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A warts-and-all view of Avantogen's pancreatic cancer chances

If there's one thing guaranteed to excite attention in the biotech investment field, it's the result of a clinical trial. This analyst could talk until he was blue in the face about *in vitro* data, findings from animal model work, and even anecdotal evidence that a therapeutic approach works in people. However until a company is ready to report the outcome of a properly designed clinical study, only the aficionados will really be listening, and they generally aren't people who buy much biotech stock. That's why a company called Avantogen, ASX Code ACU, is of some interest to this analyst at the moment.

If the name Avantogen doesn't ring a bell, you may know it by its pre-May 2005 name of Australian Cancer Technology, which also had the ACU ticker. When this analyst first looked at AustCancer around three years ago it was a more or less obscure developer of peptide-based cancer vaccines. Things began to change for the company in 2003 when Paul Hopper, a former private hospital executive turned technology entrepreneur, introduced a second project and helped recapitalise the company before being named CEO in August 2003, at the height of that year's biotech bull market.

Hopper had no background in biotech but he took seriously the task of going up the learning curve, and was able to do so fairly swiftly. He was also a good dealmaker, and over the next year and a half managed to bring into AustCancer a number of projects which both spread the project risk and moved the company closer to a point where marketable products would be in sight. For a while in 2003 and 2004 the market was pretty impressed. At its high point in May 2004 AustCancer stock was up fivefold on its level of twelve months before.

One of the projects that Hopper and his colleagues got hold of in 2004, and the chief reason to be looking at Avantogen right now, involves a small molecule drug that has been given the codename RP101. The compound has been showing promise as the next big thing in treating pancreatic cancer, and a Phase I/IIa clinical trial is currently being completed, with results expected in the next few months.

Sure, cancer of the pancreas isn't all that common in the Western world - there are only around 30,000 cases a year in the US - but uncommon medical conditions are often the most lucrative to target. A drug company can and often does charge the earth for drugs specific to a rare disease, and in the case of pancreatic cancer Avantogen has previously speculated that the U.S. market for RP101 is worth perhaps US$200m a year. Moreover if there's nothing out there that really works for the patients - and that seems to be the case with pancreatic cancer - the regulatory folks will generally accelerate approval of the drug.

And don't forget the tax breaks and other benefits out there for people who develop so-called 'Orphan Drugs' where the patient population is less that 200,000. All of this suggests that the pay-off from a successful clinical trial of RP101 could be both swift and lucrative from the perspective of a small company like Avantogen. Given RP101's performance to date, we think it's reasonable to expect the data from the trial to be favourable. But to understand why it's necessary to go back and look at all that early stage science. So bear with us for a moment while we explain why Avantogen thinks it is on to something good...

The 101 of RP101

The first favourable point to note about RP101 is that it's not a new drug. If you lived in East Germany in the 1980s, and to further compound your misfortune you got cold sores thanks to an encounter with HSV-1, the herpes simplex type 1 virus, or shingles from infection by VZV, the varicella zoster virus, then you were probably prescribed RP101 in the form of Zostex, from a local drug firm called Berlin-Chemie. The drug, which chemists know as bromovinyldeoxyuridine or BVDU for short, is one of those analogues to the nucleic acid bases (you know, the letters 'A', 'T', 'C' and 'G' - BVDU is based on 'T', that is, thymidine) that are good at dealing with viral infection because they effectively throw a 'nucleic acid monkey wrench' into the replication mechanism of the virus. Zostex/BVDU is still being made, Berlin-Chemie having been bought and restructured by Italy's Menarini after the Berlin Wall came down. And the drug's many years of use in treating herpes virus infections attests to its high safety profile. However the fact that Zostex/BVDU was commercialised behind the Iron Curtain meant that it really couldn't find a market in the West after the Cold War, since that would involve displacing already established anti-herpetic drugs like GSK's Zovirax. Consequently BVDU is approved in only a few European jurisdictions.

Which is all to the good as far as Avantogen is concerned, because sometime around 1995 or 1996 the German geneticist Dr Rudolf Fahrig, then labouring at a Dresden-based research institute called the Fraunhofer, discovered that BVDU was a great suppressor of gene amplification. When genes are 'amplified' it simply means that there are too many of the relevant strings of nucleic acid being produced within a cell. Fahrig was interested in this phenomena because it was known to be one of the ways in which diseased cells become drug resistant - they simply overproduce various genes known to confer resistance. A drug that could knock down gene amplification would be able to give a new lease on life to other drugs whose metier is cell killing. In this regard BVDU was almost perfect because it was orally available and of small molecular weight. We say almost perfect because one can't take it in conjunction with the chemotherapy agent 5-fluorouracil, the combination being unacceptably toxic to the patient. Nonetheless Fahrig's work demonstrated that BVDU would 'chemopotentiate' - that is, make more powerful - many other cancer drugs.

Fahrig seems to have been a more commercial geneticist than many we've met because he was careful to file for patent protection over this new use of BVDU (see WO 96/23506, priority date 8 December 1995, but only if you can read German). Later on, around 2000, he formed a company called RESprotect (the 'RP' of RP101) to commercialise the technology. And by 2003 Fahrig and colleagues had figured out just what chemical pathways in the cell BDVU

attacked in the war on gene amplification (see WO 2004/084917, priority date 24 March 2003). But more important than this, they'd also initiated proof-of-concept trials of RP101 in people to find out what tumours were most susceptible to the drug's charms.

A doubling of survival time in some pancreatic cancer patients

RESprotect's initial patient studies, in 2002 and 2003, looked at 30 patients with five types of cancer. Only a few had metastatic pancreatic cancer, but it was these patients that seemed to respond best to RP101. Consequently a few more patients with that cancer were recruited in order to investigate further. By September 2004 there was interim data from 13 patients in the pancreatic sub-group, and RESprotect's white coats had become quite excited (by German standards) with what they were seeing. Not only were there three cases of partial tumour remission, but blood tests for the pancreatic cancer marker 'CA19-9' had suggested a total remission for another two patients. Thinking about it, RESprotect's scientists reckoned that RP101 worked in pancreatic cancer because two chemical pathways the drug impacted (STAT3, a signaling pathway, and APEX, a DNA-repair gene, if you must know) were more pronounced in this cancer than the others. Whatever the biochemical reasons, RP101's success in five patients out of 13 for a disease as vicious as pancreatic cancer seemed nothing short of outstanding.

Just how well RP101 dealt with pancreatic cancer was revealed five months later when the full data set became available for the 13. Generally if one is diagnosed with pancreatic cancer one is then afflicted with a couple of harsh but not-all-that-effective chemotherapy drugs, Eli Lilly's Gemzar and an older drug called cisplatin. For all that trouble, one's chances of being alive on these drugs only 7.5 months later is 50/50. However for RESprotect's 13 patients the 50% survival rate, using the same drugs plus RP101, was only reached at the 15 month mark, with ten hardy patients living more than a year. Looked at another way, RP101 boosted to 75% a patient's chances of living with pancreatic cancer for more than twelve months. Ordinarily the probability is 25%.

All up, it looked in February 2005 like RESprotect had a registrable product in RP101, the only hitch being that Fahrig and colleagues had yet to establish the appropriate dosage for their pancreatic cancer patients. That's the purpose of the currently ongoing 22-patient Phase I/IIa trial, which was initiated in December 2004 and from which results are expected soon.

Is Avantogen positioned for success?

Which brings us back to Avantogen's role in RP101. In September 2004 AustCancer, as it was then called, joined with a New York-based biotech company called BioAccelerate to license from RESprotect the North American rights to RP101. The Australian company announced that after the Phase I/IIa dose ranging study it would initiate a placebo-controlled Phase IIb trial of RP101, with perhaps 130 patients in all, and that the trial to be conducted under an IND with the FDA.

The aim was to file for 'accelerated approval' on the back of these results. Sometimes the FDA lets a new drug onto the market after a Phase II study

without the usual Phase III if the drug meets an urgent unmet medical need - a good recent example was Millennium's Velcade, a drug for the treatment of multiple myeloma which was approved in 2003. If the FDA views RP101 in a similar light to Velcade, the drug could be selling in American as early as 2007 - that's right, next year, although 2008 is probably a more likely outcome.

It sounds exciting, doesn't it? Which begs the question as to why, if Avantogen stock was 33.5 cents last February when the previous Phase I proof-of-concept results were announced, it is now some 61% below that level. We put the current low share price down to three sentiment factors:

Firstly, Avantogen apparently went through some boardroom brawling last year, featuring a number of changes to the board and Paul Hopper's exit as CEO only two weeks after the February 2005 result (and only shortly after moving from Sydney to San Diego to run the company from there). To be fair, things seem to have settled down since the new CEO, Len Firestone, joined Avantogen, but as we've often commented in this email, no one likes investing in a biotech company that seems to change its leadership like the Italians change their governments.

Secondly, there's the issue of capital management. By our reckoning Avantogen has visited the capital market no less that six times in the last two years to raise a total of $21.7m. There were share placements in March 2004 (32 cents per share to raise $3m), September 2004 (40 cents to raise $2.3m) and December 2004 (38 cents to raise $1.9m) and rights issues in October 2004 (1 for 10 at 35 cents to raise $4.0m), April 2005 (1 for 3 at 13 cents for $5.7m) and November 2005 (1 for 4 at 11 cents to raise $4.8m - in this issue each new share came with a December 2007 option exercisable at 25 cents). We noted last fortnight that too high a frequency of capital raisings tends to exert some negative pressure on a stock, and this seems to have been true for Avantogen.

Thirdly, ownership of the RP101 project has just been restructured. Avantogen announced earlier this month that it had agreed to vend its 50% interest in the project into an affiliate company of BioAccelerate called Innovate Oncology, with Avantogen to take stock in Innovate as consideration. BioAccelerate had vended its 50% into Innovate during 2005, so this month's deal meant that control and management of the project was now being driven out of one office by one team. The deal seemed to make sense for Avantogen in that it left the company as the majority shareholder in RP101, with an expected 54% of Innovate's stock upon completion. Moreover Innovate's Chairman is Paul Hopper, the same Paul Hopper who used to run Avantogen and therefore knows the RP101 programme very well. The problem for some observers of Avantogen is that Innovate's stock is traded in the United States on the Over-the-Counter Bulletin Board, under the stock code IOVO. For those who've never dabbled in American microcap stocks, the OTCBB is a regulated stock quotation service operated by Nasdaq for stocks that aren't eligible for quotation on the conventional securities exchanges. Frankly, OTCBB stocks tend to be regarded by some as less 'respectable' than regular Nasdaq or NYSE stocks, and Avantogen observers therefore worry that the company's holding in Innovate will trade at a discount to its intrinsic value until the stock moves up to Nasdaq proper. It doesn't help that when one visits the Innovate Oncology web site the most recent investor presentation is dated March 2005, while there's no 'news' in the news section later than February 2005.

Punting on the RP101 upside

On the opposite side of the ledger one can make the case that Avantogen stock is markedly undervalued based on Innovate Oncology alone. Innovate currently has around 18.2 million shares on issue. In the current deal it will issue (to BioAccelerate) around 8.8 million shares to pay off outstanding debts and then issue 32 million shares to Avantogen to acquire 50% of RP101, making for 59 million shares in total. On 9 February Innovate Oncology stock traded on OTCBB at US$1.80 per share, which makes for a US$106.2m capitalisation on the expanded share capital, or A$144m at an AUDUSD exchange rate of 0.737. Avantogen's 54% is therefore notionally worth around A$78m. Add $3.1m cash (post the deal) and $13.4m in cash from option exercises, and divide the result by the 262.3 million fully diluted shares on issue, and one can make the case that a 36 cent share price for Avantogen is not out of the question. And we haven't even counted some interesting vaccine adjuvant technology on which Avantogen has been working.

36 cents is a lot higher than the current share price given the nearness of a Phase I/IIa result from RP101. Consequently we would argue that even if the market has had near-term issues with Avantogen, a near-term revaluation is probably in order. Like any small biotech, Avantogen is not without risk, however we think that at current prices Avantogen is a Highly Speculative Buy for Knowledgeable Professional Investors.

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