

CRT Licensing Opportunity



$\alpha\nu\beta 6$ -binding Peptides for Tumour Targeting

- Novel and proprietary peptides with high affinity and selectivity for integrin $\alpha\nu\beta 6$
- Lead peptide selectively targets $\alpha\nu\beta 6$ tumours *in vivo* for imaging and therapy
- $\alpha\nu\beta 6$ is highly expressed in many tumours and clinically correlates with poor prognosis
- $\alpha\nu\beta 6$ identified as a key target in RAS-dependent tumours of high unmet medical need

BIOLOGICAL THERAPEUTICS/ DIAGNOSTICS | *In Vivo* Proof-of-Principle

October 2009

Commercial Opportunity

The integrin $\alpha\nu\beta 6$ is an exciting emerging target for both imaging and therapy across many common tumour types including pancreatic, breast, oesophagus, head and neck, skin, lung and ovarian. Each year an estimated 279,000 $\alpha\nu\beta 6$ -positive tumours are diagnosed in the US & UK alone.

Peptides with remarkable affinity and selectivity for $\alpha\nu\beta 6$ have been identified and characterised (1). *In vitro* and *in vivo* data demonstrates the potential of these peptides as the basis for novel PET and SPECT imaging probes, tumour targeting agents and functional inhibitors of $\alpha\nu\beta 6$. Patent family WO2007/039728 protecting the peptide consensus sequence is available for exclusive licensing or collaborative development.

In vivo Imaging

The lead peptide ('A20FMDV2') has been validated *in vivo* for use in both PET and SPECT imaging with a variety of radiolabelling approaches. The labelled peptide shows rapid uptake and selective retention in xenograft tumours engineered to express $\alpha\nu\beta 6$, but not to their non- $\alpha\nu\beta 6$ expressing counterparts (2). Furthermore, A20FMDV2 has been used to successfully image both breast and pancreatic xenograft tumours endogenously expressing $\alpha\nu\beta 6$ (3) and Figure 1). Based on these data, the peptide has potential for use as a novel imaging probe in these tumours and others where $\alpha\nu\beta 6$ over-expression is observed.

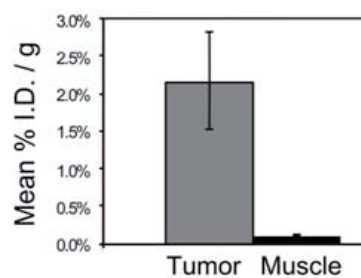


Figure 1. NanoSPECT/CT image of a breast cancer xenograft using ^{111}In -A20FMDV2 (top panel) and calculated % injected dose per gram of tissue for tumour versus muscle (bottom panel)

In vivo Therapeutic Targeting

To demonstrate the potential of the peptides for therapeutic targeting of tumours *in vivo*, the A20FMDV2 sequence was incorporated into the HI loop of the adenovirus type 5 (Ad5)

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fiber knob. The resulting $\alpha v\beta 6$ -retargeted virus exhibited up to 50-fold increases in CAR-independent transduction and up to 480-fold increased cytotoxicity *in vitro* (4). *In vivo*, the virus demonstrated enhanced tumour uptake and reduced liver sequestration. Based on these data, work is ongoing to demonstrate the ability of A20FMDV2 to deliver both nanoparticles and toxic payloads to tumours.

In vitro Data

The inventors have deduced the consensus structural motif for selective binding to $\alpha v\beta 6$ and developed a lead peptide agent 'A20FMDV2'. *In vitro*, the peptide blocks $\alpha v\beta 6$ ligand binding with an IC50 of 3nM, and shows >1000-fold selectivity over other integrins. Function-blocking abilities of the peptide have been demonstrated using $\alpha v\beta 6$ -dependent tumour cell migration and invasion assays. In addition, A20FMDV2 mediates rapid tumour cell uptake, a key prerequisite for efficacious delivery of toxic payloads (Figure 2).

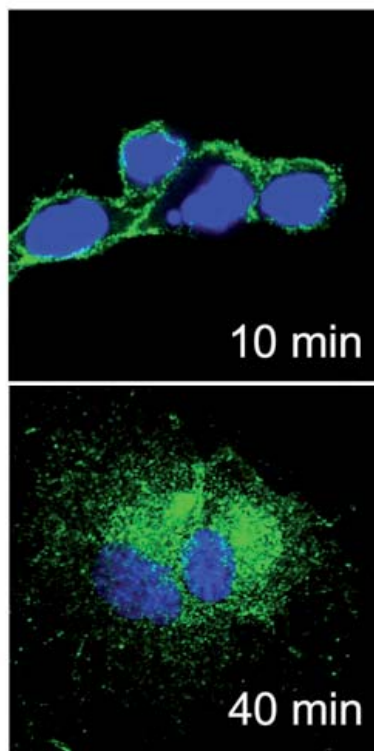


Figure 2. A20FMDV2 is rapidly internalised by $\alpha v\beta 6$ -positive tumour cells

Supporting Rationale

The expression of $\alpha v\beta 6$ is restricted primarily to epithelial cells where it is expressed at low levels in healthy tissue and significantly up-regulated during wound healing, fibrosis and

in tumourigenesis. $\alpha v\beta 6$ has multiple regulatory functions in tumours including TGF- β activation, cell proliferation, MMP production, cell invasion and survival. Antibody-mediated blockade of $\alpha v\beta 6$ has been demonstrated to inhibit tumour growth *in vivo* (5), supporting the use of $\alpha v\beta 6$ -targeted agents in cancer therapy.

In cancer patients, elevated $\alpha v\beta 6$ expression has been correlated with poor prognosis in tumours including colorectal, ovarian and lung. Numerous publications have identified $\alpha v\beta 6$ as a key regulator of the epithelial to mesenchymal transition, and more recently $\alpha v\beta 6$ has been linked with maintenance of a pluripotent cancer stem cell phenotype in oral cancer. Intriguingly, a recent study identified $\beta 6$ integrin as a key member of a "K-Ras dependency signature" and supported targeting $\beta 6$ in lung and pancreatic tumours with a K-Ras driven phenotype (6). This represents a patient set of huge unmet medical need since these tumours are largely refractory to currently available therapies.

References

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