COMMERCIAL OPPORTUNITY

The integrin αvβ6 is an exciting emerging target for imaging and therapy across many common tumour types (including pancreatic, breast, oesophagus, head and neck, skin, lung and ovarian) and also in fibrotic diseases. Targeting this integrin has considerable therapeutic potential (each year an estimated 250,000 αvβ6 positive tumours are diagnosed in the US & UK alone) and there are several companies developing agents that target αvβ6, one of which is in Phase II clinical trial for idiopathic pulmonary fibrosis (IPF). There is potential to use an αvβ6 imaging agent alongside such therapies for patient stratification and/or monitoring.

Peptides with remarkable affinity and selectivity for αvβ6 have been identified and characterised (1). In vitro and in vivo data demonstrate the potential of these peptides as the basis for novel PET and SPECT imaging probes, as well as tumour targeting agents and functional inhibitors of αvβ6. The lead peptide inhibits αvβ6-ligand binding with an IC50 of 3 nM, an activity 1000-fold more selective for αvβ6 than for other RGD-directed integrins (αvβ3, αvβ5 and α5β1, Table1).

<table>
<thead>
<tr>
<th>Peptide</th>
<th>αvβ6</th>
<th>αvβ3</th>
<th>αvβ5</th>
<th>α5β1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A20FMDV2</td>
<td>3 ± 1 nM</td>
<td>&gt;10 µM</td>
<td>&gt;100 µM</td>
<td>&gt;10 µM</td>
</tr>
<tr>
<td>[19F]FBA-A20FMDV2</td>
<td>3 ± 1 nM</td>
<td>&gt;10 µM</td>
<td>&gt;100 µM</td>
<td>&gt;10 µM</td>
</tr>
</tbody>
</table>

Table 1: IC50 values comparing the ability of A20FMDV2 and [19F]FBA-A20FMDV2 to inhibit binding of biotinylated ligands to immobilized αvβ6, αvβ3, αvβ5 and α5β1 integrins.

Patent family WO2007/039728 protecting the peptide consensus sequence is available for 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 αvβ6, but not in their non-αvβ6 expressing counterparts (2, 3). Furthermore, A20FMDV2 has been successfully used to selectively image both breast (Figure 1) and pancreatic (Figure 2) xenograft tumours endogenously expressing αvβ6. Recently, A20FMDV2 has also been used in vivo to image lung fibrosis, a condition in which αvβ6 expression is also up-regulated (Figure 3) (4). Radiolabelled A20FMDV2 is rapidly degraded and excreted via the kidneys (Figure 4), and similar levels of peptide uptake are observed following re-administration permitting repeat imaging (Figure 3). Based on these data, the peptide has potential as a novel imaging probe in diseases, such as cancer and fibrosis, where αvβ6 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).

Figure 2: MicroPET images (coronal and axial) of a pancreatic cancer xenograft using $^{18}$F-FBA-PEG$_{28}$-A20FMDV2.

Figure 3: NanoSPECT-CT imaging of $^{111}$In-A20FMDV2 in bleomycin-induced lung fibrosis. The level of $^{111}$In- DTPA-A20FMDV2 detected in the lungs was greatly increased in mice treated with bleomycin versus saline following administration of the peptide 14 days after bleomycin treatment (A) and re-administration at 28 days (B).

Figure 4: Intense signal from $^{111}$In-A20FMDV2 in the kidneys, bladder and GI tract after NanoSPECT-CT imaging. Signal from kidneys is related to non-specific clearance of the peptide.

**SUPPORTING RATIONALE**

The epithelial-specific integrin αvβ6 binds to RGD motifs in its ligands including fibronectin, tenascin and the latency-associated peptide (LAP) of TGFβ. Expression of αvβ6 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, for example αvβ6 is over-expressed in approximately 90% of oral squamous cell carcinomas, pancreatic and ovarian tumours, and 40% of lung, colon and breast carcinomas. αvβ6 has multiple regulatory functions in tumours including TGF-β activation, cell proliferation, MMP production, cell invasion and survival. Antibody-mediated blockade of αvβ6 has been demonstrated to inhibit tumour growth in vivo (5, 6), supporting the use of αvβ6-targeted agents in cancer therapy. In patients, elevated αvβ6 expression has been correlated with poor prognosis including in colorectal, ovarian and lung cancers. Numerous publications have identified αvβ6 as a key regulator of the epithelial to mesenchymal transition. αvβ6 has also been linked with maintenance of a pluripotent cancer stem cell phenotype in oral cancer, and as a key member of a “K-Ras dependency signature” in lung and pancreatic tumours (7).

**REFERENCES**


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