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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: PYC Therapeutics

By TIM BOREHAM

ASX code: PYC

Share price: 7.3 cents; **Shares on issue:** 3,732,867,135; **Market cap:** $272.5 million

Chief executive officer: Dr Rohan Hockings

Board: Alan Tribe (chair), Dr Hockings, Dr Michael Rosenblatt, Jason Haddock

Financials (September quarter 2023): Revenue nil, cash burn $11.7 million, cash of $21 million, quarters of available funding 1.8*****

***** Excludes an expected $16.1 million R&D tax credit

Major identifiable holders: Alan Tribe/Australian Land Holdings 33%, David Sietsma 7.7%, Malcolm McCusker 5.7%

While getting an early-stage drug to market is notoriously difficult and expensive, PYC Therapeutics Dr Rohan Hockings reckons the odds are in favor of the gene therapy house because it knows exactly what's causing the single-gene ailments it tackles.

Dr Hockings says the chances of success with such monogenic diseases are about five times greater than the usual seven to 10 percent odds of getting a phase I asset to market. Put another way, it's a 50:50 proposition.

By combining existing ribonucleic acid (RNA) drug design with its proprietary delivery platform, PYC says it is developing precision therapies for patients with genetic diseases that have no treatment options.

“The PYC program differs to others because all of the diseases are caused by a mutation to a single gene,” Dr Hockings says.

“We know exactly what is going wrong: they are missing one protein and one protein only.”

To date, PYC has focused on its lead program for the rare eye disease retinitis pigmentosa, as well as another uncommon optical disorder called autosomal dominant optic atrophy.

It also has a program for the crippling genetic childhood disorder Phelan-McDermid syndrome.

This week, PYC announced a foray into autosomal dominant polycystic kidney disease, the most prevalent monogenic disease in humans marked by extreme swelling of the organ.

“While it’s not our most advanced program, it could be extraordinary because it has the potential to reverse the disease,” Dr Hockings says.

Can we get a copy of this please

Normally, people are endowed with a copy for each gene on the two arms of a chromosome, but with the disorders in question there’s a mutation in one of the copies that inhibits protein production.

“We are increasing the gene expression to compensate for the unstable protein, by making two units of the protein from the good copy of the gene,” Dr Hockings says.

He says the industry is starting to understand that using RNA therapies to increase gene expression is a “really smart thing to do”.

Unlike with DNA gene technologies, the protein can’t be overexpressed.

“These are very dose sensitive genes: too little of it causes the disease, but too much of it causes the disease as well,” he says.

“The RNA approach is the only way to leave ultimate control of protein expression under the endogenous regulation of the cell, so the cell is saying ‘it is too much or not enough, I am going to make more of it or less of it’.”

Useful pack of geysers

A spin-off from the not-for profit medical research body Telethon Kids Institute, the Perth-based Phylogica (now PYC) listed in March 2005, having raised $5 million at 20 cents apiece in the initial public offer (IPO).

The company's premise was to build a library of hundreds of billions of phylomers, active protein molecules with genetic material that stems from volcanoes, geysers and deep-sea vents.

Initially, the company tackled inflammatory diseases, led by Perth biotech movers and shakers Dr Stewart Washer and Harry Karelis.

Now retired Perth cardiologist Dr Bernard Hockings - Rohan's dad - joined the register in August 2012.

In 2019, the company rebranded itself as PYC Therapeutics.

Along the way Phylogica formed a joint venture called Vision Pharma with Lion's Eye Institute, a Perth not-for-profit research body.

In effect, Phylogica delivered the vehicle (the penetrating peptides) and Lion's Eye provided the molecule, known as an anti-sense oligo-nucleotide (a precision medicine that can whomp genetic defects).

Over time, the company had big-ticket collaborations with Pfizer, Medimmune, Johnson & Johnson, Astrazeneca and Roche/Genentech, but they went nowhere.

No more dud spuds

Polycystic kidney disease (PKD) affects one in 1,000 people, equating to somewhere between five million and 14 million globally. In the US, there are 160,000 sufferers - just under the threshold of a rare disease.

PYC assesses a $US10 billion a year market.

There's one approved drug called Tolvaptan, but it is not tolerated by 85 percent of patients and carries an FDA 'black box' warning for liver failure.

"We have been interested in PKD for some time because it has a massive impact on patient lives and is highly attractive commercially," Dr Hockings says.

PYC's therapy is targeted at the 80 percent of PKD patients with the PKD1 mutation, as opposed to - you guessed it - PKD2.

Dr Hockings says cysts form in the kidneys and they grow to the "size of a Sherrin" (for non-Australian Rules followers, that's the size of a football).

More than half of patients with the disease will need a kidney transplant in their 50s.

On Monday, the company announced the results of work carried out by Denmark's Crown Biosciences, which involved growing a three-dimensional model of a kidney based on tissue removed from a patient with end-stage disease undergoing a kidney transplant.

The read-out supported the potential of the drug to address the root cause of the cysts that drive disease progression.

The next step is monkey trials to establish safety, while an eventual registration trial would enrol about 250 patients.

“We will be testing in humans by late next year,” Dr Hockings says.

He says the “gold standard” program tackles the dual problems of delivering to the target cell and modulating the target gene.

Eye see an opportunity

The retinitis pigmentosa mutation affects one in 100,000 people.

Sufferers are usually diagnosed around six years old and first lose their night vision. In teenage years they lose their peripheral vision and become legally blind in their 40s or 50s.

PYC is addressing a sub-type retinitis pigmentosa type 11 (RP11) which is only two to three percent of total cases, or 4,000 to 8,000 people in the Western world.

Still, the company estimates a $1 billion-a-year addressable market.

Recently granted US Food and Drug Administration fast-track status, PYC’s program aims to stop progression of the disease.

“You get one set of retinal cells and once they are dead, they’re dead,” Dr Hockings says.

“In theory, the drug will restore the missing protein in the retina so the disease should not get any worse.”

In early November, PYC said it had completed dosing the second of three cohorts of its candidate VP-001, in a phase I trial called Platypus.

Pending a safety analysis, the single ascending dose trial should be followed by a multiple ascending effort in early 2024.

“We may add a fourth very high dose cohort if we continue to see no signs of adverse tolerability.”

The phase I study involves nine to 12 patients. The phase II effort will enrol 30, randomized to two active groups and a sham cohort.

While the phase I study is being carried out in the US, phase II will be done in Australia.

Phase II is expected to kick off in February next year, with a primary efficacy readout in early 2025.

Will ADOA be a goer?

The blinding eye disease autosomal dominant optic atrophy (ADOA) affects about one in 50,000 people.

As with RP11, there are no drugs or more advanced clinical programs and the company estimates a $2 billion-a-year market.

ADOA stems from insufficient levels of the OPA1 gene, which inhibits normal development of retinal ganglion cells that convey visual stimuli to the brain.

This causes cell death and eventual blindness.

The company recently had a chat with the FDA about the trial pathway and hopes to lodge an investigational new device application in the first half of 2024.

Finances and performance

While there is no current treatment for the diseases targeted by PYC, the company assumes a median orphan price of $US200,000 per patient per annum.

This could be conservative, given Neuren Pharmaceuticals has managed $US375,000 for its Rett syndrome drug trofinetide, approved by the FDA as Daybue, this year.

At the end of September, PYC had $21 million in the bank, having burnt almost $12 million in the September quarter.

With a $16.7 million Federal Research and Development Tax Incentive imminent, the company hopes to be funded until the second half of 2024.

Management hopes a capital raising can be avoided with a decent out-licencing transaction.

How about one like the $US170 million upfront paid by Glaxosmithkline for the oligonucleotide assets of Wave Life Sciences, or the $US224 million collaboration between Vertex and Nasdaq gene therapy peer Entrada?

The former owner of Ikea’s Perth franchise, Alan Tribe accounts for a chunky one-third of the PYC register. Having been a loyal supporter in past capital raisings, Mr Tribe is confident of things coming together at the company somewhat more smoothly than a flat-pack desk with Swedish instructions.

Over the last 12 months, PYC shares have traded between 5.0 cents (mid-October 2023) and nine cents (mid-March this year).

The stock peaked at 58 cents in early 2006.

More than monkey business

As an aside, the life sciences world is still suffering from a Covid-induced shortage of the main species of monkey used in their research.

The ape in question - the cynomolgus monkey, better known as the crab-eating macaque - is valued for infectious disease research and thus was highly in demand for Covid vaccine and therapy work.

Dr Hockings says supply and demand is normalising. The trouble is, the monkeys need to be between three and five years old for toxicology studies, so while breeding has picked up there's still a time lag.

In the meantime, the FDA is more amenable to toxicology studies being carried out on dogs or pigs instead.

Mr Hockings says PYC is okay, because it booked its slots - and secured its simians - years in advance.

Dr Boreham's diagnosis:

Despite being afflicted with Covid this week and craving a cure, Dr Hockings was effervescent about PYC's prospects despite investor concerns the company has taken rather a long time to get to the pointy end of things.

"We are operating a platform technology on a scale unlike that of any other Australian life sciences company," he says. "We have a 50 percent shot of curing childhood blindness for our first trick, reaping millions and becoming the next CSL."

When we last covered PYC in November 2019, Dr Hockings was blunt about the drug delivery outfit's "scattergun" approach.

"We were chasing all the rabbits and catching none," he says. "Investors were saying: 'You have this nice delivery system but what are you going to do with it?'"

The addition of the kidney program shows PYC is still chasing rabbits, but given the common monogenic focus across all its efforts the company is not haring about in random directions.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. But he's a good geyser who can still pull a rabbit out of a hat when he's not erupting.