# Benitec Biopharma's ddRNAi technology

The next therapeutic revolution?

*This presentation contains **forward looking statements that involve risks and uncertainties**.*

*Although we believe that the expectations reflected in the forward looking statements are **reasonable at this time**, Benitec can give **no assurance that these expectations will prove to be correct**.*

***Actual results could differ materially from those anticipated**. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.*

# Overview:

- Potent long-lasting gene silencing platform technology
- Multiple patent protection internationally
- Proven clinical application
- Broad pipeline in multiple therapeutic areas
- Out-licenses achieved for infectious disease applications
- Benitec will realise value for investors through licensing its technology to big pharma companies, and co-development of its product pipeline to the clinic.

# Benitec has developed the equivalent of a molecular gene silencing *penknife*

- ddRNAi can silence <u>any</u> gene
- Potential application for human disease is enormous
- Programs strategically selected to showcase the breadth of therapeutic applications

Each program is positioned to:

1. Address concerns around gene therapy
2. Enter the clinic in a short time frame
3. Provide a unique solution to a significant health issue

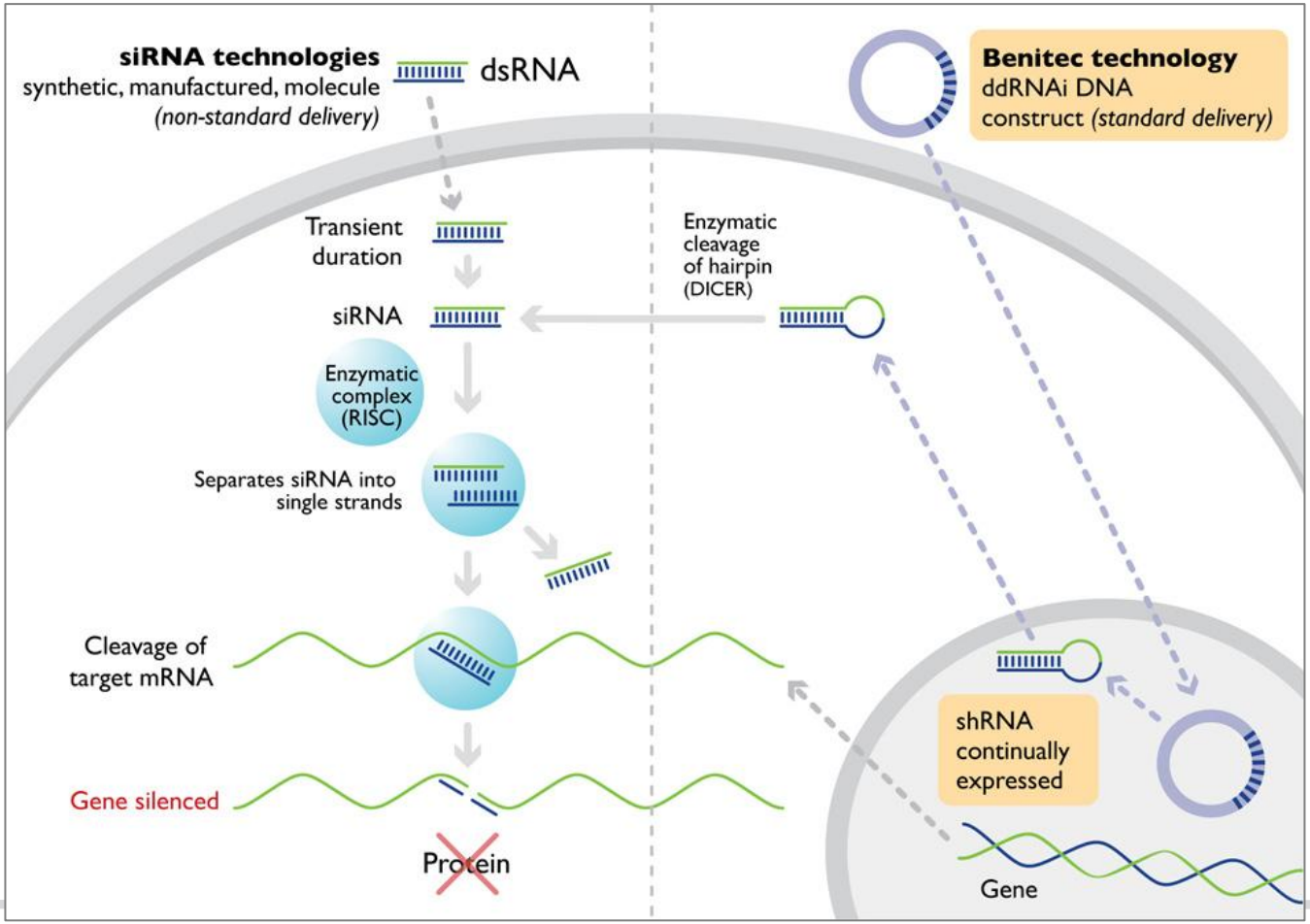
# How to make a ddRNAi product in eight steps

BENITEC BIOPHARMA
silencing genes for life™

| |
|---|
| 1. **Identify the key gene** that is critical for the development / progression of the disease |
| 2. **Identify a short region**(s) of that gene that is the gene's 'Achille's heel' |
| 3. **Design and manufacture a DNA construct** that will produce the silencing molecule |
| 4. **Test the construct *in vitro*** for its ability to silence the gene |
| 5. **Identify a delivery vehicle** that will carry that construct to the target organ |
| 6. **Test the construct *in vivo*,** looking for specific delivery and effective silencing |
| 7. **Determine toxicity** and off-target effects in two species |
| 8. **Test in clinical trials** – safety and efficacy – major inflection point for value creation |

# The ddRNAi technology

Benitec's ***ddRNAi technology*** platform utilises a DNA construct to ***continually express shRNA molecules*** which silence the target gene. This is a natural and long-lasting approach to gene silencing.



# Benitec Biopharma Goals and Strategy

**12 month corporate goal:**

- **To secure a big pharma partnering deal as a result of moving our technology into the clinic**

**Strategy:**

- **Advancement of our in-house pipeline to the clinic**
- **Out-licensing to external groups with clinical potential**
- **Acquisition of relevant late stage ddRNAi programs (areas under consideration include infectious disease, stem cell and cardiac programs)**
- **Building stem cell delivery capacity**
- **Direct contact with big pharma – awareness raising**

# Advancement of in-house pipeline programs to the clinic

- Cancer-associated pain
- Drug-resistant lung cancer
- Hepatitis B infection
- Muscular dystrophy

# Program 1:
## Cancer-Associated Pain

- Approximately 65% of all cancer patients experience pain
- 11.7 million people in the US with cancer

**The global market for cancer-associated pain products is valued at $2 billion and is expected to increase to $2.9 billion by 2016.**

# Identifying the key target pain gene

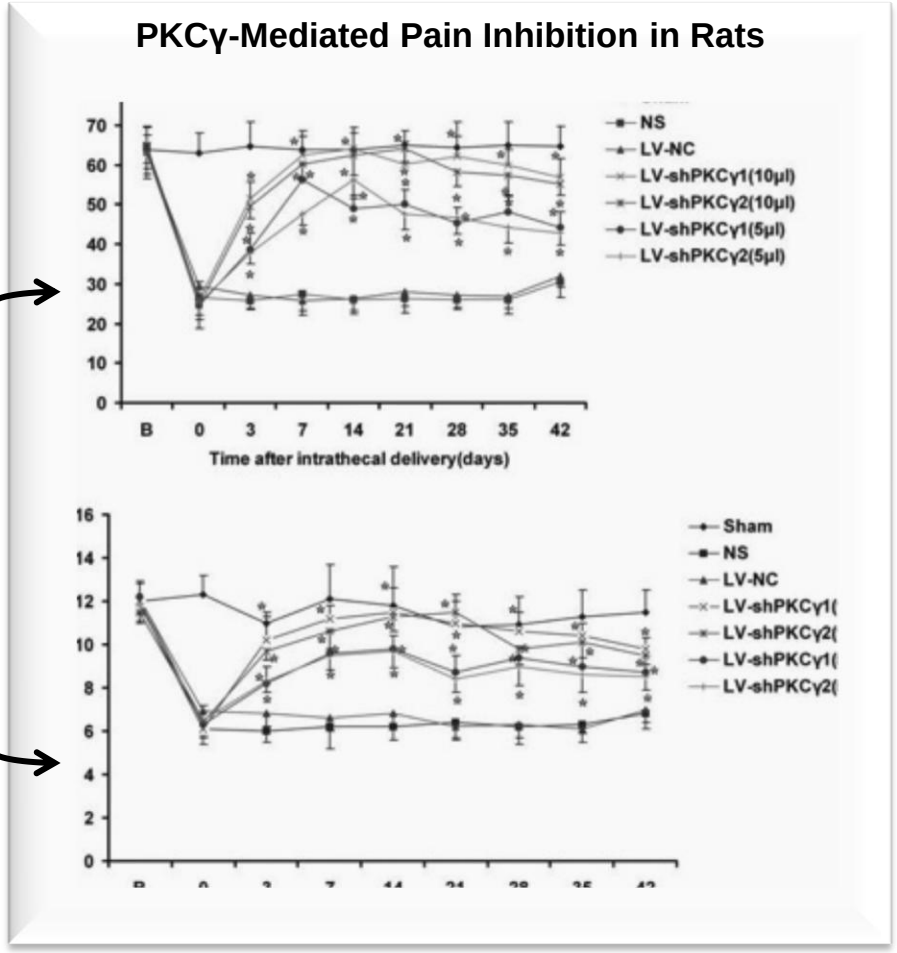
- Increased PKCγ found in the spinal cord in cancer pain

6 weeks

**One dose of PKCγ-silencing ddRNAi construct**

**No toxicity**

**Dose-dependent increase in pain threshold**




- Switching off PKCγ also overcomes morphine tolerance



Source: Results of nine KOL interviews conducted by Campbell Alliance in July and August 2011.

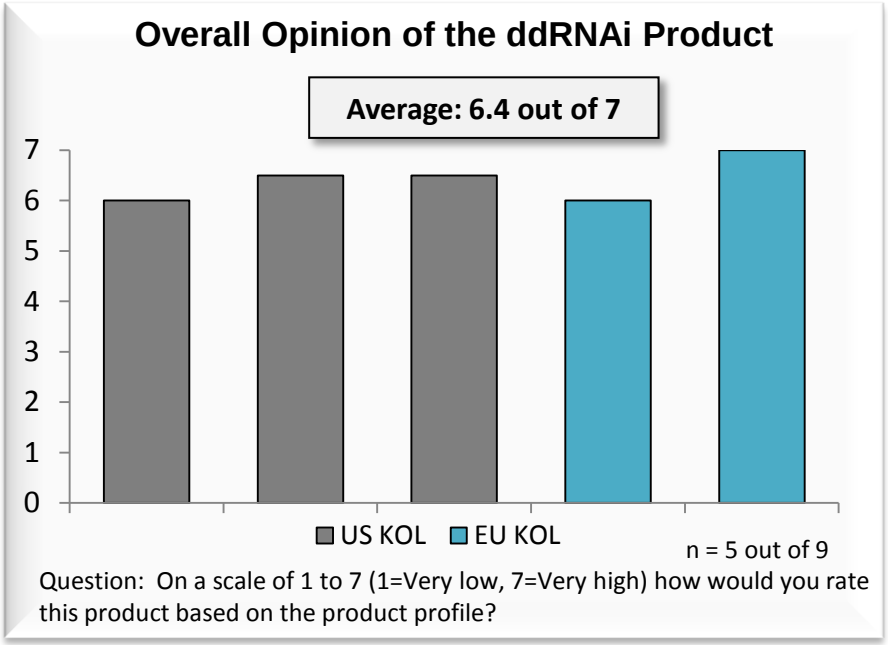
# Introducing Nervarna

# Nervarna development

| | | |
|---|---|---|
| 1. **Identify the key gene** | ✔ | PKCγ (DAO)<br>(patent application lodged) |
| 2. **Identify a short effective region**(s) | ✔ | 2 PKCγ sequences conserved across all key regulatory species and humans |
| 3. **Design and manufacture a DNA construct** | ✔ | Single and double cassettes |
| 4. **Test the construct *in vitro*** | ✔ | >80% silencing singly |
| 5. **Identify a delivery vehicle** | ✔ | EIAV (Oxford Biomedica) manufacturing in progress |
| 6. **Test the construct *in vivo*** | ✔ | Neuropathic pain rat model (preliminary) |
| 7. **Determine toxicity** | | Q3-4 2012 |
| 8. **Test in clinical trials** | | 2013 |

# Program 1:
# Feedback on Nervarna

## Healthcare Professional opinions (from Campbell Alliance, NY):




Such a product with a new mechanism of action was said to be...

**"sorely needed"**

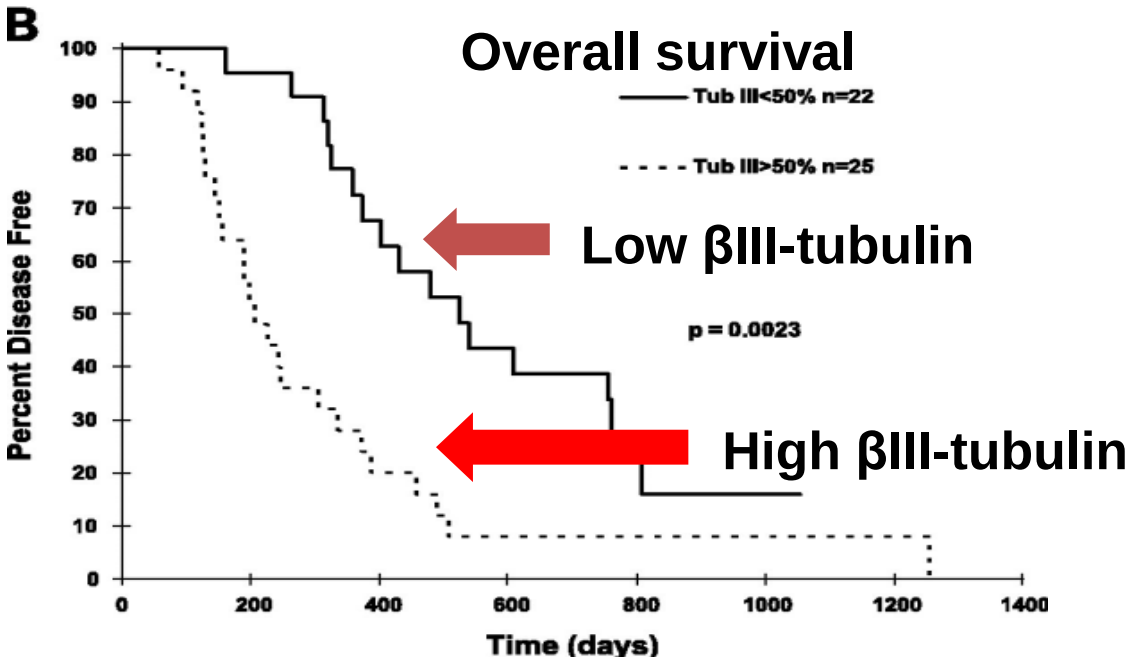


1. Zou W *et al. Brain Research* 2012; 1440: 34–46.

# **Program 2:** Drug-resistant lung cancer (NSCLC)

- Most common cancer: 1.6 M new cases per year globally
- Dismal prognosis, with a high proportion becoming resistant to conventional drug therapy within a short period of time.

βIII-tubulin associated with drug resistance

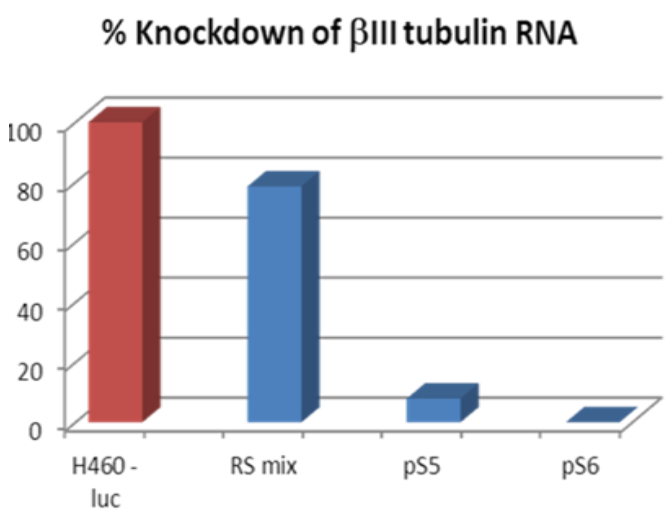


# Tribetarna development

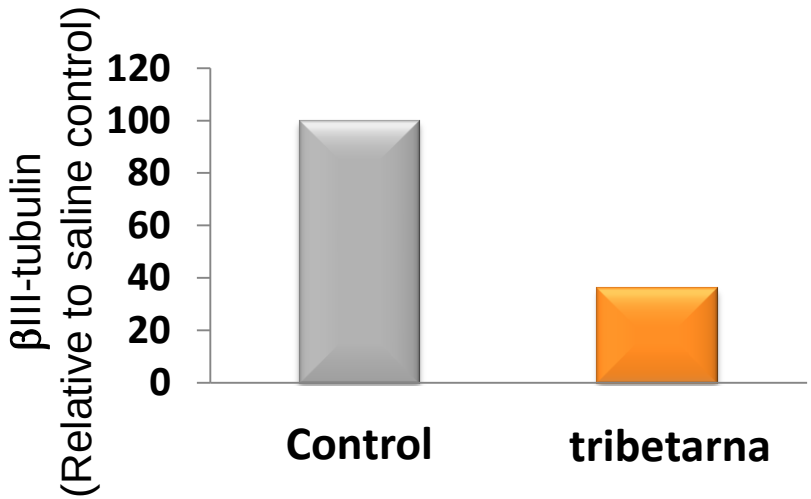
In collaboration with Children's Cancer Institute Australia, UNSW

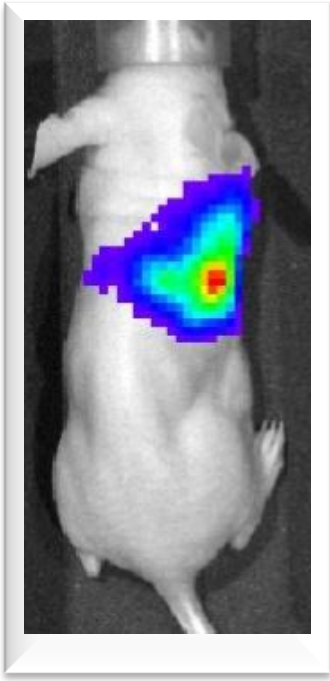

| | | |
|---|---|---|
| 1. **Identify the key gene** | ✔ | βIII tubulin |
| 2. **Identify a short effective region**(s) | ✔ | three sequences |
| 3. **Design and manufacture a DNA construct** | ✔ | A triple promoter triple cassette |
| 4. **Test the construct *in vitro*** | ✔ | 95% silencing |
| 5. **Identify a delivery vehicle** | ✔ | JetPEI specific for lung |
| 6. **Test the construct *in vivo*** | ✔ | Orthotopic mouse model (preliminary data) |
| 7. **Determine toxicity** | | Q3 2012 |
| 8. **Test in clinical trials** | | 2013 |

# Tribetarna data- silencing of βIII tubulin *in vitro* and *in vivo*




Βιιι-tubulin levels after three iv injections of tribetarna.

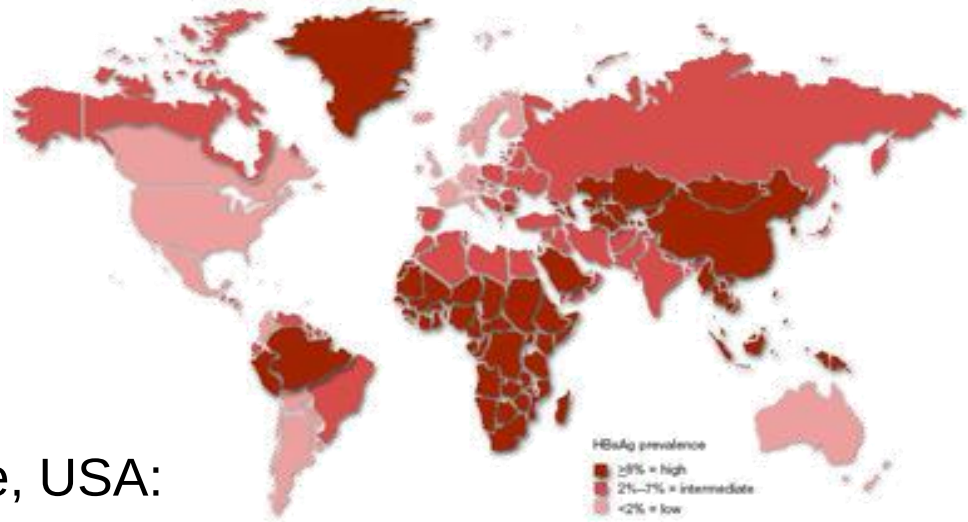


Ongoing success with tribetarna expected in 2012, including preparations for a clinical study

# Program 3: Hepatitis B

- More than 2,000 million people alive today have been infected with HBV at some time in their lives
- ~350 million remain chronically infected and become carriers of the virus




**Global Business Intelligence Hepatitis Market to 2017**

- For example, USA:
  - Over 1.25 million people living with the consequences of chronic active HBV
  - Over 60,000 new cases per year

# Hepbarna development


Collaboration with Biomics Biotechnologies Co Ltd, China

| | | |
|---|---|---|
| 1. **Identify the key gene** | ✔ | HBV DNA polymerase |
| 2. **Identify a short effective region**(s) | ✔ | 5 out of 5000 possibilities |
| 3. **Design and manufacture a DNA construct** | ✔ | A multicassette with modified promoters – May completion |
| 4. **Test the construct *in vitro*** | | May-June |
| 5. **Identify a delivery vehicle** | ✔ | AAV-8 (specific for liver) |
| 6. **Test the construct *in vivo*** | | Mouse model of HBV available June-Dec 2012 |
| 7. **Determine toxicity** | | Q1 2013 |
| 8. **Test in clinical trials** | | mid-late 2013 |

# Program 4: OPMD
## (oculopharyngeal muscular dystrophy)

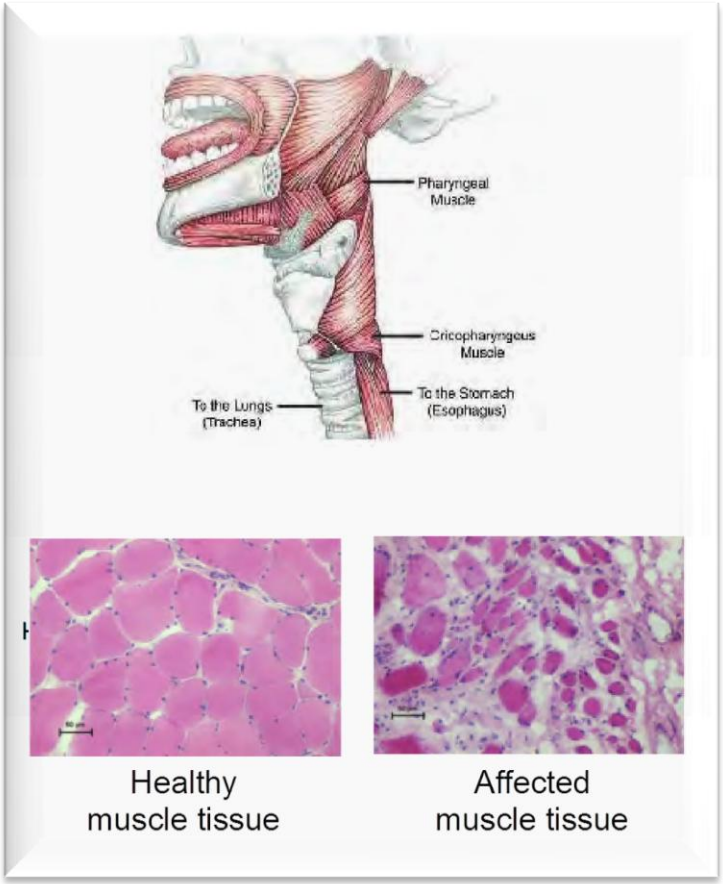
- A rare genetic disease
- No effective treatment exists
- Symptoms: Drooping of the eyelids, limb weakness, swallowing difficulties leading to choking and death

**OPMD is classified as an orphan disease.**

**It is a rare condition**

**(1 in 100 000 in Europe)**

**with a worldwide distribution.**






Source: http://healthmedcare.com/Health/muscular-dystrophy/

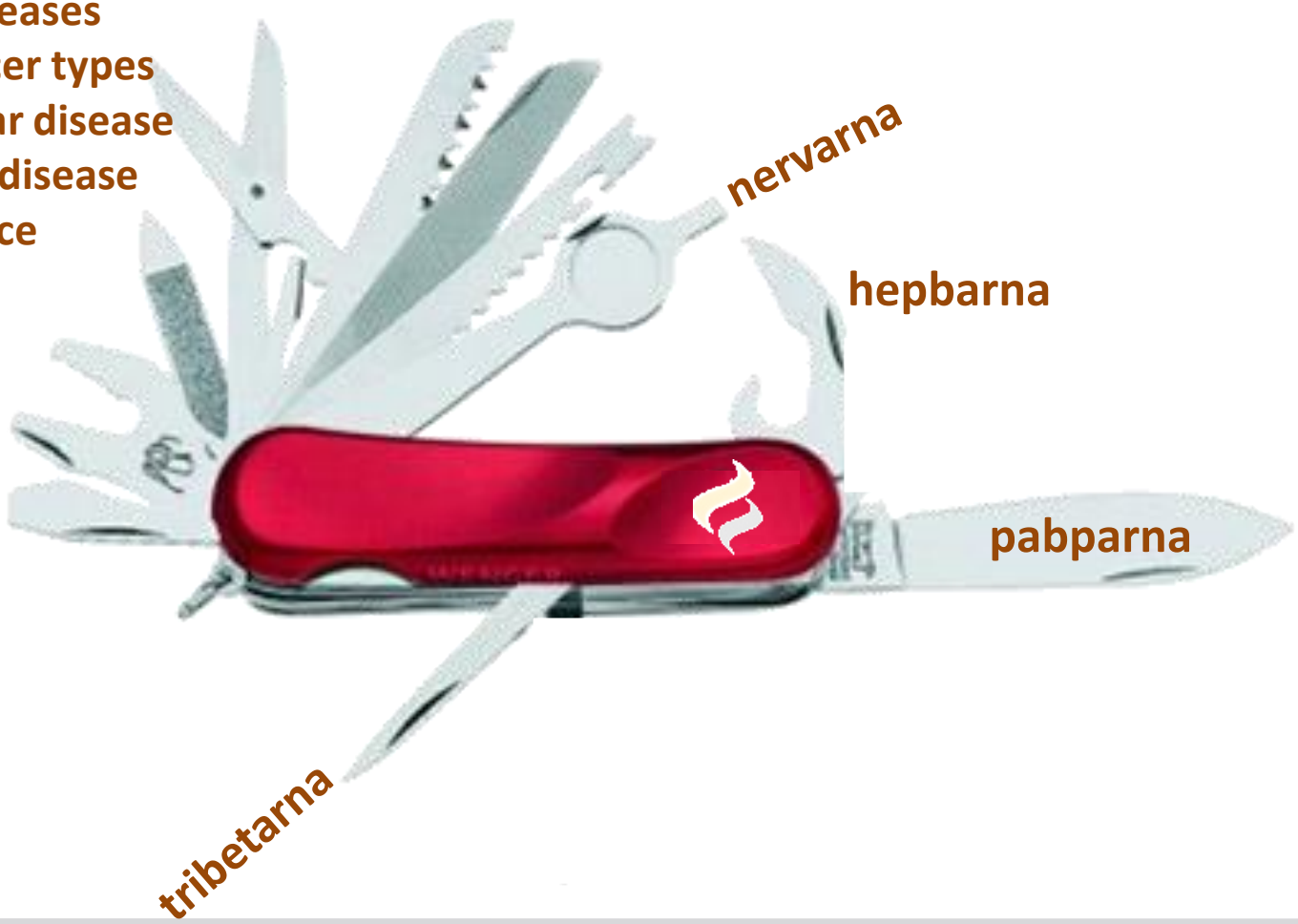
# Pabparna development

In collaboration with Royal Holloway, University of London


| | | |
|---|---|---|
| 1. **Identify the key gene** | ✔ | PABPN1 |
| 2. **Identify a short effective region**(s) | ✔ | Candidate sequences |
| 3. **Design and manufacture a DNA construct** | ✔ | In progress |
| 4. **Test the construct *in vitro*** | | |
| 5. **Identify a delivery vehicle** | ✔ | AAV-8 or lentivirus (TBD) |
| 6. **Test the construct *in vivo*** | | Mouse model available |
| 7. **Determine toxicity** | | |
| 8. **Test in clinical trials** | | Likely 2014-15 |

# Other potential applications…

- Infectious diseases
- Multiple cancer types
- Cardiovascular disease
- Huntington's disease
- Drug resistance
- Autoimmune
- Stem cells



# Outlicensed projects utilising Benitec Biopharma's ddRNAi technology

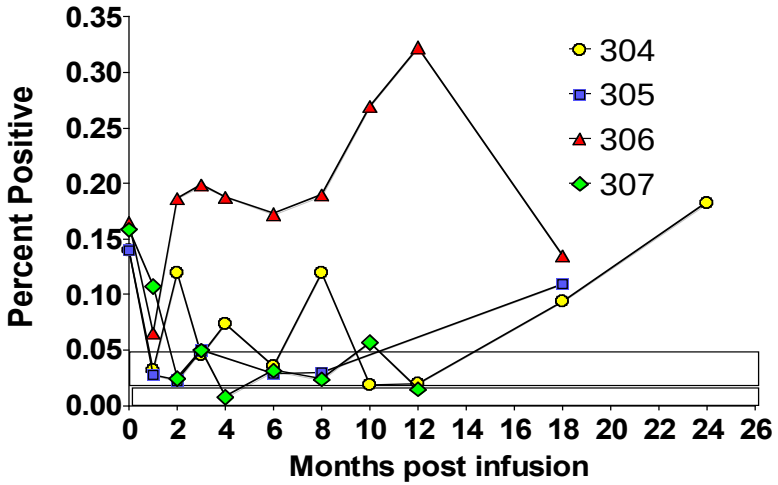
HIV/AIDS - Calimmune, USA

Hepatitis C - Tacere Therapeutics, USA

# First human ddRNAi clinical trial: **HIV/AIDS** (City of Hope)

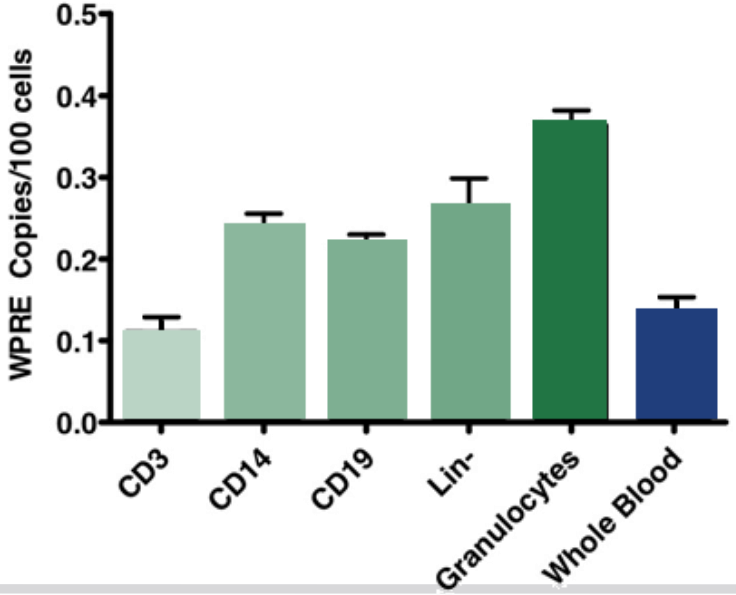
- Following only one stem cell-delivered treatment, constructs still present and active in stem cells and all immune cells after 3 years (data not shown)
- A completely new and resistant immune system potentially

**Gene Marking of Peripheral Blood Monocytes**




Expressed shRNA persists **for >2 years**

**Gene Marking in Immune Cells**



# Three groups using ddRNAi to tackle HIV/AIDS

**Berkhout Group, Amsterdam**

- Extensive research using multicassette
- Potential spin off and licensing opportunity

**City of Hope, US**

- 2nd clinical trial underway

**Calimmune, US**

- non-ex license agreement with Benitec Biopharma

1. DiGusto DL, *et al. Science-Translational Medicine* 2010; 2(36)

# Calimmune HIV ddRNAi product development

| | | |
|---|---|---|
| 1. **Identify the key gene** | ✔ | |
| 2. **Identify a short effective region**(s) | ✔ | |
| 3. **Design and manufacture a DNA construct** | ✔ | |
| 4. **Test the construct *in vitro*** | ✔ | |
| 5. **Identify a delivery vehicle** | ✔ | |
| 6. **Test the construct *in vivo*** | ? | |
| 7. **Determine toxicity** | ? | |
| 8. **Test in clinical trials** | | Expected in 2012 |

# Hepatitis C

## Hepatitis C is attracting huge interest in and deals for clinical assets

**Nov 2011**: Gilead paid **$11 billion** to buy Pharmasset's oral compound in Phase II testing.

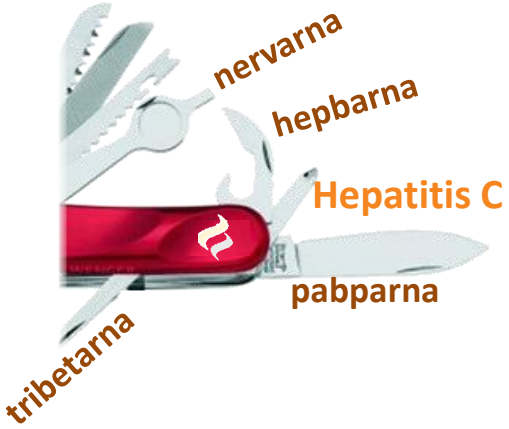
**Mar 2012**: Gilead announced the compound failed to suppress HCV in difficult-to-treat - or null - patients who had also failed prior therapy. Of eight with genotype 1, the most common form of the virus, all relapsed within four weeks after stopping the 12-week regimen.

**Jan 2012**: Achillion's CEO projected **HCV treatments would fetch $20 billion by the end of this decade.**

**Jan 2012**: "Our goal is to be a leader in hepatitis C, and we will do what it takes to get there," **Merck** CEO Pomerantz said. "**We would consider small deals to large deals, whatever is necessary to lead in hepatitis**."

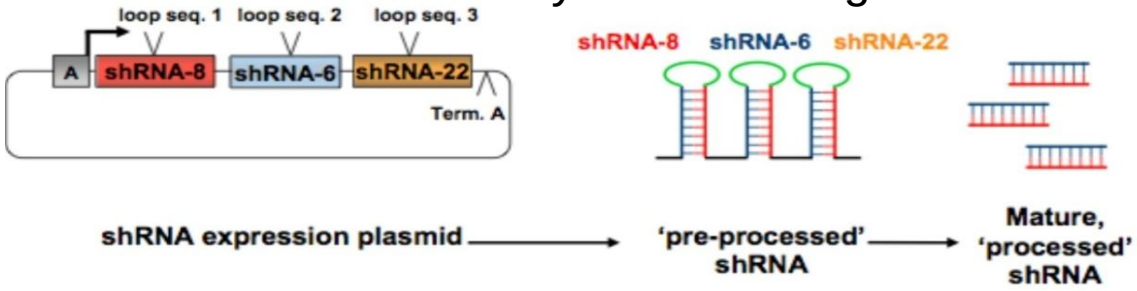
# Hepatitis C Program

## TT-0034 – a ddRNAi-based therapeutic targeting Hepatitis C virus genome




- **Multi-target construct (three sequences) to prevent viral escape in a single drug "cocktail"**
- **Delivered using AAV-protein coat encapsidation**
- **Licensed to Tacere Therapeutics Inc - USD$143M deal with Pfizer Inc**
- **Benitec has an equity stake in Tacere**

Pfizer closed Sandwich facility in 2011. Program on hold



# Tacere/Pfizer HCV TT-0034 product development

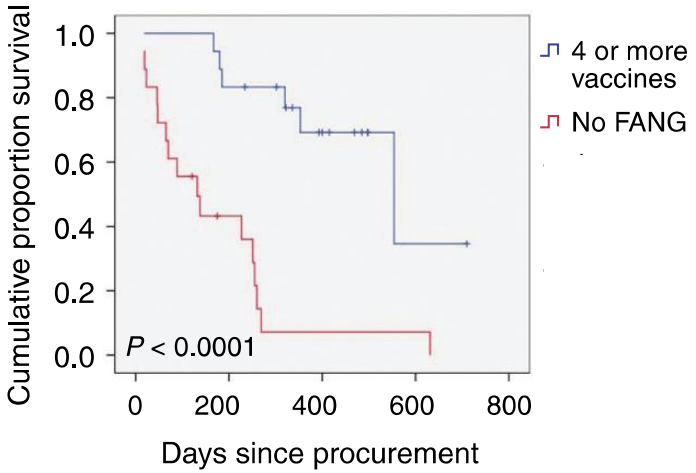
| | | |
|---|---|---|
| 1. **Identify the key gene** | ✔ | HCV genome target |
| 2. **Identify a short effective region**(s) | ✔ | Three sequences |
| 3. **Design and manufacture a DNA construct** | ✔ | Triple cassette with modified promoters |
| 4. **Test the construct *in vitro*** | ✔ | |
| 5. **Identify a delivery vehicle** | ✔ | AAV-8 (specific for liver) |
| 6. **Test the construct *in vivo*** | ✔ | NHPs |
| 7. **Determine toxicity** | ✔ | Minimal toxicity |
| 8. **Test in clinical trials** | | |

# Many other groups using ddRNAi technology

5700 publications in 2011

# ddRNAi construct within a vaccine: "FANG" anti-cancer vaccine (Gradalis)

- Phase I clinical trial of **systemically-delivered**, monthly vaccine delivering a bifunctional shRNA:
  - Targeting over expressed immunosuppressive factors promoting tumour growth
  - **Tested in advanced stage cancer patients**.




- 93.5% reduction of targeted over-expressed TGF-β isoforms
- >4 treatments **significantly increased survival**
- No adverse effects

**Gradalis has plans for a Phase II clinical trial**

# Progress in ddRNAi-based programs

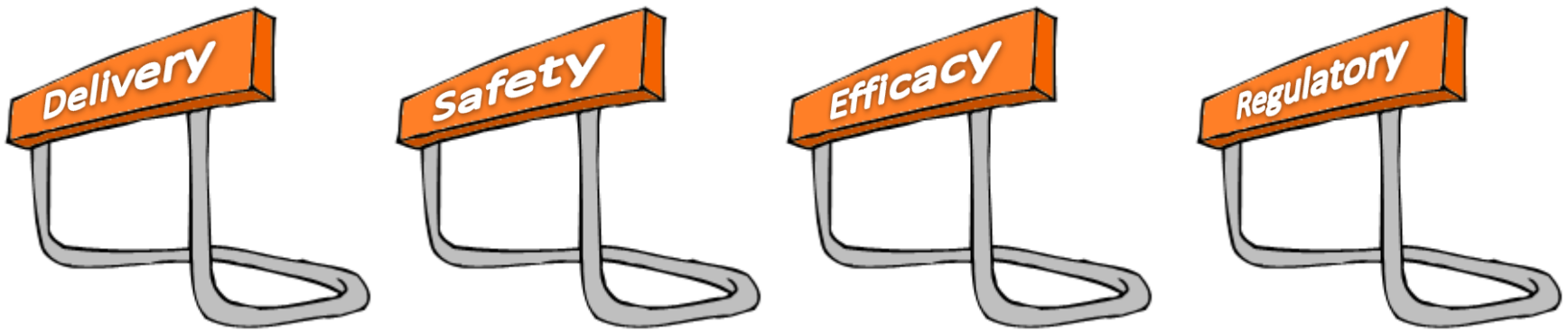
BENITEC BIOPHARMA
silencing genes for life™

| Indication | Discovery | Pre-clinical | Human clinical | External party(s) | Market |
|---|---|---|---|---|---|
| Cancer-associated pain | | | | University of Queensland (Australia) | $2.6 billion by 2016 |
| Drug resistant lung cancer | | | | University of New South Wales (Australia) | Leading form of cancer worldwide |
| Hepatitis B | | | | Biomics Biotechnologies (China) | 400 million globally, resulting in 60-80% of all primary liver cancers |
| Oculopharyngeal muscular dystrophy | | | | Royal Holloway, University of London | Orphan disease effecting 1 in 100,000 in Europe, no treatment available |
| Hepatitis C | | | | Tacere (Pfizer) (US) | >170 million people worldwide, 3-4 million new infections each year |
| HIV/AIDS | | | | Calimmune (US), City of Hope (US), Berkhout Group (Holland) | 1/200 infected with HIV worldwide |
| Anti-cancer vaccine | | | | Gradalis (US) | 11.7 million in the US alone |



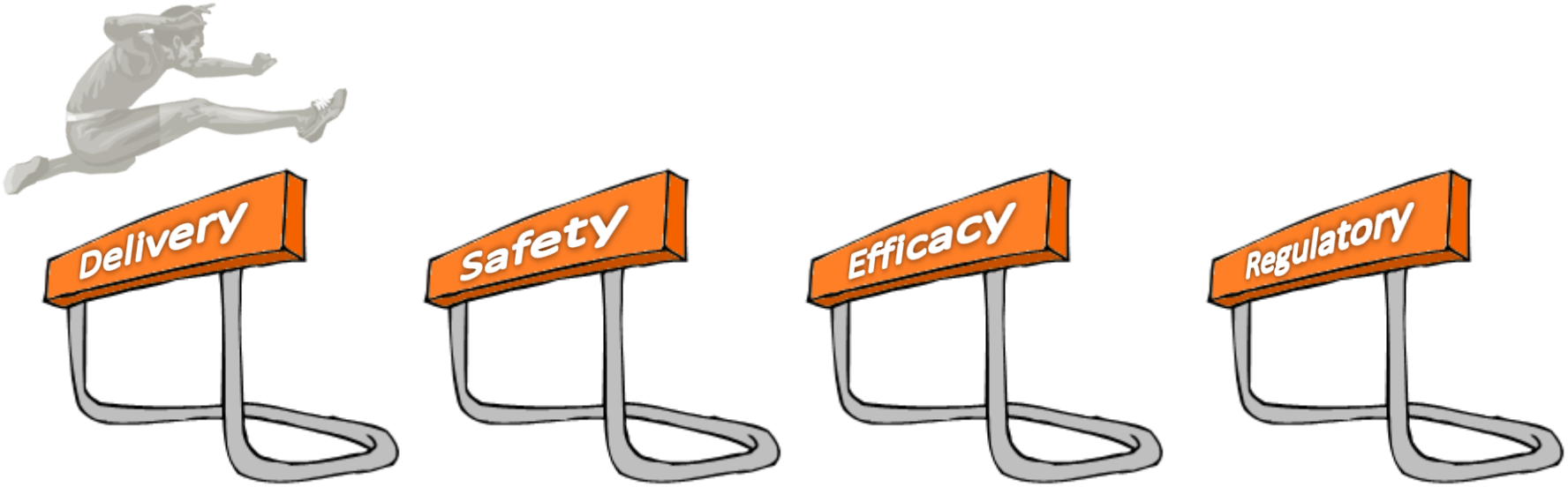
Benitec funded programs
Partnered program
Licensed program
External program

# Hurdles to the market



# Hurdles to the market

**Delivery proven both directly and systemically**



# Hurdles to the market

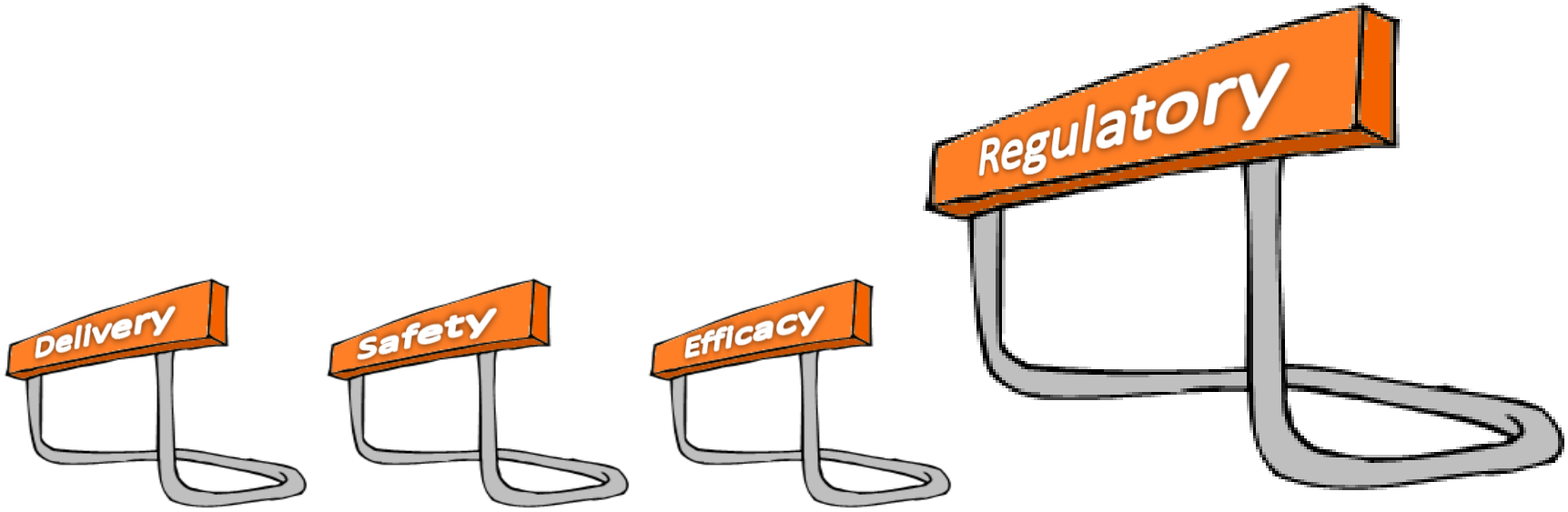
**Safety demonstrated in animal models and clinically in humans**

# Hurdles to the market

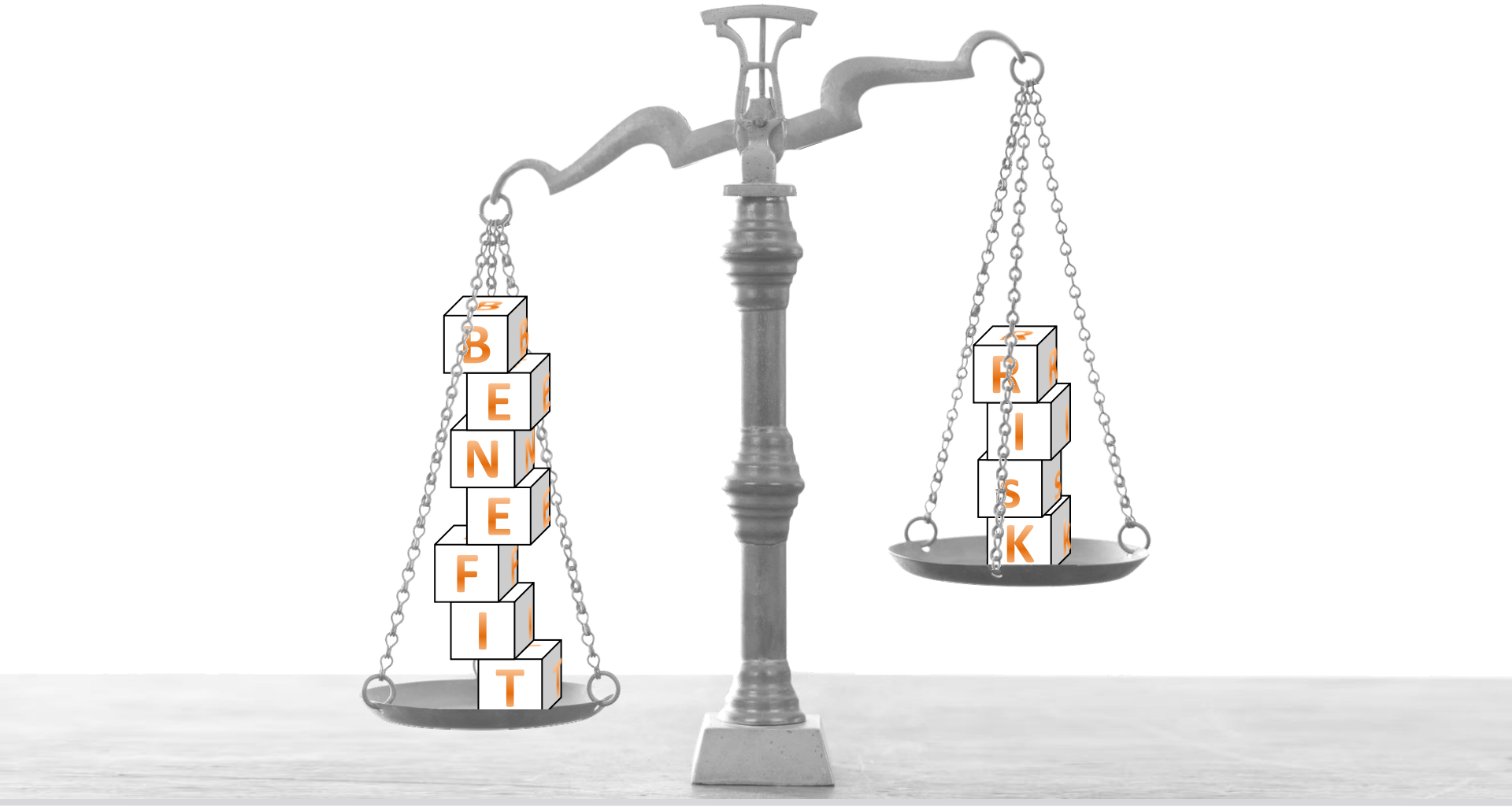
**Efficacy already proven in more than one therapeutic area**

# Hurdles to the market

## Regulatory is the next hurdle

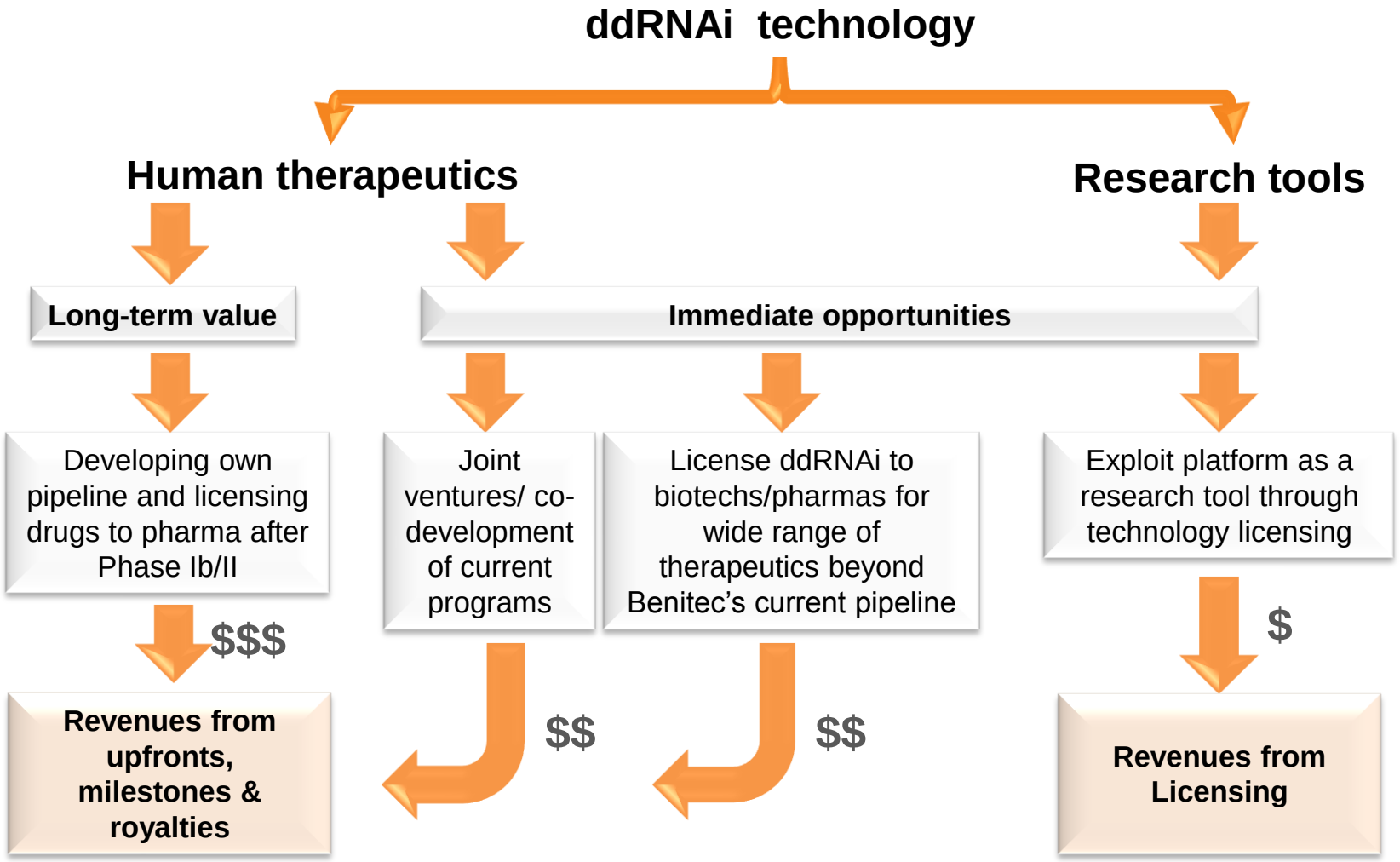


# Benitec Biopharma's strategy gives more weight to benefit



# The benefit-risk ratio should help propel Benitec's programs over that final hurdle

# Strategy to build value



# Big Pharma are doing big deals in Benitec's program areas

**Phase 1 clinical trials are Benitec Biopharma's next significant inflection point.**

| Companies | Condition | Stage | Deal | When |
|---|---|---|---|---|
| Xenon / Genentech | Pain | Phase II | A$646 million deal – undisclosed upfronts and milestones. | Jan 2012 |
| Enanta / Novartis | Hep C | Phase I | $36 million upfront, as much as $404 million more on clinical, regulatory, and commercial milestones | March 2012 |
| Gilead / GlobeImmune | Hep B | Phase Ia | undisclosed upfront payment plus additional milestone payments and, potentially, royalties | Oct 2011 |
| Avila / Clovis | Non small cell lung cancer | Pre clinic | unspecified upfront and regulatory and sales milestones that add up to $209 million | May 2010 |

# In summary:

- Potent long-lasting gene silencing platform technology
- Multiple patent protection internationally
- Proven clinical application
- Broad pipeline in multiple therapeutic areas
- Goal is to secure multiple big pharma partnering deals following commencement of clinical trials