Irish technology to enable metabolic disorder screening among newborns in the developing world and remote locations

Having received ISO certification for a single-step, enzyme-based test for the metabolic disorder PKU, the next challenge for Enzolve Technologies is to convert know-how into sales. ***Claire O'Connell*** *reports.*

NEWBORN SCREENING-KIT DEVELOPERS TAKE FIRST STEPS INTO THE MARKETPLACE

It's a moment that few new parents in Irish hospitals forget – when their precious newborns are whisked off to be relieved of a drop a blood from their heel.

Why the need for bloodletting at such a tender age? To screen for rare, debilitating and sometimes fatal disorders which, if diagnosed early, can be successfully managed or treated.

It's a practice repeated for millions of babies born in developed countries each year, and, increasingly, among those born in countries with a medium development index.

Now a University College Dublin-based company has developed a new approach to screening that they claim is faster, cheaper, more robust and accurate than other tests on the market.

Earlier this year, Enzolve Technologies Ltd launched their single-step enzyme-based test for the metabolic disorder PKU, which can lead to severe developmental problems if it's not diagnosed in infancy, and they now hope to add further tests to their NeoScreenPak platform.

Entering a global market where millions of heel-pricked babies are already being screened each year seems ambitious, but Enzolve's co-founders argue that their innovative product can do the job cost-effectively and reliably without the need for high-tech equipment, so it's ideal even for remote areas or developing regions.

THE SCIENCE BIT The company's technology uses enzyme engineering to make the tests quicker and cheaper than competitor products, explains Prof Paul Engel and Dr Suren Aghajanian. The idea of developing screening kits with specialist enzymes sparked about a decade ago, explains Engel, who was based in Sheffield at the time, and who later took up the chair in biochemistry at UCD.

"It grew out of the general research of my group, which is protein engineering - the idea that you can take existing natural proteins, enzymes for example, and change them to alter their function," he says. "Sometimes, it's purely to increase our understanding, but sometimes you can make them do useful things."

One of those useful things is using enzymes to screen for disorders in blood samples, explains Aghajanian, who was a post-doc in Engel's lab, and who had previous experience in Armenia developing enzyme-based screening tests for hospitals.

From that kernel grew both the company, founded in 2002, and the screening tests, which use specially engineered dehydrogenase enzymes to measure specific markers in blood samples.

Enzolve Technologies' novel newborn screening test kit for PKU.

BENEFITS Enzolve also cuts out a chemical step in the assay by using a stable diaphorase in the colorimetric reaction, meaning the test is effectively a one-step affair. Additionally, the stability of their enzymes means the kits don't need much pampering in transport or storage, notes Aghajanian, Enzolve's CEO.

"We sent samples to Brazil for testing, and they got delayed in the US for a week, but they still worked perfectly," he recalls. "And if you are doing the test in Egypt or Turkey where it is quite hot, our enzymes are very stable under those conditions too."

Cost is also an issue; because the company makes its own enzymes, the test platform can work out considerably cheaper than comparable products. And when compared to the expensive 'gold standard' of tandem mass spectrometry for newborn screening, the Enzolve system proves reliable.

"That's the beauty of this; it means you don't need sophisticated high-cost equipment – a simple plate reader can do the job very successfully, automating that will be easy and again doesn't require sophisticated techniques," says Aghajanian. "So it's easy to carry out, not only in centralised laboratories where you have high throughput of hundreds of samples per day, but also in hospitals where they have small laboratories."

Enzolve launched their CE-marked PKU test last April. So far, it has ignited interest in Georgia, Armenia, Canada, and Egypt, and the company plans to get on the road in Europe later this year. The team is also developing further tests, and, ultimately, they plan to offer screening for seven disorders in their single-platform NeoScreenPak kit. But for now, the biggest challenge is finance, according to Engel and Aghajanian.

A TEST IN TIME

PKU, or phenylketonuria, is an enzyme defect that prevents people with the disorder from metabolising the dietary amino acid phenylalanine. If undiagnosed, the condition, which affects one in around 15,000 newborns globally and up to one in 4,500 in Ireland, can lead to mental retardation, poor growth and seizures. But if it's picked up in time – and most developed countries have screening programmes – avoiding phenylalanine in the diet manages the problem, and PKU patients have gone on to earn university degrees.

The stark effects of not screening newborns for PKU were highlighted to Enzolve co-founder Prof Paul Engel when their PKU-screening kit underwent its first large-scale trials in Armenia. "We tested over 2,000 newborns, and, as it happens, out of those births there wasn't a single PKU positive. But they also used the test at a home for the mentally handicapped in Armenia, and around half of the people there were PKU positive. "It was quite dramatic," Engle says. "This is precisely what was found in the US and the UK around 50 years ago, that there were huge numbers of people who had been shut away in institutions who had not been diagnosed at birth."

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(l-r) Dr Suren Aghajanian and Professor Paul Engel, co-founders of NovaUCD-based Enzolve Technologies.

The NovaUCD-based company has received financial and business support from Enterprise Ireland and funding through InterTrade Ireland as well as considerable input from private investment, but the venture capital route has been a non-starter to date.

However, with ISO certification now under their belt, a product on the market and plenty of innovation in reserve, they hope to weather the current squeeze.

OTHER RODS IN THE FIRE Enzolve has other potential rods in the fire too, including using enzymes to make specialist chemicals for biotech and pharma. "[The diagnostic kits] use enzymes with very narrow specificity to help you identify and measure one particular biochemical. But for chemical application and synthesis, you want to go the other way - to create broad specificities and use enzymes as tools to make a whole range of compounds," says Engel, who received EI funding to pursue this strand of research.

"That [research] has been scientifically very successful, and we can now produce all sorts of modified amino acids that can be used in organic solvents, that can be used under really tough conditions and that can potentially make really good building blocks for chemistry."

The trick is to commercialise the scientific output, and an ideal scenario would see Enzolve teaming up with a specialist pharma company in need of such particular chemicals. "If we can get [Enzolve] properly established, and we have 10 or 20 employees and it's starting to branch out, that's a direction we could go," says Engel, who chairs Enzolve's board of directors. "Our test has advantages, but it needs good marketing people," adds Aghajanian. "This company has huge potential; it's just a matter of being able to use it."

ENZOLVE'S SUITE OF OTHER ENZYME-BASED TESTS

Enzolve is developing NeoScreenPak, a suite of enzyme-based tests on a single platform to screen for seven disorders in newborns:

Phenylketonuria – prevents the metabolism of the amino acid phenylalanine, which can result in mental retardation and poor growth. Early detection and dietary intervention can lead to normal development. Occurs in around one in every 15,000 newborns.

Maple Syrup Urine Disease – affects the metabolism of branched-chain amino acids, leading to neurological problems and seizures. Dietary treatment can prevent severe mental retardation and death. Occurs in around one in every 200,000 newborns.

Homocystinuria – prevents the metabolism of homocysteine, resulting in mental retardation and 75 per cent mortality by age 30. Strict dietary management can result in normal development. Occurs in around one in 68,000 newborns in Ireland.

Tyrosinemia Type I –affects tyrosine metabolism and can lead to liver or kidney failure. Pharmaceutical and dietary intervention can help protect those organs. Occurs in around one in 80,000 newborns.

Galactosaemia – an inability to metabolise galactose, found in milk sugar, which if left untreated can retard development and growth. Dietary intervention is effective. Occurs in around one in 40,000 newborns, but that increases to one in around 450 newborns in the Irish travellers' community.

Glucose-6-Phosphate Dehydrogenase Deficiency – a deficiency in an enzyme that protects red blood cells, it can lead to anaemia and neurological damage and occurs in one in around 20,000 newborns, but parts of Asia report incidences of up to one in 65. Dietary intervention can help.

Biotinidase Deficiency – an inability to access biotin in the body, which can lead to hearing and skin problems, developmental delay and seizures. A biotin supplement provides effective treatment. Occurs in one in around 60,000 newborns.