

## Letter to Shareholders

The massive downturn in global financial markets is having an impact on all of us. This letter outlines the current status and future outlook for Genesis. Detailed below are summaries of the major Genesis programmes, including scientific progress and commercial prospects.

### Key Points

#### Product Development Progress

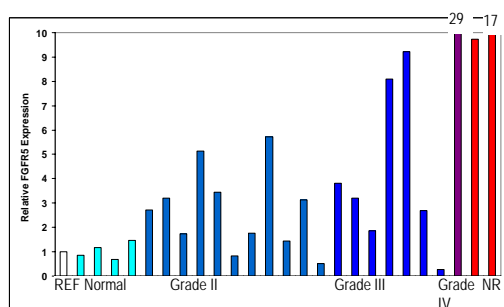
- Zyrogen for Prostate Cancer
- RNAi oncology therapeutic
- Novel gene silencing technology

#### Funding

- New capital required

### Zyrogen

Genesis identified and patented the 5<sup>th</sup> receptor in the fibroblast growth family, a molecule now known as FGFR5 or FGFR1. We have undertaken extensive *in vitro* biological studies (i.e. studies undertaken with cells in a laboratory) and identified interesting relationships with various bone and autoimmune diseases. In addition we have shown that FGFR5 is implicated in advanced prostate cancer.



FGFR5 expression in prostate cancer

The expression in the 4 normal samples was averaged to generate the reference point (REF) and the tumour samples were compared to the reference. The severity of the cancer was determined histologically as Grade II, III, IV or was not recorded (NR).

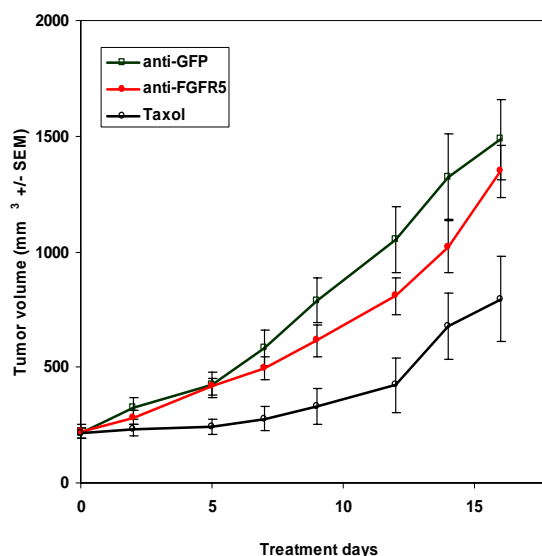
A therapeutic for this gene target would be a drug that blocks the action of FGFR5, such as a small chemical molecule or an antibody. As reported previously, Genesis collaborated with MorphoSys in Germany to develop a panel of fully human antibodies that might block the action of FGFR5 to prevent or reverse disease. After *in vitro* testing to validate that the antibodies bind to, and block, FGFR5, we selected one antibody and arranged for MorphoSys to produce sufficient quantity to allow further *in vivo* studies to be undertaken.

Although our data has generated a lot of interest from potential licensees and collaborators, the real test is whether *in vivo* results can be achieved. These studies are much more difficult, as we can't administer proposed therapeutic drugs to humans without first trying them in laboratory animals, for

obvious safety reasons. However, such animal studies are a poor substitute for the likely results in a human, and might incorrectly show either a positive or negative result.

In the last 6 months we have tested this antibody in a prostate cancer model and confirmed that further studies are warranted. The results showed some activity against prostate cancer but suggest that either higher and more frequent dosing might be required, or that the antibody needs to be made more potent. This can be achieved through a technical process known as affinity maturation.

The red line on the graph below shows that twice weekly dosing of anti-FGFR5 antibody had a beneficial effect on prostate tumour size but was not as effective as Taxol (dosed three times per week). Our antibody was better than the control treatment shown on the green line.



We now plan to undertake further studies with higher and more frequent dosing of our antibody to FGFR5.

Shareholders have commented that we report positively on the potential for our projects but so far haven't achieved a major commercial blockbuster, so it is worth adding a note of caution. The scientific world has many reports of a particular gene being associated with a disease. However blocking many of these genes won't necessarily prevent or treat disease, or might induce an unacceptable side effect. In the same manner, we can't guarantee that this programme will proceed through clinical trials and become a marketed

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therapeutic, but we remain hopeful that another company will recognise the potential and will wish to fund further studies or license the project from us and develop it with their own resources.

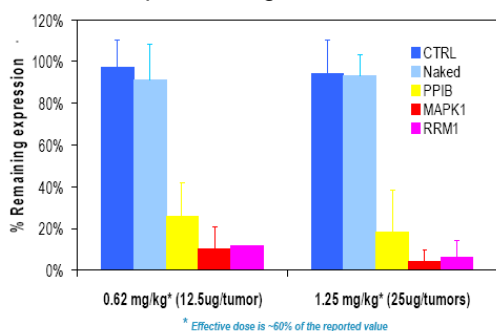
Currently we are in discussion with a number of potential partners or licensees, including pharmaceutical companies from 3 different continents, who are examining our data and determining whether they are interested in being involved with the project.

## RNAi

Genesis has had an RNAi therapeutic development programme since 2003. Early work on silencing targets in allergic disease has led to our current focus on oncology, with particular interest in the altered nutrient uptake and metabolism in cancer cells. The aim of the programme is to develop therapeutics that kill cancer cells in solid tumours and/or improve the effect of existing chemotherapeutic drugs.

We have identified a number of genes with strong potential as therapeutic targets in cancer and have demonstrated that silencing these target genes inhibits tumour cell growth both *in vitro* and *in vivo*, and sensitises cells to clinically used chemotherapeutic drugs. The screening programme has been expanded to generate intellectual property covering a wide platform of potential targets that are suitable for internal development or external licensing. Rigorous testing has been undertaken to determine the best siRNA design and chemistry and to confirm gene knockdown through measuring RNA message and protein.

With our lead siRNAs we have achieved excellent *in vivo* results following intra-tumoral delivery of the siRNA, formulated in a delivery compound. We have prioritised a gene known as RRM1 as our results suggest that siRNA targeting RRM1 could form the basis of a therapeutic strategy for cancer, either alone or in combination with various chemotherapeutic drugs.



Single intra-tumoral injection at two different doses shows substantial *in vivo* knockdown of the RRM1 gene

We are in discussion with several groups to determine whether they wish to collaborate with

Genesis to develop siRNA against RRM1 as a therapeutic. It is likely to be a number of months before we know the future for this project.

## Gene Silencing

We announced at the annual meeting of shareholders, held in May 2008, that we had commenced work on a novel gene silencing technology. Since then we have been working hard to develop the technology, which is likely to take a further two years before it is commercially proven.

We have not been able to say much about this programme until we completed a specialist review of our intellectual property position. However 3 patent applications have now been filed and the review has been completed. It confirmed the patentable novelty of our technology, and our freedom to operate (i.e. it is not caught by other issued patents). Recently we disclosed some limited information to a number of companies who we have assessed as being suitable collaborators to help fund and speed the development of the technology. They have all expressed strong interest in the technology, so we expect discussions to occur in the next few months which will indicate the likelihood of external funding for this project.

The novel gene silencing technology being developed by Genesis is very exciting as it has the potential to solve the siRNA delivery problem by combining the delivery advantages of antisense oligonucleotides with the potent gene knockdown of siRNAs, to yield a novel and vehicle-free gene silencing technology. Our technology will deliver separate complementary strands of RNA and let them anneal inside the cell where they can induce gene specific RNAi.

Technology	Advantages	Disadvantages
Antisense	Enters cells easily <i>in vivo</i>	Difficult to design efficient antisense
RNAi	Easy to design Potent activity	Difficult to deliver into cells <i>in vivo</i>
Genesis ssRNAi Gene Silencing Technology	Potent activity, easy to design and enters cells readily <i>in vivo</i>	

## Premises

Late last year we relocated all our operations on one level of our leased premises at Fox St, Parnell, allowing our rent to be reduced by 37%. The renovations were fully funded by the landlord.

## Other Assets

Genesis also has royalty rights for various products that are being developed by other parties in the fields of agriculture, bioinformatic software,

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forage grass, forestry, horticulture, etc. resulting from previous collaborations.

Shortly we hope to be able to announce an important commercial development of one of these programmes.

## Share Market

In common with most other listed equities, we have had a further reduction in our share price over the last few months, as shown in the graph below.



The volume of shares traded has been quite low, indicating that most existing shareholders recognise that biotechnology stocks such as Genesis probably need to be held for a long period before achieving a commercial breakthrough, and also because there are few new investors as most have reduced funds and are focusing on investments with high levels of security.

## Funding

In our last announcement to the stock exchanges detailing the failure by Pure Power Global to meet its settlement obligations for the \$2 million owed to Genesis, we mentioned that we are considering opportunities to raise capital from existing shareholders and new investors. Our cash balance at 31 December was \$859,000 (substantially lower than planned due to the PPG settlement failure) and we are due a R&D Tax Credit refund of nearly \$700,000.

As outlined above, we think that the projects we are focusing on have significant potential and warrant further development. However this costs us about \$300,000 per month so we need new funding.

The pharmaceutical market is what eventually drives the funding of biotechnology companies, as it is the pharmaceutical companies that acquire or in-license projects and clinical products. Fortunately the pharmaceutical companies have substantial cash balances and continue to license or acquire projects that fit their strategic needs and pass their commercial and scientific assessment.

We have maintained contacts with many biotechnology and pharmaceutical companies, through our directors and through attendance at major partnering meetings such as BioUSA and BioEurope. As mentioned above, we are in

discussion with a number of these companies and hope that this will lead to new commercial relationships which will provide funding for our business.

We are also exploring grant funding but this is extremely competitive.

The last time we sought funds from shareholders was in September 2000 when Genesis undertook an IPO. Since then we have generated funds by selling several projects that did not fit our current strategy. Now we need to augment our funding by investment of new capital. As well as looking to existing shareholders, we are actively exploring opportunities to introduce new substantial shareholders.

We expect to provide further information over the next 2 months.

## Publications

I am pleased to recognise the staff who contributed to the work which has been included in several recent publications and presentations. This includes:

- Reid G, Coppieters T, Wallant N, Patel R, Antonic A, Saxon-Alliifaalogo F, Cao H, Webster G and Watson JD. 2009. Potent subunit-specific effects on cell growth and drug sensitivity from optimised siRNA-mediated silencing of ribonucleotide reductase. *J RNA Gene Sil*, *in press*
- Sensitive and specific detection of cleaved mRNAs from *in vivo* samples using Molecular Beacons and real-time PCR, Annette Lasham, Mike Herbert, Sheryl Feng, Marika Eszes, Helen Cao and Glen Reid, *submitted*
- A Model System to Test the Effects of Design and Modification on siRNA Activity, Dr Glen Reid: RNAiEurope, Stockholm, Sweden, 16-18th September 2008
- Invitrogen Gene Silencing & Epigenetics Showcase, Dr Glen Reid: Brisbane, Sydney, Canberra & Melbourne, November 10-14th 2008
- eMBRACE: a rapid, sensitive & specific method to detect siRNA-mediated cleavage *in vivo*, Dr Glen Reid: Therapeutic Modulation of RNA Using Oligonucleotides, Keystone Symposium, 8-13th February 2009

## General

There is nothing that I or the directors and staff of Genesis would like more than to announce a commercial breakthrough that would benefit shareholders. We believe that is possible, and are working extremely hard to make it happen, but success isn't achieved quickly in this industry.

I hope that shareholders will continue to support Genesis so that they can share the future benefits from the position we have achieved.

Sincerely

Stephen Hall  
Chief Executive  
2 February 2009

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### Sharemarket Ticker Symbols

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