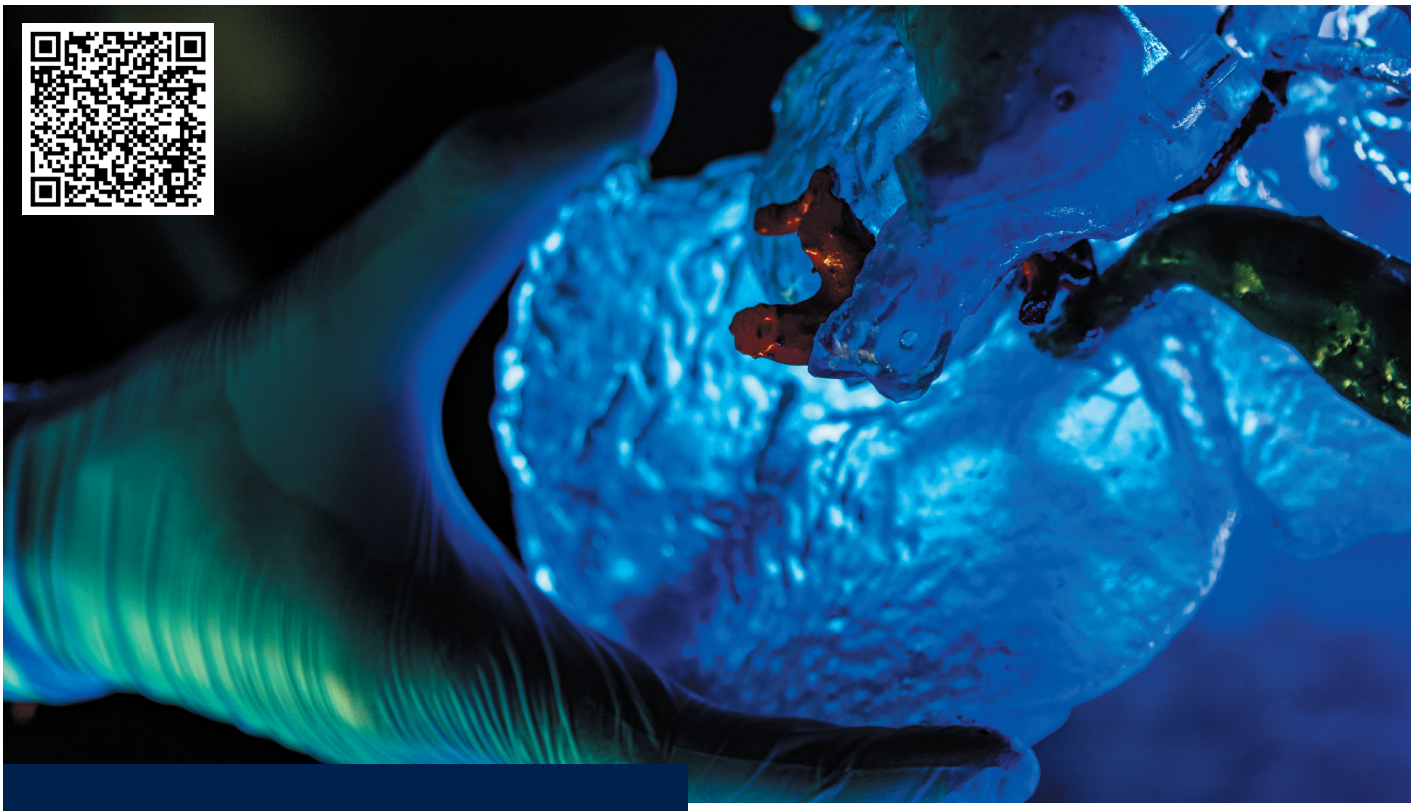
CSIR C3
collaborate.create.commercialise.



LIVER-IN-A-DISH SCREENING SERVICE: ASSESSING DRUG SAFETY IN AFRICAN POPULATIONS

A genome-engineered stem cell tool that mimics the metabolism of pharmaceuticals in genetically diverse African populations

Addressing a problem and responding to market demand

Drug regimens have not been optimised for individuals of African descent

Drug regimens have not been optimised for individuals of African descent. This is due to several converging factors, including Africa's diverse genetics, disproportionate disease burdens (and consequently a high dependency on specific drug regimens), as well as under-representation of local population groups in clinical trials. Consequently, adverse diverse drug reactions are responsible for one in 12 people being admitted to hospital in South Africa where hospital services account for approximately R125 billion in healthcare spending annually.

The South African Health Products Regulatory Authority (SAHPRA) is responsible for assessing and approving all potentially marketed drugs based on, among other key features, efficacy and safety data from clinical trials. However, understanding the magnitude of impact, which observed adverse drug reactions may have within a specific population, and evaluating previously unreported adverse drug reaction during post-marketing surveillance, is a challenge because clinical trials predominantly enrol Caucasian populations (from Europe and North America). South Africa encompasses vast genetic diversity (including within the liver drug metabolising genes, thus impacting best treatment outcomes), consequently there is limited preclinical or clinical data to support data-driven decision-making for drug approval and marketing.

Therefore, innovative tools that contribute to evidence-based decision-making making, in the context of optimised drug regimens, are needed on the continent. Such a tool must be inexpensive, reproducible, physiologically functional (i.e. act like our liver cells) and contain African-relevant genetic variants of interest.

The technology on offer

A cellular tool to mimic liver metabolism of pharmaceuticals inclusive of African genetic diversity

Combining synthetic biology tools, including induced pluripotent stem cell technology and CRISPR genome engineering – a technique in which a specific sequence of DNA can be precisely modified inside a cell – the CSIR has created a nano-scale cellular tool that mimics liver metabolism of drugs inclusive of African genetic diversity.

CSIR researchers demonstrated functionality of this bioengineered liver-in-a-dish using liquid chromatography tandem mass spectrometry, the gold standard for assessing drug metabolism. Using this method, the CSIR team was able to confirm the metabolism of the sedative drug, midazolam, in the liver-in-a-dish model as occurs within cells in the human liver. This indicates that a key phase I metabolising gene, *CYP3A4*, is functional in the CSIR-developed African liver-in-a-dish. The gene is responsible for the metabolism of 50% of the drugs on the market, including drug classes such as antidepressants, antipsychotics, antihypertensives and painkillers. The technology therefore provides a significant degree of confidence to pursue the development of the technology to a minimum viable product within the next two years.

The innovation makes it possible to understand how individuals of African descent might metabolise new drugs and to understand adverse drug reactions in diverse populations.

Value proposition and competitive advantage

Incorporating critical African genetic diversity when determining the safety and efficacy of drug regimens

The African liver-in-a-dish screening service provides several advantages over existing models in addressing the lack of data to inform optimal treatment options given the lack of representative local clinical trials.

Existing immortalised cells are predominantly cancer-derived and lack African genetic diversity. Primary human hepatocytes – the cells making up some 80% of the liver's mass – are the gold standard in cellular testing but can only be derived from ethically sourced liver biopsies and thus are a rare commodity in Africa. An induced pluripotent stem cell-derived liver holds the combined potential of being of unlimited supply and representative of African genetic diversity. Therefore, this tool offers the advantage of being easily accessible, while incorporating critical African diversity.

The value proposition lies in the convergence of having localised the necessary technologies, and access to local cellular sources which represent unique genetic liver gene mutations not found in Caucasian populations. This enables an African-centric view of drug metabolism.

Liver-in-a dish screening service value proposition. Within the scope of an African hepatic modelling platform, the CSIR-developed product is derived from African induced pluripotent stem cells.

Market opportunity

Serving markets with genetic diversity

The impact and management of adverse drug reactions in South Africa is estimated at R93 billion per annum due to increased hospitalisation and additional clinical investigations. In South Africa, the total addressable market for pharmaceutical companies is estimated at US USD2.7 million, based on an average of 140 new compounds applications to SAHPRA per annum. Notably this estimate does not include the potential of moving into the Southern African Development Community and other parts of sub-Saharan Africa, with potential to serve global populations characterised by genetic diversity.

Investment and return on investment

Investing in technology for data-driven decision-making of drug approval

Adoption of the CSIR-developed cellular tool would be advantageous for drug screening during the approval of drugs (new and approved chemical entities) developed by pharmaceutical companies seeking market entry in South Africa. The cost for the service would be covered by pharmaceutical companies, who would benefit from access to data to advance their market opportunities in other global diverse populations. Specifically, pharmaceutical companies would gain access to drug metabolism data coupled to rich genetic backgrounds that are not readily accessible in the global North and which are becoming more relevant to preclinical drug design requirements imposed by the Food and Drug Administration and European Medicines Agency. This compliance would further support African regulatory agencies and support local clinical research organisation capabilities and growth through evidence-based decision making – therefore enabling proactive drug surveillance.

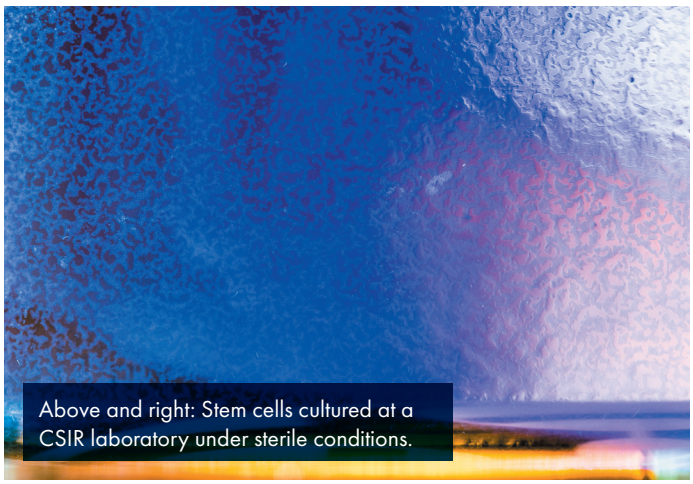
The cost to generate a minimum viable product – to create functional bioengineered liver-in-a-dish – is R25 million.

Milestones and timelines

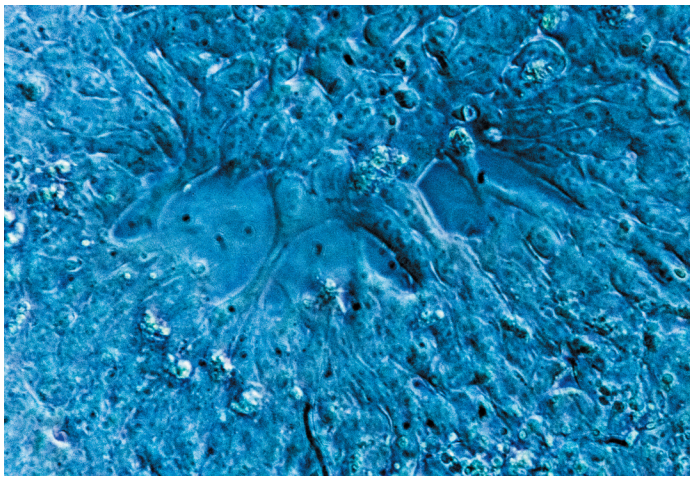
Pre-commercialisation activities for the development of a minimal viable product are estimated to take two years. In year three, the product will be validated in conjunction with a local clinical research organisation.

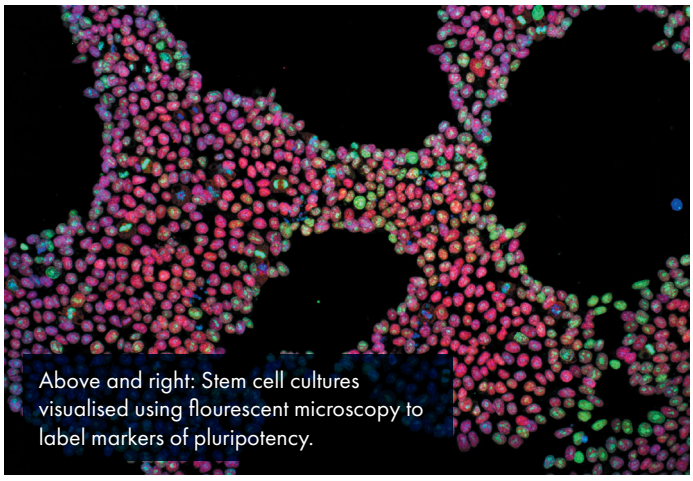
A team of experts in genome engineering and cellular modelling

The technical team comprises highly experienced postdoctoral researchers with expertise in advanced cellular modelling, stem cell technologies and genome engineering. The nano-scale cellular tool is generated within a specialised biosafety-certified tissue culture laboratory.

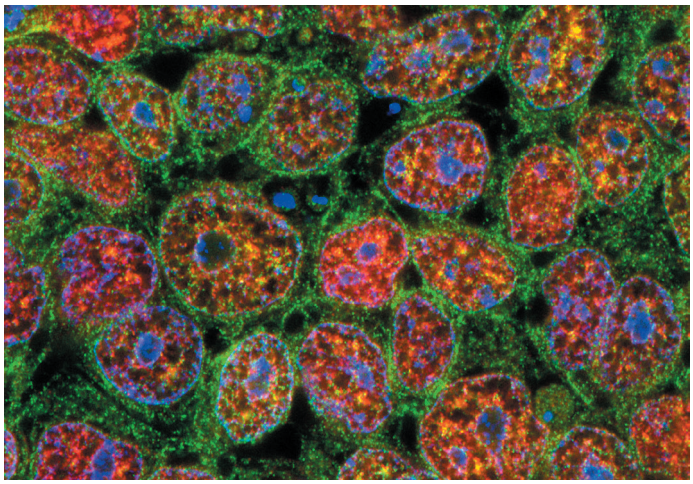


Above and right: Stem cells cultured at a CSIR laboratory under sterile conditions.

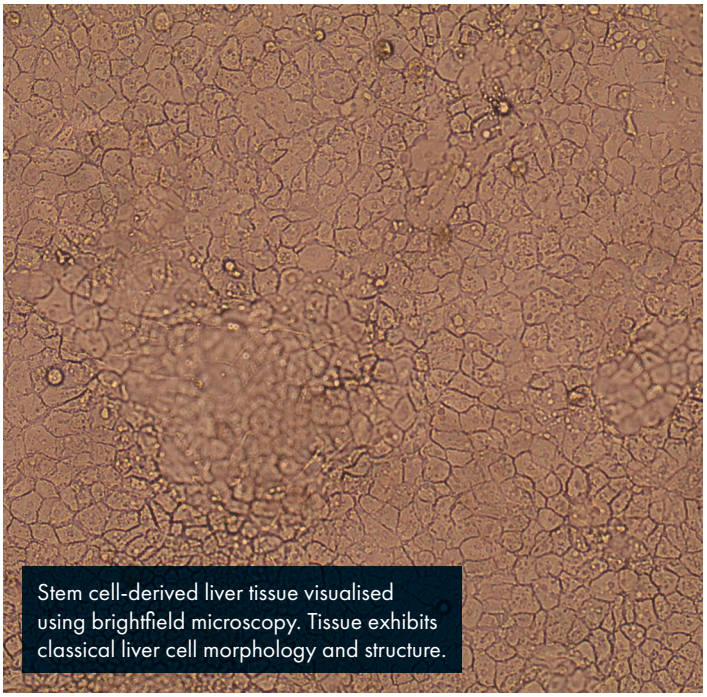




Above and right: Stem cell cultures visualised using flourescent microscopy to label markers of pluripotency.



Above and left: Stem cell-derived liver tissue generated at the CSIR using a novel method developed by the CSIR research team.



Stem cell-derived liver tissue visualised using brightfield microscopy. Tissue exhibits classical liver cell morphology and structure.

ENQUIRIES:

>> Charmaine Twala
ctwala@csir.co.za