Target therapy for bone metastatic prostate cancer with Micro RNA145 inhibits tumor growth in vivo

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Prostate cancer

- Most common malignancy in men
- Second cause of death

Treatment

- Active surveillance
- Radical prostatectomy
- Radiotherapy
- Hormone therapy

Localized prostate cancer 5 year survival – 100%
Metastatic prostate cancer 5 year survival – 28%

The microRNA

- **20 – 24 nts**
- **Endogenous**
- **Eukaryotes**
- **Single-stranded**
- **Dicer dependent**
- **Ago subfamily**
- **3'/5'-UTR/promoter/coding reg/pseudogene**
- **mRNA degradation/transcriptional or postranscriptional silencing (HUMAN)**

- **21 – 23 nts**
- **Endogenous or exogenous**
- **Eukaryotes**
- **Double-stranded**
- **Dicer dependent**
- **Ago subfamily**
- **mRNA or gene promoter**
- **mRNA degradation/transcriptional or postranscriptional silencing**
Characteristics of miRNAs

• Stable in different specimens
  – Control of at least 30% of human genes.
  – Regulate important cell process (apoptosis, proliferation...)
  – Related to the development and progression of cancer

Mitchell et al. *PNAS 2008;105:10513*

http://microrna.sanger.ac.uk/cgi-bin/sequences/browse.pl
Tumor suppressor miRs

**miR-15a and 16-1**
Target – Bcl2, CCND1, CCND3, CCNE1, CDK6, VEGF, FGF2, FGFR1

**miR-143/145**
Target – **RAS, Myc**, BNIP3, FSCN1, OCT4, SOX2, KLF4

OncomiRs

**Cluster miR-17-92**
Target – PTEN

**miR-221/222**
Target – p27, p57, DDIT4, PTEN, TIMP3

**miR-21**
Target – PTEN, RHOB, RECK, PDCD4, TIMP3
miRNA and prostate cancer

• Volinia et al. (2006)
• Porkka et al. (2007)
• Cancer stem cell maintenance – ↓miR-34a (CD44)
• Epithelial mesenchymal transition – ↓miR-200b (ZEB1,2)
  Kong et al. Stem Cell 2009;27:1712
• Tumor suppressor miRs – miR-15a, 16, 143, 145
  Musumeci et al. Oncogen 2011;30:4231
• OncomiRs – miR-221, 222
  Galardi et al. 2007;282:23716
  Zheng et al. Med Oncol 2012
MicroRNA and treatment

  - Xenograft of prostate cancer
  - anti-miR-221 / 222
  - Impairs tumor cell growth

- Takeshita et al. *Mol Ther* 2010;18:181
  - Xenograft of prostate cancer
  - miR-16
  - Suppression of tumor growth

- Humans
  - Anti-miR-122 - Miravirsen®
  - Phase II trial (NCT01200420)
  - Treatment of hepatitis C
<table>
<thead>
<tr>
<th></th>
<th>HGPIN</th>
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<th>Metastasis/Cell lines</th>
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### PCR after transfection

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* p<0,05

NE: not expressed
Purpose

Study the effects of treatment with intravenous miRNAs 145 in a pre-clinical model of disseminated bone metastatic prostate cancer.
Methods

- Balb/c NUDE mice – 9-11 weeks (n=8)
  - Intraventricular injection of PC-3M-luc-C6
  - IVIS® Spectrum (Caliper)
  - miRNA and atelocollagen
Atelocollagen
300 kD – 300 nm (c) – 1.5 nm (d)

miR145 ou scramble

Takeshita et al. PNAS USA 2005;102:12177
In vivo studies - Xenograft

PC-3M-luc-C6 $2 \times 10^6$
RESULTS

D21
Begin of treatment

D27
End of treatment

D34

D48
End of experiment

Mir145  Control

Mir145  Control

Mir145  Control

Mir145  Control
RESULTS

<table>
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<tr>
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<th>D7</th>
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(n=8)
CONCLUSION

- In animals with diffuse metastatic disease, the treatment with mir145 leads to a temporary response due to a fast degradation and to cancer cells mechanisms of escape and resistance.

- Further studies with this purpose and design will permit the development of novel target drugs based on microRNAs to suppress the metastatic prostate cancer growth.
THANK YOU
Intra-cardiac injection
PC3-luc-C6

Treatment

Necropsy

D0 → D7 → D14 → D21 → D24 → D27 → D34 → D41 → D48

IVIS