotent stem cells (iPSC) and patient derived (disease) organoids is supporting the development of population and patient specific model systems reflecting human physiology and disease. However, there remains a significant underrepresentation of non-European, especially African model systems. The development of such models should be enthusiastically embraced by Sub-Saharan African countries (SSAC) and middle-income countries (LIMC) to direct their own research focused on the improvement of health of their own populations at a sustainable cost within their respective funding environments. Great care needs to be taken to develop national frameworks to direct, sustainably fund and support such efforts in a way that maximises the output of such models for the investment required. Here, we highlight how advanced culture models can play a role in vitalising local healthcare research by focusing on locally relevant health care questions using appropriate cell culture models. We also provide a potential national platform example that could maximise such output at the lowest cost. This framework presents an opportunity for SSAC and LMIC to base their healthcare research on locally relevant models to ensure that developed health care initiatives and interventions are best suited for the populations they serve and thus represent a reset in global health care research at large.

Introduction

If one were to use the representation in genome wide association studies (GWAS) as a proxy for global population distribution, one would be mistaken to think that almost 95 % of the global population is European, 4 % Asian, and only 0.2 % African (Fig. 1A). More concerning is the fact that there has not been a significant shift in these numbers in the last 15 years regardless of efforts such as The Human Hereditary and Health in Africa (H3Africa) initiative that supported African genomics research from 2012–2022 (Fig. 1B) [1]. A specific illustration of such underrepresentation can be seen in breast cancer research. Of the 75 breast cancer cell lines available in the American Tissue Culture Collection (ATCC) only 11 are from African donors. Moreover, 65 000 articles have been published using just the two most popular breast cancer cell lines (MCF-7 and MDA-MB-231) while only 7000 articles in total have been published related to breast cancer in African women. The same is true for human pluripotent stem cell (hPSC) repositories, such as hPSCreg, where 73 % of all hPSC lines are of European ancestry and only 3 % have an African genetic background [2]. Thus, it is clear that non-European populations, but Africans in particular, are severely underrepresented with regards to both genomic studies and in vitro model systems even though the continent hosts approximately 14 % of the global population. Moreover, only 1 % of all published research and

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Glossary

ALTBio	African Liver Tissue Biorepository
ATCC	American type culture collection
AU	African Union
BME	Basal membrane extract
ECM	Extracellular matrix
GDP	Gross domestic product
GMP	Good manufacturing practice
GWAS	Genome wide association studies
HIV	Human immunodeficiency virus
hPSC	Human pluripotent stem cells
hPSCreg	Human pluripotent stem cell registry
HUB	Hubrecht Organoid Technology
iPSC	induced pluripotent stem cells
LMIC	Low and middle income country
NAFLD	Non-alcoholic fatty liver disease
NRF	National Research Foundation
OECD	Organisation for Econimic Co-operation and Development
PDO	patient derived organoid
PSA	prostate specific antigene
SADC	Southern African Development Community
SKA	Square kilometre array
SSAC	Sub-Saharan African countries
SAMRC	South African Medical Research Council
TIA	Technology Innovation Agency

only 10 % of published health research contains at least one African scholar [3].

Why does such underrepresentation persist?

The reasons for this disparity in research coverage between the Global North and Africa are multifactorial. A recent article highlights that although North-South research partnerships offer immense benefits, there is a risk that the collaboration can be unequal [4]. In 2007 >77 % of research expenditure occurred in developed countries and only 23 % in developing countries even though these countries make up 70 % of the world population [4]. Research still is executed by a small core of countries while most other countries operate in the periphery. The reasons for such underrepresentation are also related to a dearth of African scholars in this field due to factors such as a lack of mentorship, medical research training institutions, funding and infrastructure, and a deferral to a handful of well-known scholars [3]. Large pan-African efforts such as H3Africa have delivered on empowering a group of researchers and introducing new technology into Africa but they lack the focused attention to specific Africa-centric health problems and a related holistic approach to improve such a condition.

Why is African health research and specifically locally relevant health research important?

Genetic diversity and the presence of many potentially pathogenic variants in African genomes suggest there may be much to learn from studying this diverse population [5]. A recent paper highlights the genetic diversity found in Africa which emphasises the importance of studying African populations. Whole genome sequencing of 12 indigenous populations from across Africa revealed that African and non-African populations separated first, as expected. However, between African groups divergence already started 150 000 years ago. Interestingly, this study identified 5.3 million previously unreported variants across the genome. Of 154 previously predicted pathogenic or likely pathogenic variants, 44 had frequencies much higher than that expected of pathogenic variants, suggesting that analysis of African populations can assist in correcting false conclusions from data collected in the European ancestry population. Simultaneously, specific population linked variants such as an IL6 variant common in the Fulani population, plays a role in resistance to malaria and presents a target for improved malaria treatment suggesting that the global population could benefit from African based knowledge [6].

While genomic analysis can point to alterations with potential effects on protein function and physiology, functional analyses need to be performed to confirm and further elucidate these within the physiological background of the relevant population. However, a lack of models representing African populations makes this very difficult. The direct consequence of this is that most medical practice in African countries is based on results obtained from study participants or cell lines of European origin.

Developing locally relevant disease models for research and treatment development offers an important avenue for African scholars to pursue locally relevant health issues and improve our standing in the international health research field while making strides to improve the health of our own population. In this article we will advocate for such an approach using newly developed in vitro models in South Africa as a representative example for other Sub-Saharan African countries (SSAC)

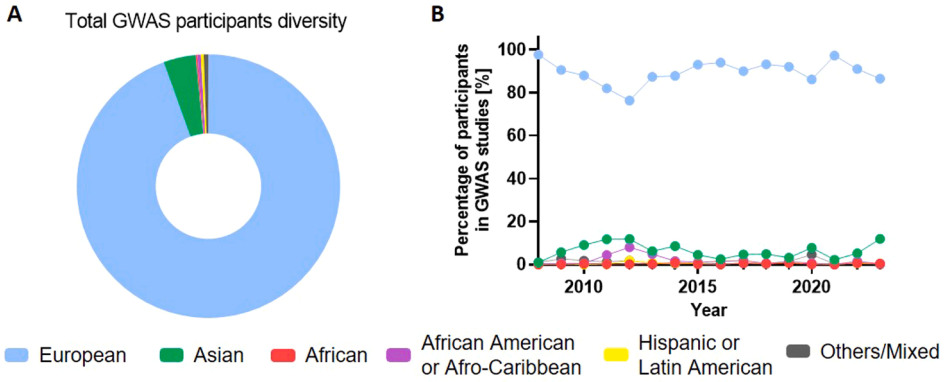

Fig. 1. Ethnic diversity in GWAS studies.
(A) Ethnicity of GWAS participants as reported in GWAS diversity monitor on 19.11.2024. (B) Percentage of GWAS participants from 2008 until 2023. Data are obtained from GWAS diversity monitor [1]. Blue – European, green – Asian, red – African, purple – African American or Afro-Caribbean, yellow – Hispanic or Latin American, grey – Others/Mixed

and low and middle income countries (LMIC) countries. This approach should harness technology, funding, and resources currently available locally but also assist in establishing equitable and profitable partnerships with researchers in the Global North. This internal focus on self-reliance is important in the face of shifting priorities of large funder countries such as the USA.

Biological determinants are a factor driving health disparities in South Africa

It is important to acknowledge that biological and genetic differences between population groups can play a role in certain diseases including disease presentation, treatment responses, and adverse effects. For instance, the COVID19 pandemic highlighted that such disparities in disease outcome exist between different population groups [7]. While for some diseases such disparities are heavily influenced by socio-economic factors, not all disease outcome disparities can be explained by such factors alone (review for cancer: [8]) suggesting that biological, physiological, and genetic factors do account for some of these differences. Examples of such disparities exist throughout medicine. For instance, cutaneous melanoma is 10 times more prevalent in white South Africans compared to black South Africans with the superficial spreading subtype being most common while black South Africans commonly present with the acral lentiginous subtype rarely seen in white patients [9]. Breast cancer prevalence is significantly lower among South African black women compared to white women, but it presents mostly before menopause while in white women it is predominantly diagnosed postmenopausal (Fig. 2) [10]. These characteristics have little influence from socio-economic background, cultural, educational or health access differences. Similarly, prostate specific antigen (PSA) levels in men with prostate cancer are more commonly elevated above 20 ug/l in South African black men (83.2 %) when compared to African American men [11]. Such a difference can be attributed to the genetic background of these populations with South African men mainly originating from the Southern Bantu ethnolinguistic group while African American men have West African and coastal Central African ancestry along with significant admixture of different groups.

Therefore, the genetic differences observed between Africans and non-Africans and between different African groups need to be further explored to determine the impact such differences may have on the physiology of the patient and the disease. Advanced cell culture models are a suitable tool to investigate diverse population groups, as they reflect the genetic diversity of the individuals from which the tissue or cell material are derived.

Advanced cell culture models for African medical research

The advent of advanced cell culture models such as iPSCs, 3D cell culture, and patient derived organoid cultures along with the focus on disparities in disease outcome, have raised the importance of genetically and physiologically representative models. Many countries, including South Africa, now actively seek locally relevant answers to clinically important questions and therefore want to use investigation platforms and models that represent their population. Such studies need to move beyond genetic studies such as GWAS to investigate functional outcomes of genetic differences. Thus, advanced cell culture models represent both a new beginning for many countries such as South Africa and a broadening of the application of research outputs for established research-intensive countries represented by the Global North. As such, advanced cell culture models representing local populations may represent a golden opportunity for many LMIC researchers including South African researchers to produce value, develop relevant models, and attract international collaboration and funding, even though limitations exist within their research environment.

Advanced cell culture models

Historically, preclinical models consisted of 2D cell lines which were derived from patient material through continuous passaging until the emergence of a hyper proliferating, homogenous cell population, or of in vivo animal models including small mammals such as mice and rats. Cell lines were the systems of choice due to their accessibility, low cost, scalability, and the availability of established protocols and standardised reagents [12,13]. However, their predictive value to in vivo physiology is limited by a lack of complexity and 3D tissue structure as well as racial and gender disparities. Additionally, cell lines are grown in unlimited nutrient and growth factor conditions with access to near atmosphere-like levels of oxygen which limits their clinical relevance and translation. It is well appreciated that while such cell lines have enriched our understanding of health and disease [14,15] and have underpinned the development of numerous drugs, they are far removed from the human in vivo situation [16]. Animal models on the other side are costly, time consuming, and too often fail to predict results obtained in human trials [17–19]. As a result, many promising pre-clinical phase drugs failed to show efficacy in humans or led to life-threatening toxicity. This discrepancy can be explained by differences in anatomical layout, biological barriers, receptor expression and immune response. Additionally, animals host divergent microorganisms, have different pathological mechanisms and are mostly inbred. This does not

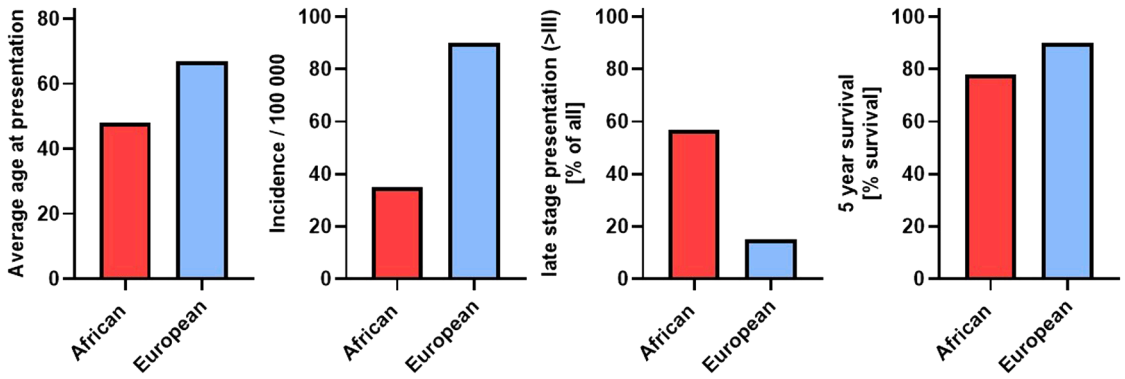

Fig. 2. Disease disparities in breast cancer between South African women with African or European ancestries.
The single graphs show the average age at presentation, the incidence of breast cancer per 100 000 women, the percentage of late stage presentation which is defined as stage III and IV, and the five year survival rate between different population groups in South Africa. The data were obtained from the [10]. Red – African, blue – European

reflect the genetic and ethnic diversity of humans and therefore is not ideal to pick up drug safety and efficacy issues only affecting certain subpopulations in humans [20]. This leads to drug failure as well as the risk of missing effective drugs in the pre-clinical phase. Moreover, about 50 % of drugs that are currently in the development phase are biologicals (including antibodies, siRNA, viral gene vectors and others) that are human specific and therefore need to be developed and tested in human based model systems [21]. It is estimated that the global pharma industry could generate over $24 billion per year through increased research and development if applying advanced cell culture models in drug development [22]. However, it is quite difficult to precisely estimate the cost-effectiveness of these models as not only the costs for harmful and ineffective drugs must be considered, but also an estimate of potentially effective drugs that never became drug candidates. On the contrary, there are different examples that prove that data from organoid models translates accurately to patients [23,24]. The response to radiation and/or chemotherapy of a panel of 80 colorectal cancer organoids was compared to the actual patients' outcome and revealed an accuracy of 84 %, a sensitivity of 78 %, and a specificity of 92 % [25]. In another study the positive predictive value of metastatic colorectal organoids was 88 % and the negative predictive value was 100 % [26]. Moreover, initial preclinical testing of lead compounds can now be done on a large range of diverse tumour models. For instance, a screen of over 500 bispecific antibodies against WNT integration site and receptor tyrosine kinase targets was conducted on a biobank of colorectal cancer and identified MCLA-158 as the most effective antibody with regards to tumour growth inhibition [27]. Taken together advanced cell culture models reflect patient responses and disease state more accurately than traditional animal models, are less time consuming, and more cost effective. Advanced cell culture models incorporate multiple features that approximate or mimic the in vivo environment and cellular context it represents. Such models include but are not limited to co-culture systems, spheroid models, patient-derived organoids, assembloids, iPSC-derived (differentiating) systems, multicellular transwell models, microphysiological systems, scaffold-based cultures, microfluidic devices, organ-on-chip technology, and bioprinted models [28]. The advantages of these models are the inclusion of complex multicellular structures, tissue-specific architectures and functions, the presence of extracellular matrix (ECM) proteins, cell-to-cell and cell-to-ECM interactions, appropriately defined nutritional media, or simulated tissue perfusion, all resulting in a more natural-like cell morphology and physiology. Therefore, multi-cellular responses, early tissue and disease development, spatiotemporal interactions, multicellular and multi-organ responses and tissue structures can be investigated using such models. Cells in advanced cell culture models frequently present with physiologically representative morphology, improved function, maturity, and metabolism compared to cell lines, as well as differentiation and gene expression patterns closely representing the human in vivo situation [28]. Hence, recreating an environment in which cells can execute their physiological function and behaviour as in tissues, allows for the investigation of underlying mechanisms of human development and diseases [29]. Compared to animal models, advanced cell culture models circumvent the challenges of interspecies comparisons and the ethical concerns of animal use [30,31].

To represent local populations, the most suitable models can be established from donor/patient material from the respective populations and used to generate iPSC and patient PDOs. Microphysiological systems also present a powerful tool to create highly individualised model systems, enabling the study of physiological processes such as barrier functions, recruitment of immune cells, fluid shear stress and pharmacokinetics [21]. However, a prerequisite for microphysiological systems to develop their full potential is the combination of multiple individual model systems on a chip and integrate them through a fluidic flow. This requires extensive biotechnical engineering expertise at a higher cost compared to iPSC or PDO. Overall, microphysiological systems are powerful and important in elucidating the understanding of human physiology in health and disease but are not the focus in a sub-Saharan African context, yet. iPSC are the basis for many advanced cell culture models as they can be expanded almost indefinitely and can be differentiated into most somatic cell types [32]. Therefore, iPSC derived model systems provide an opportunity to study human development in health and disease, e.g. cancer initiation [33], organ development [34,35], psychiatric disorders [36], neurodegenerative diseases [37], and viral infections [38,39]. By differentiating specific cell types, it is possible to gain knowledge about molecular processes involved in their development and the physiological processes supporting their function. As iPSC can be genetically engineered, they can be used to generate isogenic human disease models, providing the opportunity to investigate disease mechanisms [40]. In general, iPSC-based models vary in their complexity ranging from monocultures to more complex organotypic cultures like iPSC-derived organoids. As mentioned earlier, iPSCs are not limited in their numbers, hence yielding scalable quantities of differentiated cells that can be utilised in drug development [41]. Based on their human origin, iPSC-based models can be used to uncover population-specific molecular mechanisms of drug action. Contextualised models incorporating the genetics of specific populations such as black Africans in South Africa in iPSC-based studies [42] may permit the discovery of specific adverse effect mechanisms or resistance mechanisms missed by traditional animal models or currently utilised iPSC lines of European ancestry. Detailed descriptions of the generation and quality control of iPSC have been widely reported and can be found in several reviews [43–45].

PDO are advanced cell culture models consisting of primary cells isolated from human participants cultured in a defined medium in 3D to preserve and support the tissue specific stem cells. The ability of PDO culture to retain stem cells and recapitulate tumour or tissue architecture has allowed their use as a preferred model system to investigate for instance intestinal physiology [46], metabolism [47], tumour heterogeneity [48], epithelial-to-mesenchymal transition [49], tumour microenvironment [50], the phenotypic effect of sequential mutations [51], and the stem cell niche [52]. Despite limitations such as a lack of vasculature, organised extracellular matrix, and immune cells, organoid cultures have been successfully employed in drug efficacy screens [53], translational nanomedicine screening [14] and therapeutic antibody discovery studies [27]. Organoid cultures have also been envisioned to be drivers of functional personalised medicine [54] as they can be used as patient explants for drug sensitivity testing. The promise of these models in cancer precision medicine is exemplified by the clinical validity for patient-derived tumour organoids as predictive models for treatment response [55]. Moreover, patient-derived breast cancer organoids have been used to investigate intratumour heterogeneity and its relation to treatment resistance [56]. PDO based organoid biobanks have been created and used to investigate the link between genetics and drug response as a prelude to clinical trials [57].

Additionally, they are used in CRISPR screens to identify actionable proteins of interest in disease [58], and to create specialised knock-out cell lines to target specific disease-related mutations [59]. As patient-derived model systems, organoids present themselves as a valuable tool for population-specific medical research which can combine genomics, proteomics, and cellular biology in pursuit of the understanding of disease biology in underserved populations. In general, PDOs are generated in close collaboration with hospitals. First, informed consent of the patient is obtained (see text box 1 for further ethical considerations). During surgery or biopsy a piece of the removed

Table 1
Current research groups in South Africa with advanced cell culture model expertise. Group leader or PI name, location, and a short description of model types employed are included.

Current research groups with advanced models	Type of model available	Reference
African Liver Tissue Biorepository (ALTBio) Consortium Group leader: C. Masimirembwa	Isolation of primary hepatocytes and subcellular fractions of African origin for drug metabolism, pharmacokinetics, and pharmacogenetics research	[61]
Bioengineering and Integrated Genomics Group (CSIR) Group leader: Janine Scholefield, Tracey Hurrell, Jay Naidoo	Human induced pluripotent stem cells from individuals of Black African ancestry in South Africa with a focus on hepatic and neuronal modelling	[42]
Cancer biology group (University of Pretoria) Group leader: Iman van den Bout	PDO models of breast cancer from black African patients with genomic analysis of 50 cancer genes, morphological characterisation, and response to three common chemotherapies PDO models of pancreatic adenocarcinoma with response to common chemotherapy	
Human-Based New Approach Methodologies for Biomedical Research (North-West University) Group leader: Chrisna Gouws	Dynamic spheroid cancer models, including for small cell lung cancer, non-small cell lung cancer, melanoma, hepatocarcinoma, triple-negative breast cancer, glioblastoma Several include drug-resistant versions. Developing dorsal forebrain cortical organoid models with African genetics for drug delivery studies. 3D Bioprinting (Extrusion- and Digital Light-based)	[62,63]
Integrative Cancer Biology Research Laboratory (University of the Witwatersrand) Group leader: Mandeep Kaur	PDO models of colorectal cancer with morphological characterisation, co-culturing with T cells, chemotherapy response, and cholesterol level.	
Stem Cell Modelling Laboratory (University of Cape Town) Group Leader: Mubeen Goolam	Cerebral organoid models from African iPSCs to study brain development and disease pathogenesis. Neural tube organoid models from African iPSCs to investigate neural tube defects. Stem-cell-based embryo models to investigate early cell fate decisions	[64]
Human Metabolomics (North-West University) Group leader: Roan Louw	Human induced pluripotent stem cells to model mitochondrial complex I deficiency	[65]
Cancer Research Group (Stellenbosch University) Group leader: Anna-Mart Engelbrecht	PDO models of cervical cancer	

tissue will be used to generate the PDO. Briefly, the resected tissue will be cut into smaller pieces with a scalpel and thereafter the cells of interest will be freed from the surrounding connective tissue by digesting it with collagenase. This will be followed by a red blood cell lysis. The tumour cells will be plated in domes of extracellular matrix proteins e.g. BME or Matrigel that are allowed to set. Afterwards, the wells will be filled with tissue specific media. A comprehensive overview of methods to establish PDOs and how they are applied in oncology research has been published [60].

In South Africa, some iPSC-based models and patient-derived organoid models have already been established (Table 1). The involved groups may act as useful accelerators to establish a unified, national framework that promotes the development of more advanced cell culture models within South Africa.

Limitations of advanced cell culture models in SSAC

While advanced cell culture models are a promising prospect for developing research capacity to better serve currently underserved populations, several limitations exist that need to be considered, particularly in the South African research environment. These limitations can be divided into model-based limitations and resource-based limitations.

All advanced cell culture models face the dual challenge of reproducibility and relevance to the in vivo physiology. Similar to animal models, patient derived models such as organoids and iPSC derived models contain inherent variability due to inter participant variability not seen in simple, homogenous, 2D cell line cultures. Such inter participant variability can be minimised through experimental repetition and by making use of multiple donors [66]. To assure standardisation and reproducibility of model generation and downstream biological assays across different laboratories, good cell and tissue culture practices for the establishment, maintenance, and use of advanced cell culture models needs to be established and implemented [28]. This is especially important if biological differences are investigated in geographically distant laboratories. Unlike cell lines that have travelled the world with some cell lines being almost ubiquitous in cell biology laboratories globally, it is unlikely that iPSC and organoid lines will spread so readily. Thus, standardisation to allow comparisons across models established by different groups is important for comparative analysis.

Besides the model-based limitations discussed above it is also important to consider resource limitations affecting research infrastructure, investments, and expertise in a South African, SSAC and LMIC context. The complexity of generating advanced cell culture models results in a significant increase in cost over 2D cell line cultures [67]. The increased costs are due to long establishment times, the need for specialised media, the use of extracellular matrix mixes, and the need for equipment to maintain and exploit some advanced cell culture models. Projects involving such models can quickly become too expensive for single research groups with local funding only, as national funding remains limited. In 2007, the African Union (AU) set a target for its member countries to spend at least 1 % of their national GDP on research and development. Yet, 18 years later none of the AU member states have achieved this with an average spend on research and development of only 0.42 %. This compares poorly with the global average of 1.7 % [68]. This lack of funding leads many researchers to seek funding outside of Africa, mostly in the Global North, which will be focused on health issues related to their populations not directly overlapping with the needs of African patients. A dearth of national investment also means there are very few sustainable funding tracks that can support the long-term development of models and their implementation in broader research programs. Additionally, compared to the Global North, access to well-trained, expert scientists is a challenge. This lack of human capital is illustrated by the small percentage of the South African population with a PhD (0.2 %) compared to other LMIC countries such as India (3.4 %) or the OECD (1.3 %) [69]. The sophistication of advanced cell culture models means that they are labour intensive, requiring highly skilled personnel to master these culture techniques, as well as expertise in advanced analysis techniques including live cell imaging, single cell genetic analysis, and proteomic analysis. As a result, very few researchers in South Africa are currently able to generate and utilise such models. There is thus a need for training in advanced cell culture models and downstream applications to increase the levels of local

expertise in these specialised techniques and for the import of scarce skills through attracting foreign researchers and through collaborations based on training of local scientists to strengthen local capacity. Therefore, the establishment of a national framework to enhance advanced cell culture models in a South African context must include an extensive training programme comprising different levels to be sustainable.

The above limitations have resulted in a lack of genetic diversity within available advanced cell culture models and severe underrepresentation of non-European genetics in these models. This is particularly striking when looking at the genetic representation of African populations in the iPSC lines used. It has been >15 years since the generation of the first human iPSC [70] and the publication of the first paper describing an organoid model [71]. However, African iPSC and organoid lines have yet to emerge in the global science environment. To change this, it is of utmost importance that collaborative activities must be initiated in South Africa.

It is clear that advanced cell culture models offer important advantages despite its current limitations. But their development and utilisation within resource restricted countries such as South Africa needs to be rationally approached in a different way than in countries with a well-funded research environment and strong research capacity.

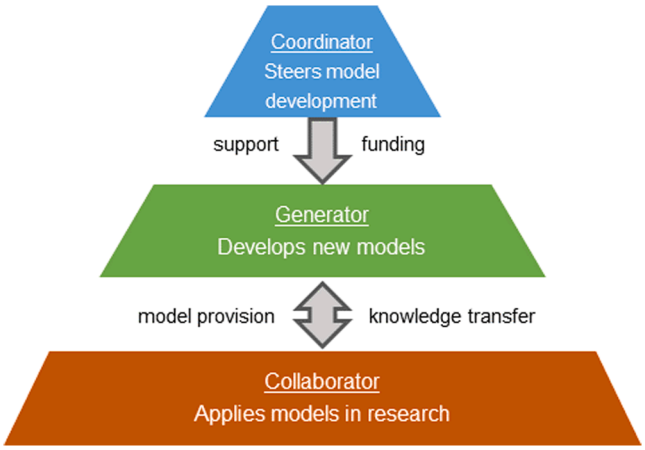

Fig. 3. Depiction of the proposed national framework.
Overview of a proposed national framework for the optimization of advanced cell culture support and output in an African research environment showing three tiers with the coordinator steering, the generator developing new models, and collaborator tier making use of such models.

An approach to implement advanced cell culture models in South Africa

It is important to define the general purpose of model systems that will be developed in South Africa since iPSC and organoid models can be used for preclinical investigations but also for clinical approaches such as transplantations and personalised medicine applications. The framework we propose here is focused on preclinical investigations [72]. Clinical use of these models would require a much larger investment in GMP practices, clinical trials etc. which we believe is currently out of reach of local economic, clinical and scientific capacity. With the limitations discussed above in mind, it is necessary to develop a rational plan to leverage these technologies in a cost-effective way to be available to as many researchers as possible within the country. This means that model development should be conducted in a small group of specialised laboratories while use of such models is enabled among many research groups. As such, a national framework for advanced cell culture models ought to contain the following elements to be successful: (i) source secure, sustainable funding streams for the development of appropriate models, (ii) consolidate and expand infrastructure and human capital needed for model development, (iii) ensure capacity among national research groups to take advantage of developed models, (iv) encourage and support the establishment of strong, long term collaborations between national and international research groups to leverage developed models. We propose a tiered, national organisational system to address all the components needed for the successful development and utilisation of these models (Fig. 3).

As mentioned above, it is essential to coordinate the generation of models between the research groups nationally, as this avoids unnecessary duplication, saving large amounts of funds. Moreover, many research groups do not have the expertise to successfully generate models nor the access to patient material needed. A steering body or coordinator with national reach is essential for the coordination of efforts to develop new models. The coordinator would constitute the first tier of the national organisational framework (Fig. 3). Many countries including SSAC countries like South Africa have national science bodies constituted by government with a national budget for the development of science and research. For instance, South Africa has the National Research Foundation (NRF), and the South African Medical Research Council (SAMRC), both agencies with broad science and innovation aims as well as the Department of Science and Innovation (DSI) through their Technology Innovation Agency (TIA). These agencies have a track record in coordinating national efforts. For instance, the NRF coordinates and funds the South African Radio Astronomy Observatory which operates the Meerkat radio telescope as part of the international square kilometre array (SKA) telescope. This project is a great example of concentrating expertise through sustained funding and providing coordination while leveraging international collaboration to attract larger funding streams. The DSI through TIA meanwhile coordinates the Distributed Platform in Omics (Diplomics) which is a national effort to support the development of infrastructure, equipment, and human capital in all Omics platforms in South Africa. This platform is available for all national researchers. In fact, Diplomics acts as a particularly good blueprint for a national framework for model development and application. In other countries, like Japan and Europe, a multicentre strategy has been developed [72]. However, this model relies too much on individual centres being able to not only develop models but also utilise these. Moreover, it supposes that adequate human capital is available at each centre to make effective use of such models. We believe that in South Africa as in many LMIC countries this may not be the case and hence propose a somewhat more centralised approach.

Like the Diplomics network, the coordinator will support a small number of groups with proven track records in model generation and initially support these groups to standardise model conception and generation including storage, quality control, protocol development, and distribution. The coordinator will be able to identify and prioritise disease areas, provide funding while also improving existing ethical and legal guidelines to support the ethical use of advanced cell culture models (See text box for further explanation). In parallel, the coordinator will embark on a national education campaign among researchers to raise awareness of the existence of these models and to support the training of researchers to exploit these models effectively. Lastly, the coordinator will administrate the grant process to fund research groups that will use these models to address specific research questions.

Part of the coordinator's role will be to identify and prioritise areas of research that will derive significant benefit from the establishment of appropriate population specific model systems. Such benefits can include immediate or large impact on disease diagnosis and treatment, the identification and development of new drugs, and the investigation

of diseases prevalent in South Africa. The coordinator can limit its focus on diseases with a clear genetic or biological disparity component specifically negatively affecting the South African population as is illustrated for breast cancer in this article.

The coordinator will open a call to fund the establishment and characterisation of a disease model which will be open to the generator tier. The generator tier will consist of a limited group of national laboratories that have established expertise in model generation such as iPSC lines or PDO lines. Generator groups will be able to compete for model generation funding from the coordinator which will fund medium term projects to establish, annotate, and validate models. Model development can take place solely nationally or in collaboration with international experts. Besides model generation, funding will also be provided by the coordinator for the expansion of local expertise and knowledge transfer from international collaborators to South African partners. This can be part of the collaborator tier funding programs and would also cover the storage and delivery of the newly established and validated model systems to collaborators. Within the generator tier, strong intra-tier collaboration needs to be in place to standardise isolation, establishment and expansion methods and documentation for generating the different models. This will ensure inter-laboratory reproducibility and allow for standardised conditions across large geographic distances as well as promoting a collaborative development of new models. Standardisation is especially important for these models as many are derived from patient material and thus inherently display heterogeneity. Quality control measures need to be implemented and enforced before models are allowed to be entered into a national biobank system. Such quality control methods would include at least partial genomic characterisation, and histological and functional characterisation where applicable as suggested by the European Bank for Pluripotent Stem Cells [73].

Currently, in South Africa a few generator groups are present that have established iPSC lines, advanced in vitro models, and patient derived organoids (Table 1). It is important that commercial research and development, as well as the pharmaceutical industry at large are not ignored in this endeavour. While exploitation remains a significant fear in Africa with regards to genetic material of humans, plants and animals, it is imperative that research conducted in Africa also assists in drawing investment into these countries. Advanced cell culture models provide a possibility of attracting significant funding from industry for the use of such models. This should be encouraged within a carefully developed, ethical, and economic plan to keep Africans as the custodians of their own genetic and biological resources.

Following successful model development, the coordinator will open a call for funding to make use of the model, e.g. to investigate specific disease aspects, to develop new treatments or test current treatments against the disease, or to develop diagnostic strategies. Such funding can be applied for by single collaborator groups or as multi-group collaborations including the generator groups. The collaborator tier itself will consist of local research groups at academic institutions with expertise in the disease for which the coordinator has issued a request for models. Collaborators will also include international research groups who wish to pursue research making use of the models generated. As best practice they should always be a part of a collaboration including at least one South African research group and have a strong commitment towards knowledge transfer and investment in training and development of local South African research capacity. Collaborators do not need to be experts or have experience in advance culture models but should have the infrastructure needed to maintain the cell culture model they require for their study. Collaborator groups will have access to the models developed by the generator group. Such access can follow a model such as the ATCC with no purchasing cost calculated. Lastly, collaborators will be encouraged to include in their applications generator groups as collaborators so that knowledge transfer also occurs between these two tiers.

Other approaches to model establishment and distribution on a large scale have been successfully executed by the HUB (Hubrecht Organoid Technology) a centralised organoid model generator spun off from the lab of Hans Clevers and the Cancer Organoid program at the Wellcome Sanger Institute. Both these entities are independently run organisation depending on multiple funding streams although the Sanger Institute obtains most of its funding from the Wellcome Trust. While their approach has some similarities with what we propose here, their funding model is different and their model development wider ranging and more prospective. We propose a research focus driven model development plan supported by research aims that will deliver maximum impact rather than prospective model development such as is pursued by these two entities.

To illustrate how the proposed national framework and the tier system approach could work to efficiently address research questions, we have developed two examples with direct relevance to the local medical research environment that include currently available models in South Africa.

Case study 1: Improving breast cancer outcomes among the South African female population

As discussed above, breast cancer disparities related to genetic or physiological differences between different population groups in South Africa exist (Fig. 2) and significantly and negatively affect both the quality of life and disease outcomes of black South African women while also exerting an economic toll on the country's health system. To improve disease survival several facets of cancer diagnosis and treatment need to be addressed. These include improving early diagnosis and patient stratification, and investigating drug resistance and adverse effects. It is thus clear that a multimodal research strategy is needed to significantly improve breast cancer outcome in black South African women. With the above aims in mind, the coordinator will develop a research program that focuses on patient stratification for improved treatment response, the development of new treatment regimes, and identification of markers predictive of liver toxicity related to adverse effects.

PDOs have been established exhibiting the histological complexity and genetic heterogeneity of the related tumour [74] and reviewed in [75]). These have been used as tools for functional precision medicine, for the discovery of drug resistance, and the investigation of physiological processes related to cancer progression such as metastasis [75, 76]. Generating population-specific patient-derived tumour organoids would serve to deconvolve unique genetic and environmental aspects of breast cancer aetiology and pathogenesis but also treatment efficacy in black South African patients.

While cancer biology has some unique characteristics in black African populations, there are also differences in liver dependent metabolic capacity between different population groups. For instance, the CYP2D6×17 variant is non-functional, limiting the metabolism of tamoxifen to endoxifen. It is common in some African populations with a frequency of up to 34 % which may have a significant effect on treatment success and cytotoxic liver accumulation in this group [77,78]. Thus, establishing population specific liver models for drug efficacy and adverse drug reaction testing would greatly enhance the development of effective treatments and can be paired with breast PDO models. Such a model has been established to investigate oxaliplatin induced liver injury to identify markers with liver damage predictive value [79].

Once the model approach and research plan has been established, the coordinator will create a budget for the program and the relevant

generator groups will establish the breast cancer models. Funding will be available to generate the models, verify them, and establish a repository of these lines. Simultaneously, the coordinator will engage with the collaborator tier to raise awareness of the research program and the development of the models. This will be followed by a research funding call to attract proposals for the use of developed models to pursue the stated aims of the research program. This will be open to all research groups and can include international collaborators. In this case a funding call will be made to perform drug response screens and to develop therapy response markers that can be evaluated in clinical studies. Simultaneously, genomic and proteomic data along with cell biology investigations will be funded to explore potential biological reasons for the prevalence of breast cancer in premenopausal black South African women and to identify potential risk factors. To assess the efficacy of drug metabolism and the identification of markers related to liver dependent drug resistance and adverse toxicity, the coordinator will also obtain proposals from generator groups for the establishment of a relevant liver model. Collaborator groups will make use of the liver models to perform metabolic and genomic studies to assess the efficacy of drug metabolism and identify the related genetic variations associated with differing performance which can be further developed into genomic based risk stratification tools.

Case study 2: Utility of iPSC with an African genetic background to model disease pathophysiology

The need for more representative model systems of health and disease is not only limited to cancer research but also includes other non-communicable diseases. Besides PDO, African based iPSCs can provide the basis for suitable model systems to study a variety of non-communicable diseases. Here, we provide a second case study showing how African iPSC can be utilised to model chronic liver disease.

Non-alcoholic fatty liver disease (NAFLD) is the most common disease underlying chronic liver disease and is strongly associated with comorbidities such as type 2 diabetes and dyslipidemia. However, it is also associated with HIV as it is estimated that 38 % of people living with HIV also suffer from NAFLD [80]. Despite the high burden of HIV in South Africa, little is known regarding the link between NAFLD in people living with HIV and potential risk factors in the sub-Saharan population [80–82] GWAS and candidate gene studies have identified several genetic variants associated with NAFLD. However, most studies are limited in the representation of ethnic diversity [83–85]. There is thus a rationale for the coordinator to support the development of locally relevant models to investigate the biology of NAFLD in African patients and the influence HIV.

Liver models to recapitulate the metabolic activity of the liver have been developed at an impressive pace. Moreover, human iPSC-derived models of NAFLD have been established [86] with iPSC derived liver and endothelial cells in vascularised organ-on-chip models as the latest iteration of this development [87]. To investigate NAFLD and the impact of HIV, an iPSC derived liver model embedded on a perfusion chip has been developed [88] by a local generator group in collaboration with international experts of organ-on-chip models. The use of iPSC lines of African origin would enable researchers to incorporate genetic groups with known liver specific gene variations.

Once established the coordinator will publish a grant call for proposals to make use of the liver model by collaborator groups. Included aims of the call will be genetic studies, identifying unique NAFLD markers and testing these within the model for their impact on the progression or characteristics of NAFLD. Furthermore, to assess the impact of HIV and HIV treatment on NAFLD, the models can be infected with HIV.

Ethical considerations

Ensuring benefits outweigh risks in a constricted setting such as SSA and even LMIC in general requires special attention to ethical considerations. Summarised are key points for consideration. (Adapted from answer generated by Grok [89] complete unaltered answer included as supplemental file) [90]

Informed Consent Challenge

In LMICs, obtaining informed consent can be complicated due to language barriers, low literacy rates, and cultural differences. Patients might not fully understand what donating cells for organoids/ advanced models means, especially if explanations aren't in their native language. To fix this, use clear, culturally appropriate consent forms, involve local staff for explanations, and allow verbal consent with witnesses where literacy is low [91].

Risk of Exploitation

Patients in LMICs might feel pressured to participate due to limited healthcare access, risking exploitation without fair benefits. This could mean patients don't understand they will not get direct medical benefits. To mitigate this, it is important to ensure they know the research purpose, are offered fair compensation like ancillary care, and equitable partnerships with local institutions are build and maintained [92].

Data Privacy and Security

Genetic data extracted from organoids/advanced models could be at risk in LMICs with weaker data protection laws, potentially leading to misuse. To address this issue, strong encryption, limited data access, and international standards like general data protection regulations should be used. This ensures patient information stays secure, especially given the unique identifiability of genetic data [93].

Equitable Access to Benefits

There's a danger that research benefits, like new treatments, won't reach local populations, widening global health gaps. In fact, any research including treatments that are not feasible within the local context should be discouraged or, if possible, plans should be developed for affordable access, including investments in local healthcare, while LMICs must share in outcomes whether it be technology and knowledge transfer, infrastructure building, or improved treatment localisation. This aligns with global calls for equitable data sharing in health research [94].

Quality and Safety Standards

Laboratory facilities in LMICs might not meet current global standards, affecting research reliability and safety. Any collaborations should include local laboratory upliftment to attain global standards, providing training, and following international guidelines to maintain quality [95].

Cultural and Religious Concerns

Local beliefs might be in conflict with organoid/advanced model research, especially if seen as unethical/ immoral. To understand such opinions, partners need to engage with community leaders, understand and respect their customs, and ensure research aligns with cultural values to build trust [96].

Intellectual Property and Benefit Sharing

Without fair benefit sharing, LMICs might lose out on intellectual property gains, like new drug royalties. Clear agreements for sharing benefits need to be established before any work commences, including involving local partners in decision making processes, and including technology transfer [97].

Conclusions

The research landscape of human disease biology has seen seismic changes in the last 15 years which include the development of advanced cell culture models that have created novel possibilities to advance our knowledge of many diseases and promote the development of new treatments. At the same time, there is now a clear acknowledgement that health disparities do exist between different population groups that cannot exclusively be ascribed to non-biological reasons. Furthermore, recent political developments around the world have highlighted the fact that South Africa and other LMIC countries need to invest in their own locally relevant health research instead of depending on aid from other countries. As a result, it is now possible to imagine a significant shift in medical research to move away from the one size fits all, Global North centric medical research paradigm to a more locally relevant and locally focused research environment where researchers make use of models relevant to the people they serve. To make maximum use of this opportunity, South Africa needs to develop frameworks suited to its circumstances and requirements to avoid exploitation, improve their own scientific capacity through funding and human capital development, and establish strong collaborative frameworks to leverage new technologies and models. The development of the proposed framework will leverage local funding and research capacity to optimally make use of this technology.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used xAI.Grok3 in order to compile the ethical considerations and references for these that need to be adhered to for the implementation of the proposed framework. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication. Moreover, the AI tool has been cited as per APA guidelines in-text and in the reference list.

CRediT authorship contribution statement

Stefanie Klima: Writing – original draft, Visualization, Conceptualization. **Tracey Hurrell:** Writing – original draft. **Mubeen Goolam:** Writing – original draft. **Chrisna Gouws:** Writing – original draft. **Anna-Mart Engelbrecht:** Writing – original draft. **Mandeep Kaur:** Writing – original draft. **Iman van den Bout:** Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2025.102391.

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