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Company spotlight: Cizzle Biotechnology

Cizzle Biotechnology, founded in 2005 as a spinout from the University of York, describes itself as an early stage biotech firm, developing gene-based strategies for the treatment and diagnosis of cancer. Though still young, the company already has a potential therapeutic in animal studies, with related candidate diagnostics.

By Suzanne Elvidge

Cizzle Biotechnology's focus, and the source of its name, is the Ciz1 gene and its splice variants, and the company is developing Ciz1-targeted therapeutics and diagnostics for lung cancer. This technology stems from Dr Dawn Coverley's work at the University of York in the UK. The university remains a shareholder in Cizzle, but it has transferred all rights to the technology to the biotech, which Dr Coverley co-founded and of which she is chief scientific officer.

The Ciz1 gene and protein

The role of the normal p21Cip1-interacting zinc finger protein 1 (Ciz1) is to stimulate DNA replication by promoting cell cycle progression in normal and cancer cells – the company's scientists have confirmed this in cell-free and cell-based assays. Alternatively spliced forms of Ciz1 are seen in embryonic cells, suggesting that Ciz[1] splicing may contribute to the regulation of DNA replication during development.[1] However, alternatively spliced variants of the Ciz1 gene are also associated with various cancers including Ewing's sarcoma, with the company focusing on the variant seen in small cell lung cancer (SCLC).

According to the charity Cancer Research UK, 20 out of every 100 cases of lung cancer are SCLC, and the disease is almost always caused by smoking. According to the US National Cancer Institute, SCLC is the most aggressive of the lung cancers. It is more likely to have spread by the time of diagnosis, and median survival from diagnosis is only two to four months, with overall survival at five years of 5-10%.

"Cizzle Biotechnology has a unique patented way of detecting lung cancer early, which could be linked with therapy and potentially save lives," said Dr Rod Adams, the company's chairman. This is based on utilization of the naturally occurring process of RNA interference (RNAi), where a specific gene is 'silenced' by a short section of RNA, known as small interfering RNA (siRNA). Cizzle has conducted *in vitro* studies of siRNA targeting the spliced variant, showing reduced proliferation of SCLC cells.

The Ciz1 variant is also sufficiently specific to use it as a biomarker in the early detection of SCLC. "As we are targeting the variant, we hope to produce powerful diagnostics, as well as targeted therapeutics with few side effects," added Dr Adams.

"Lung cancer is the company's focus, because it is a seriously unmet need," said Dr Adams, "By developing siRNA-based products, we are, as far as I know, the only company in this specific field". There is no diagnostic on the market for early detection, and no biotech-based therapeutic for lung cancer, he adds. Thus Cizzle believes it has the potential to exploit a large market opportunity – there are around 150,000 deaths from cancer in the UK each year, with 33,000 of these from lung cancer, and the market is predicted to grow to $25 billion by 2011.

Applications of gene silencing

As prospective cancer therapeutics, siRNA oligonucleotides which act by binding to genes associated with disease and preventing their expression have the advantage of specifi-

cally targeting tumors, so having less potential for systemic side effects. This specificity has advantages for diagnosis as well, as it could precisely locate tumors, or even show a propensity for disease.

Cizzle Biotechnology is competing with around 60 companies globally, developing around 85 lung cancer drugs, but most of these are chemotherapeutics, which may be more likely to have adverse effects than siRNA therapeutics.

There is a range of companies developing cancer therapeutics and diagnostics based on siRNA. The most advanced appears to be Calando Pharmaceuticals' lead candidate CALAA-01 – the company has received FDA approval to begin a Phase I trial, and believes that it will be the first clinical study using targeted, systemic delivery of siRNA in oncology. Calando Pharmaceuticals, which is based in the US, is using its cyclodextrin-containing polymer RONDEL (RNAi/Oligonucleotide Nanoparticle DELivery) technology to create an internal R&D pipeline of potential siRNA therapeutics, as well as to work with partners. The delivery system protects the siRNA and has potential for targeting delivery to specific tissues and allowing intracellular delivery without triggering an immune response. RONDEL siRNAs have shown specific delivery and tumor inhibition in preclinical studies.

The European company Silence Therapeutics is developing siRNA therapeutics, known as AtuRNAi compounds, using its AtuPLEX delivery system. The delivery system protects the siRNA against degradation, increases bioavailability and circulation times, and targets diseased tissues and cells. The company plans to begin clinical development of AtuRNAi compounds for cancer, such as gastrointestinal and non-small cell lung cancer, in 2008. Two of Silence Therapeutics' AtuRNAi compounds began clinical trials with partners in 2007 – RTP-801i-14 for age-related macular degeneration and AKLi-5 acute kidney injury.

US based Alnylam Pharmaceuticals is developing ALN-VSP01 for the treatment of primary and secondary liver cancer. This targets two genes associated with tumor growth and development, and may also have potential in other cancers. The company uses a liposomal technology to deliver the siRNA to the liver, and preclinical studies show gene silencing.

Nucleonics' technology is based on eiRNA (expressed interfering RNA) products, delivered as plasmid DNA coding for the required siRNA. These can target multiple disease genes and/or multiple sites on a target gene. This potentially provides a more stable product and increases the number of siRNA molecules and the length of time they are available. The US firm has a prostate cancer product in preclinical development, with an ovarian cancer product at the discovery stage.

Intradigm, also a US firm, is developing Nanoplex, a delivery system for the systemic administration of unmodified siRNA, along with a pipeline of siRNA-based oncology therapeutics. This technology could be targeted to specific tissues or cell types, and could allow the simultaneous administration of a number of siRNA molecules against a number of different disease targets.

ToleroTech, a Canadian firm, is developing an siRNA-based cancer vaccine and many big pharma companies are also moving into the siRNA arena – these include Hoffmann-La Roche partnering with Alnylam Pharmaceuticals; AstraZeneca partnering with Silence Therapeutics; Ortho-McNeil partnering with Isis Pharmaceuticals; and Merck & Co acquiring Sirna Therapeutics; all these transactions occurred in 2007.

Proving the principle

Results of *in vitro* studies of Cizzle Biotechnology's Ciz1-based platform have been positive, and the company will be conducting a study of Ciz1 siRNA in mouse SCLC xenograft models at the US Southern Research Institute, with the hope that this will prove the technology's potential to stop proliferation, and validate the target. The company has released few details on its technology and how it will be targeted and administered,

"If the *in vivo* study is effective, we will try a similar therapeutic approach in other cancers," said Dr Adams. As well as looking at siRNAs as potential therapeutics, the company plans to assess monoclonal antibodies targeted against a variant of Ciz1 as diagnostic agents. This could be developed for use in blood or sputum samples, and may even have potential for mass screening.

Creating the company

The decision to spin out the company was based on the potential of the technology. "We had good science that we felt could (and should) be exploited," said Dr Coverley.

In founding the company, Dr Coverley received support from the Bioscience Yorkshire Enterprise Fellowship (BYEF), an initiative from the Regional Development Agency (RDA) for Yorkshire and the Humber, Yorkshire Forward, to provide practical support to commercialize ideas and research findings from the region's universities.

Dr Adams said the company faced difficulties in securing funding - a common challenge for all spinouts. "Because of this, many small companies start with grants, such as the White Rose Technology Seedcorn Fund (WRTSF), which works with York, Sheffield and Leeds Universities in the north of England. Another route is to use business angels, who are generally interested in investing in higher risk (and often highest reward) start-ups. Perhaps the highest risk route for the individual involved is getting a personal bank loan."

The University of York provided proof of principle funding to Cizzle, and subsequent funding came from the BYEF program and Yorkshire Forward. Later, further funding came from the White Rose Technology Seedcorn Fund in 2006. "When I joined the company, my first job was to raise more money, as the initial funding had run out. We needed £550,000, and we have successfully raised more than this, with investments from a number of sources including White Rose Technology, The Viking Fund and Yorkshire Cancer Research," said Dr Adams. The sums are small change by big pharma standards, but Cizzle has focused on local funders and has raised enough to cover its needs for the next two years. "This allows us to retain as much equity as possible," Dr Adams explained. The money raised is being used to set up the company's first animal study.

The partnering model

The lung cancer therapeutic currently in development is likely to be delivered as an aerosol locally into the lung, as

RNA is not stable in the bloodstream and cannot be delivered orally, and Cizzle Biotechnology will seek a partner with a specialty in this area. "We will look to collaborations or licensing agreements with big pharma to create delivery systems for our therapeutics and to get them to market," said Dr Adams. Cizzle Biotechnology is already in discussions with an undisclosed big pharma company.

Looking forward

"Our greatest achievement so far is Dr Coverley's proof that Ciz1 has potential as a therapeutic," said Dr Adams.

As it is still small, with only two employees, Dr Adams expects Cizzle's R&D to remain based in the biology department of York University. The team will include a CEO, a few scientists, and a part-time business development manager. Cizzle Biotechnology has created a link with Hull York Medical School for access to samples of tissue, and has recruited a postdoctoral scientist on a short-term contract, who is working on the pipeline in collaboration with Dr Coverley. Because it works with contract research organizations, the company has the option to remain small.

The people behind the company

Dr Coverley co-founded Cizzle Biotechnology with her husband Dr Justin Ainscough. Dr Coverley splits her time between her role as CSO and as principal investigator of an academic DNA replication research laboratory at the University of York. Following her PhD, funded by Cancer Research UK, she worked on DNA metabolism, repair and replication in a cell biology laboratory at Cambridge University. In 2001, she established a new research laboratory at the University of York, where she developed the research that became Cizzle Biotechnology's platform technology. Dr Ainscough is now a senior research fellow in the division of Cardiovascular Medicine at the University of Leeds, and advises on aspects of the science on an informal basis.

Dr Adams joined Cizzle Biotechnology as chair in August 2007; his role also includes representing the WRTSF. He has a long history within the pharmaceutical industry, moving from research, through analytics to production. "This gave me a scientist's view of production," he explains.

Dr Adams' career started with Glaxo in Liverpool, beginning as a development chemist and rising to head of packaging. He then worked for a number of pharmaceutical companies as production director and general manager, before becoming managing director of the healthcare division of DePuy International from 1991 to 1997.

Dr Adams then founded Adams Healthcare in 1997, and remained managing director until 2003. DePuy International bought Chas Thackray in 1990, from which Adams led a management buyout of the healthcare division in March 1997 for £9 million. In 2000, Medical Solutions bought out Adams Healthcare in a £13 million reverse takeover, which recruited Dr Adams as chief operating officer of Medical Solutions, and retained him as managing director of Adams Healthcare. His next move was to sell the Adams Healthcare division to ECOLAB in December 2002, which involved him becoming European projects director for ECOLAB, based in Germany, where he remained until 2004.

In 2004, Dr Adams returned to the UK and focused on supporting new biopharma companies, becoming involved in the Viking Club, part of the Viking Fund, a Yorkshire-wide, Department of Trade and Industry-funded co-investment venture capital fund. In the same year, he became a board member and shareholder of Syntopix, a spinout from the University of Leeds founded in 2003 and focusing on acne and skin infections, and became chief executive officer in 2005. The company went through an IPO in 2006 and Dr Adams became the chair of Syntopix in January 2007. As well as this, he is a non-executive director of another University of Leeds spinout, Perachem (now Green Chemicals), a company developing environmentally friendly chemicals for the textiles industry, and co-founded Neoceuticals in January 2008, a niche company focusing on pediatric supplements and pharmaceuticals.

"The science is the driver but for start-ups, the transition from academia to commerce is difficult, and companies need both money and advice – this is where I can help," said Dr Adams. "For Cizzle Biotechnology, I would expect at some point in the future a buyout by a major player, or a key partnership. Using siRNA is still a new approach and the technology is very attractive to pharmaceutical companies."

References

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