Lands of Opportunity for ddRNAi

July 2013
Disease Invades our Lands
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Benitec Biopharma has the Battlefield in its Sites
1. The ddRNAi construct is delivered to the target cell by a proven and approved vector, where it is transported to the nucleus.

2. Cellular machinery continuously produces short hairpin RNAs (shRNAs) from the DNA constructs, which are transported to the cytoplasm and processed into small interfering RNAs (siRNAs).

3. The siRNAs are incorporated into the RISC complex that binds the matching target mRNA, signalling for its degradation and “silencing” the target gene.

Long term expression of shRNA by ddRNAi provides a potential “single-shot cure”
Benitec is Fighting on Multiple Fronts
Benitec Biopharma
Fighting on Multiple Fronts

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* Non-small cell lung cancer and other chemotherapy-resistant cancers
**Oculopharyngeal Muscular Dystrophy, an orphan disease
***Age-Related Macular Degeneration
Disease Invades our Lands
Hepatitis C

Chronic hepatitis C: 150 million = Russia
MISSION: Hepatitis C

Chronic hepatitis C: 150 million = Russia
AAV is a clinically approved vector for delivery of DNA to cells. AAV-8 homes specifically to the liver, making it an ideal candidate for the HCV therapeutic.
Hepatitis C
Virus-seeking missile: TT-034

- 3 independently transcribed RNAi elements target 3 separate, well-conserved regions of the HCV genome:

- TT-034 prevents the processes of:
  - Viral packaging, replication and capsid production ➔
  - Helps prevent the generation of viral escape mutants

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**TT-034 is a combination therapeutic providing broad patient applicability while maintaining exquisite tissue and gene specificity**
Hepatitis C
Virus-seeking missile: TT-034
Hepatitis C
Phase I/IIa Clinical Trial

- US-based open-label dose-escalation Phase I/IIa trial
  - Trial to be run at two US sites with a US-based CRO
    - Duke Clinical Research Unit, North Carolina (Dr Keyur Patel)
    - University of California, San Diego (Dr Robert Gish)
  - Dose escalation study on 14 patients who have failed current standard of care

- Favourable review from NIH Recombinant DNA Advisory Committee (RAC)
- Pre-IND meeting with FDA followed by IND filing planned for Q3, 2013
- Trial initiation expected Q4 2013
- Positive efficacy and safety data will be a significant value-inflection milestone
  - Results will also validate other programs in Benitec Biopharma’s arsenal
Market Entry Opportunity – Liver Transplant

- 2000 transplants performed annually in USA for hepatitis C.
- All hepatitis patients will need a new transplant because they become re-infected eventually
- Treatment of the liver with TT-034 could protect against re-infection
- An orphan condition?
MISSION: Hepatitis B

Hepatitis B: 350 million = US + Argentina
Hepatitis C
Significant Market Opportunity


75% of HCV cases are genotype 1. This totals about 10 million in US & EU.

Emerging combination therapies are predicted to cure about 80% of patients.

This leaves a significant market (>4M patients) for the next generation therapies.

In addition there is a huge emerging market outside US & EU.

In practice a large number of untreated or non-responding patients will remain.

40 million HCV infected outside US & EU.
Disease Invades our Lands
Hepatitis B

Hepatitis B: 350 million = US + Argentina
Hepatitis B
Significant Commercial Opportunity

Worldwide, HBV is three times more prevalent than HCV

In the top Western markets HCV is two times more prevalent than HBV

Chronic HBV and HCV prevalence worldwide

Prevalence of chronically infected subjects worldwide (million)

HBV and HCV prevalence in top 7 markets*

*US, EU5 (UK, France, Germany, Italy, Spain), Japan

Sources: Datamonitor 2004, 2007 to 2011. WHO, CDC, IMS, analyst reports
There is a significant unmet need for treatments for hepatitis B viral infection
• ~350 million people are chronically infected

Vaccines and therapies exist but...
• Current therapies only halt viral replication – like HIV therapies, they do not cure the patient
• For therapeutic effectiveness, patients must take drugs correctly for life
• Compliance is poor

Benitec Biopharma’s HBV therapy uses an identical approach to TT-034
• The DNA construct will encode three shRNAs that target three highly conserved regions of the HBV genome for prolonged silencing
• The construct is delivered using the same liver-targeting vector
• Most preclinical studies from the HCV program apply to the HBV molecule

Following clinical success in HCV, the HBV program should move quickly into the clinic
MISSION: HIV

HIV: 34 million = Canada
HIV/AIDS Phase I/IIa: Calimmune ddRNAi trial

Phase I/IIa clinical trial commenced July 2013 to assess safety and feasibility of Cal-1, a ddRNAi-based therapy for HIV/AIDS using stem cells treated with a lentiviral vector.

Cal-1 is designed to inhibit HIV infection through 2 active parts:
- Silencing CCR5 (HIV-1 co-receptor) on bone marrow and T cells
- Producing C46 (HIV-1 fusion inhibitor) on bone marrow and T cells
Lung cancer: 16.1 million diagnoses 2008 = Chile
Drug-Resistant Lung Cancer

• With around 65% of patients dying within one year of diagnosis, non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide
• The rapid emergence of drug resistant NSCLC cells provides a major challenge in the treatment of the disease.

A significant opportunity exists for a therapy capable of restoring and/or improving the effect of therapeutic drugs in resistant cancer and minimising side effects associated with chemotherapy treatment.
Non-small cell lung cancer (NSCLC) expressing high levels of βIII tubulin is resistant to paclitaxel-based therapeutic regimens, resulting in lower survival rates. This same correlation is seen in several other cancers.

By silencing the βIII tubulin gene, cancer regains susceptibility to chemotherapy.
Jet-PEI-based complexes can deliver DNA constructs to tumours with very high efficiency.
Proof-of-principle is established:

A single injection of Tribetarna™ effectively silences the βIII tubulin gene in vivo and in vitro

Tribetarna™ significantly enhances survival in a preclinical model of lung cancer in combination with chemotherapy

Longer survival than cisplatin alone

71.6% reduction

Tribetarna/cisplatin (n=8) (cisplatin 1.66 mg/kg)
European-based open-label Phase I/IIa trial

• Aim to enrol 24 patients with advanced lung cancer who have failed chemotherapy and have tumours that express high levels of βIII tubulin

Trial initiation aimed for late 2014

With clinical success in lung cancer, this approach can be developed to target other cancers that express high βIII tubulin (breast, ovarian, gastric\(^1\))

Invasion is Extensive
Neuropathic Pain

Neuropathic pain: 250 million = 15 Southern countries of Africa
Silencing Neuropathic Pain with ddRNAi

Preliminary animal studies demonstrate the ability of PKCy-targeted ddRNAi to achieve pain inhibition for at least six weeks post injection.

- Animals showed a significant *increase in pain threshold* to mechanical (A) and thermal (B) stimulation.

- The increase in pain threshold was dose-dependent and *lasted for the duration of monitoring*.

Disease Invades our Lands
Macular Degeneration

Age-related macular degeneration: 25-30 million = Saudi Arabia
Leading cause of vision loss in over 60s

The current standard-of-care in the US is repeated intraocular injections using an anti-vascular endothelial growth factor (anti-VEGF) agent, such as Lucentis or Avastin. Cessation of repeated injections results in rapid disease recurrence and vision loss.

$2 Bn market

Benitec’s therapeutic is designed to provide years of silencing of VEGF from just a single injection (same route of administration as current standard of care)
Disease Invades our Lands
The list goes on and on...

...cancers, infections, autoimmune disease...
With the Weapon of ddRNAi...
With the Weapon of ddRNAi
Significant Territory can be Reclaimed
Some diseases can’t be targeted

• **On target:**
  Any disease caused by or associated with one or a small number of unwanted genes
  - Viral infections
  - Genetic disorders
  - Cancers
  - CNS disorders

• **Out of range:**
  Diseases caused by multiple genes, or for which the cause is unknown
  - Bacterial infections
  - Psoriasis
  - Multiple sclerosis
  - ALS
Benitec’s ddRNAi: Risk of Friendly Fire?

• **Immune response**
  • Other gene silencing molecules such as small interfering RNAs (siRNAs) can activate innate immune responses through cell-surface Toll-like receptors
    • ddRNAi constructs are delivered directly into the cell by approved vectors

• **Toxic effects due to over-expression**
  • High levels of shRNAs have been shown to be toxic
    • ddRNAi constructs are designed to ensure levels are controlled

• **Off-target effects**
  • shRNAs with low specificity could target genes sharing sequence homology
    • Careful selection of shRNA sequences and thorough preclinical testing ensures that off-target activity is minimised
Profile Summary

- Product-focused biotechnology company
- A new therapeutic modality:
  - Unique and proprietary long-term gene-silencing platform
- Lead HCV program near to clinic
  - Success will demonstrate the technology’s ground-breaking potential
  - Significant value inflection expected
- Diverse pipeline poised to maximise ddRNAi’s potential and reduce risk

Company Aims

- Initiate first clinical phase I/IIa trial in Hepatitis C in 2013
- Out-license development in other disease areas
- Significant milestones soon to be met by existing licensees:
  - Calimmune ddRNAi HIV/AIDS therapeutic in the clinic in July 2013
- Expand preclinical data for pipeline therapeutics
- Establish new and build upon existing relationships with potential partners