

CRT Licensing Opportunity



Integrin-binding Peptides for Tumour Targeting

- $\alpha v \beta 6$ is over-expressed in many tumours and is a target for imaging or delivering therapeutics
- A20FMDV2 is a novel and proprietary peptide with high affinity and selectivity for $\alpha v \beta 6$
- Used successfully to image $\alpha v \beta 6$ -positive human xenografts by PET and SPECT
- Structural basis of high-affinity binding elucidated and subject to PCT patent application

DIAGNOSTICS | Validation

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Introduction

A series of peptides showing high affinity and specificity for the integrin $\alpha v \beta 6$ has been identified. The peptides have significant potential for tumour imaging and delivery of therapeutic agents. The consensus sequence for high affinity binding is subject to a patent application available for licensing.

The Technology

The inventors have deduced the consensus structural motif for high affinity and specific binding of peptides to $\alpha v \beta 6$ (described in Dicara *et al.* 2007). The studies provide a structural platform for the design of $\alpha v \beta 6$ antagonists and have identified a promising 20 amino acid lead compound, A20FMDV2. Using flow cytometry and ELISA the inventors have shown that A20FMDV2 binds to $\alpha v \beta 6$ with both high affinity and selectivity. The peptide inhibits $\alpha v \beta 6$ -ligand binding with an IC_{50} of 3 nM, an activity 1000-fold more selective for $\alpha v \beta 6$ than for other RGD-directed integrins ($\alpha v \beta 3$, $\alpha v \beta 5$ and $\alpha 5 \beta 1$; Figure 1).

Peptide	$\alpha v \beta 6$	$\alpha v \beta 3$	$\alpha v \beta 5$	$\alpha 5 \beta 1$
A20FMDV2	3 ± 1 nM	>10 μ M	>100 μ M	>10 μ M
[19 F]FBA-A20FMDV2	3 ± 1 nM	>10 μ M	>10 μ M	>10 μ M

Figure 1: IC_{50} values comparing the ability of A20FMDV2 and [19 F]FBA-A20FMDV2 to inhibit binding of biotinylated ligands to immobilized $\alpha v \beta 6$, $\alpha v \beta 3$, $\alpha v \beta 5$, and $\alpha 5 \beta 1$ integrins.

Importantly, *in vivo* nanoSPECT/CT and microPET imaging of mice bearing $\alpha v \beta 6$ -positive and -negative human xenografts has successfully demonstrated the utility of 111 Indium and 4-[18 F]-fluorobenzoic acid-labelled A20FMDV2 in the selective detection of $\alpha v \beta 6$ -expressing tumours. The labelled peptide shows rapid uptake (< 30 minutes) and selective retention (> 5 hours) with rapid renal clearance of non-specifically bound activity (Figure 2).

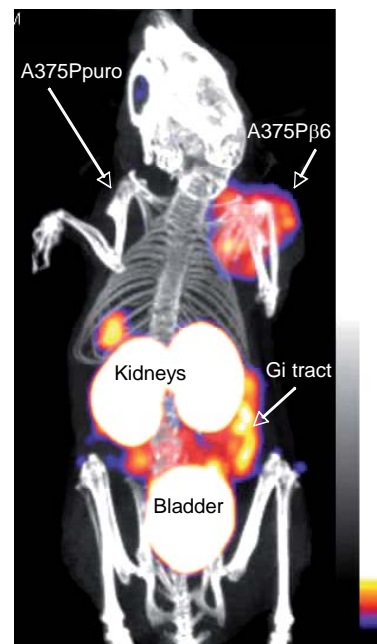


Figure 2: NanoSPECT/CT imaging of $\alpha v \beta 6$ -positive (A375P $\beta 6$) and $\alpha v \beta 6$ -negative (A375P Puro) xenografts with 111 Indium-labelled A20FMDV2.

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A recent publication has also confirmed the utility of $\alpha\nu\beta 6$ -specific peptides for the selective targeting of toxins to tumour cells (Guan et al. 2008). CRT's peptides have been shown to undergo rapid internalisation into tumour cells, demonstrating the therapeutic potential of this technology (Figure 3).

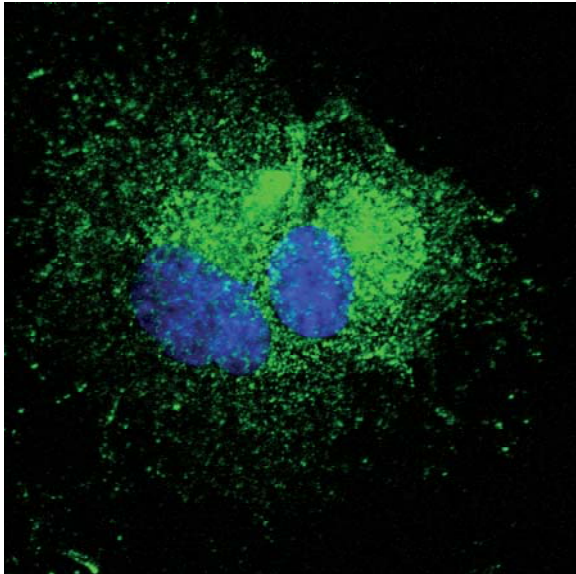


Figure 3. Labelled peptides are rapidly internalised by tumour cells

Background

The epithelial-specific integrin $\alpha\nu\beta 6$ binds to RGD motifs in its ligands including fibronectin, tenascin and the latency-associated peptide (LAP) of TGF β . $\alpha\nu\beta 6$ is usually absent from most healthy adult tissues but is over-expressed in a range of tumours including more than 90% of oral squamous cell carcinomas (OSCC), pancreatic and ovarian tumours, and approximately 40% of lung, colon and breast carcinomas. As such, $\alpha\nu\beta 6$ is a tumour-specific target for the development of imaging and therapeutic agents. The high expression of $\alpha\nu\beta 6$ at the invasive front of OSCC indicates that imaging agents based on targeting $\alpha\nu\beta 6$ may aid in surgical resection of tumours, where recurrence is often traced to incomplete removal of the primary tumour.

Furthermore, $\alpha\nu\beta 6$ promotes tumorigenesis *in vivo* through effects on invasion, migration, cell survival and activation of TGF β . $\alpha\nu\beta 6$ over-expression is associated with poor prognosis in OSCC, colon and breast cancer patients. These data indicate that agents that interfere with $\alpha\nu\beta 6$ function may also have direct therapeutic applications.

Intellectual Property

CRT has filed National/Regional patent applications in US, Canada, Europe and Japan which are available for exclusive licensing or collaborative development for therapeutic and/or imaging applications together with associated data.

References

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