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PATIENTS ON ANTIRETROVIRALS TO BENEFIT FROM A NEW-GENERATION DIAGNOSTIC KIT FOR EARLY DETECTION OF ACUTE KIDNEY INJURY

A kit for the early detection of kidney injury

Addressing a problem and fulfilling a market demand

Dated assay technology and a lack of accurate acute kidney injury diagnostics

Acute kidney injury presents as a rapid decrease in renal function and can be caused by severe trauma, illness, surgery or chronic medication – such as the use of antiretroviral treatment.

Many assays used in disease detection were developed decades ago and their performance is lacking. This is the case with the diagnosis of kidney injury. Diagnosis is based on enzymatic tests for increased serum creatinine levels and a decline in glomerular filtration rate. But glomerular filtration rate often generates misleading results as serum creatinine levels and renal filtration are in a state of continuous homeostasis, even under normal kidney function.

A decline in glomerular filtration rate, coupled with increased blood urea nitrogen and serum creatinine levels are hallmarks of acute kidney injury; however, the rate of increase in blood urea nitrogen and serum creatinine levels does not necessarily occur in parallel to decreasing glomerular filtration rate. Serum creatinine levels are also affected by non-disease-related factors such as age, diet, muscle mass and physical activity. Another major criticism of increased serum creatinine levels as a marker for kidney function decline is that it manifests after significant kidney damage has occurred, meaning that early changes are not detected.

More recently, genetic-based diagnostic tests have been developed to guide optimal treatment, such as antiretroviral regimens. Although these can provide information on patient predisposition toward drug hypersensitivity, they add little value once patients are on a particular treatment, as the static nature of the genome does not permit continuous monitoring of the treatment as it progresses.

The technology on offer

A diagnostic for the early detection of acute kidney injury

To address the challenges outlined, CSIR researchers applied a novel approach powered by liquid chromatography-mass spectrometry-based proteome profiling to develop a diagnostic test capable of monitoring HIV/Aids patients on antiretrovirals, specifically Tenofovir disoproxil fumarate (hereafter referred to as Tenofovir), for the early onset of acute kidney injury. The research team monitored renal function using urine as the biological sample; it is non-invasive and the abundant biofluid in the form of urine is directly associated with the kidneys as the site of the disease – thus making it ideal as a prognostic indicator for acute kidney disease.

The application of machine learning to extract highly specific molecular patterns for acute kidney injury adds to the novelty of the approach. Using multiplexed protein panels (or signatures), rather than single protein molecules as has been the status quo, allows much more accurate detection of kidney damage before it becomes significant or irreversible, in addition to being able to differentiate between the various stages of kidney injury, which current clinical tests are not capable of doing efficiently. This makes it possible to address the most urgent needs regarding the diagnosis of kidney diseases: early and accurate detection, monitoring the response to therapy and predicting progression across the various stages of kidney injury.

Value proposition and competitive advantage

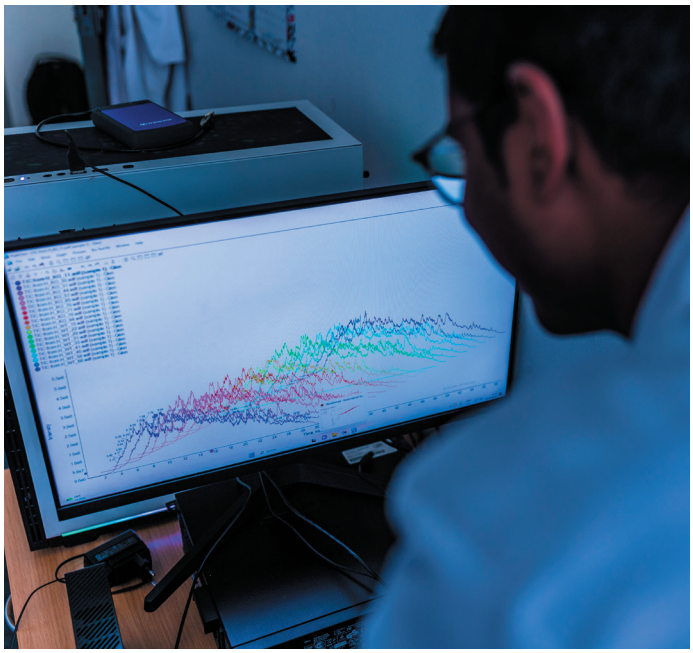
An accurate diagnostic that differentiates between different stages of kidney injury

One of the main drivers for the adoption of the novel diagnostic model(s) for acute kidney injury resulting from Tenofovir treatment, is the significantly improved performance compared to current clinical tests for kidney injury, namely serum creatinine levels and glomerular filtration rate. For example, despite >50% loss of renal function in some patients, serum creatinine levels remain normal while the glomerular filtration rate also shows only moderate specificity for renal dysfunction. In contrast, the CSIR-developed and verified multiplexed protein panel exhibits specificity and sensitivity of above 90%.

In addition, the technology makes it possible to differentiate between different stages of kidney injury. Ultimately, this leap in predictive power for Tenofovir-associated acute kidney injury detection will allow better guidance of antiretroviral regimens for improved patient health and reduce costs for the health system.

Considering the cost of dialysis and kidney replacement, the financial impact of late/inaccurate acute kidney injury detection that can be avoided by early and more accurate diagnostic tests, is enormous. In addition to this burden on the health system, many patients are not able to access the treatment as it is available in less than 10% of public hospitals in South Africa.

Protein extracts from patient urine samples being quantified using an ultraviolet-visible spectrophotometer.



Mass spectrometry raw data being inspected prior to biomarker analysis.

A high-resolution mass spectrometer suitable for in-depth proteomics analysis.

The clinical team is unaware of any intervention that adequately addresses the challenge of early and accurate detection of Tenofovir-associated acute kidney injury in HIV/Aids patients. Traditionally, renal injury detection is performed by monitoring the glomerular filtration rate, serum creatinine, blood urea nitrogen, creatinine clearance and urinary electrolytes, as well as through microscopic examination of the urine sediment and radiological studies. These, however, are insensitive and nonspecific indicators that do not allow for early detection of the disease.

The main competitive advantage is derived from the diagnostic accuracy of the multiplexed test at a specificity and selectivity of ~90%; and the ability to differentiate between the various stages of kidney damage and thus detect early proteome changes induced by the antiretroviral regime.

Market opportunity

Providing a solution for those who require constant monitoring for kidney injury when using antiretrovirals

The diagnostic kit is for Tenofovir-associated acute kidney injury and thus the serviceable market could be estimated from the number of HIV/Aids patients receiving this form of treatment. In 2020, there were approximately 23 million HIV/Aids patients on these regimes across the potential target markets of East and Southern Africa, West and Central Africa, Asia and Pacific, and Latin America. The current recommendation in South Africa is for ongoing (bi-yearly) screening to monitor for altered kidney function and potential acute kidney injury occurrence. This would result in a medium-term target market of ~30.2 million annual tests (East and Southern Africa) and an initial market of ~8 million annual tests in South Africa.

A 5% yearly growth in available market size for acute kidney injury tests in East and Southern Africa has been estimated based on new infections.

An additional indirect market for the new diagnostic kit is that of the Hepatitis B Virus, where Tenofovir-based treatment has proven to be an effective treatment option that will require a diagnostic screen to monitor kidney function. With ~248 million people worldwide estimated to be chronically infected with this virus, and with ~4.5 million new annual infections, this presents a viable new market opportunity for the acute kidney injury detection kit.

Customers include private and public sector routine testing laboratories that currently provide assays using alternate biomarkers in Africa, Latin America, Asia and the Pacific. It also includes government, donor agencies, and philanthropic organisations that support HIV/Aids treatment in several developing countries.

The proteomics laboratory where CSIR researchers started their research into biomarkers for acute kidney injury.

Business opportunity

Producing and selling acute kidney injury diagnostic kits

The initial serviceable market in South Africa is estimated at 8 million annual tests, whereas the East and Southern African market is estimated at 22.2 million annual tests. A preliminary techno-economic assessment based on the serviceable market in South Africa and the East and Southern African market over 10 years indicates a net present value of R158 million.

Investment and return on investment

Invest to capitalise on the need for an accurate acute kidney injury diagnostic kit

An investment of R55.7 million is required for clinical validation and utility, which include diagnostic kit optimisation and robustness test, external evaluation and clinical trials, upscaling (including capital costs) and registration with the South African Health Products Regulatory Authority.

Milestones and timelines

A commercial partner (licensee/start-up) is expected to turn a slight profit in year two and a notable profit in year three.

A team of proteomics experts

The research and development team has over 40 years of combined expertise in mass spectrometry-based proteomics and includes three CSIR senior researchers and one senior technician. They are highly experienced in working with high-end equipment suitable for high-throughput clinical proteomics studies.

Magnetic beads in suspension used for automated sample preparation of patient urine samples.

Furthermore, the team has secured a clinical and implementation partner, Prof. Neil Martinson of the University of the Witwatersrand, as an advisor. He is also the Chief Executive Director at the Perinatal HIV Research Unit at the Chris Hani Baragwanath Hospital and an Assistant Professor at the Johns Hopkins University Centre for TB Research.

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