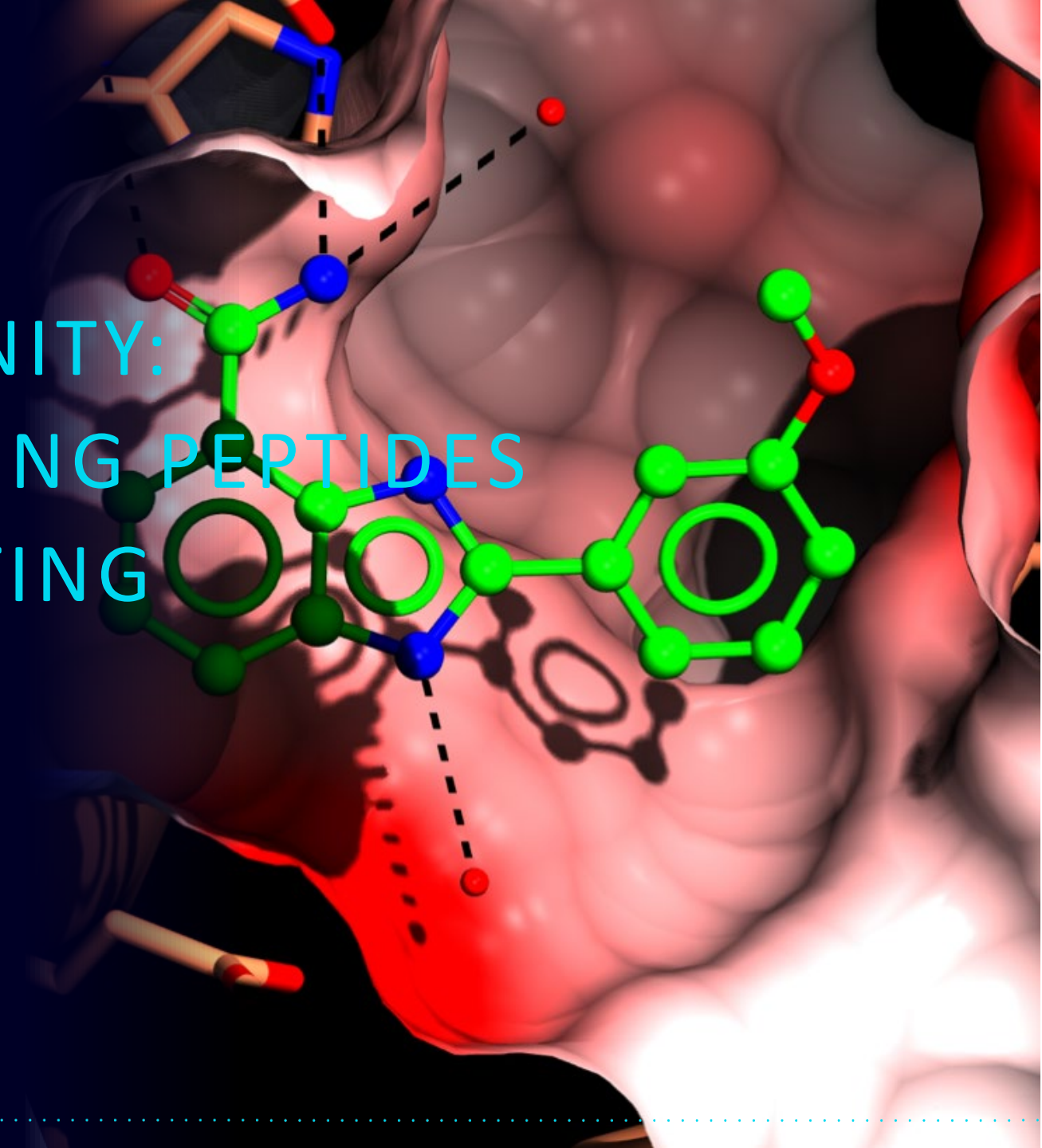


CANCER
RESEARCH
HORIZONS

FURTHER FASTER TOGETHER

LICENSING OPPORTUNITY: INTEGRIN AVB6-BINDING PEPTIDES FOR TUMOUR TARGETING & IMAGING

SEPTEMBER 2023



OPPORTUNITY OVERVIEW

Lead inventor: Prof John Marshall (QMUL)

High affinity $\alpha v\beta 6$ -specific lead peptide A20FMDV2

- Novel and proprietary peptides with high affinity and selectivity for integrin $\alpha v\beta 6$
- Lead peptide selectively targets $\alpha v\beta 6$ +ve tumours and fibrotic lesions in vivo for imaging and therapy
- Toxin-labelled A20FMDV2 controls or clears, in vivo murine xenograft pancreatic tumours
- Clinical efficacy as PET tracer in solid tumour patients

Intellectual property

Two patent families relating to the $\alpha v\beta 6$ -Binding Peptides:

- Claims under prosecution cover peptide consensus sequence, novel variants, as well as peptide, conjugate and method of treatment claims (including conjugation to detectable moieties for imaging and therapeutic moieties)
- Granted claims to lead peptide and pharmaceutical composition

$\alpha v \beta 6$ - SELECTIVE TARGET IN CANCER

$\alpha v \beta 6$ is a RGD-motif binding integrin expressed on the cell surface

- Epithelial specific expression
- Low/undetectable expression in normal adult tissues, elevated during tissue remodelling, fibrosis and multiple cancer indications
- Estimated 279,000 new $\alpha v \beta 6$ +ve tumours diagnosed each year in UK and US combined (excluding melanoma)

Tumour site	% $\alpha v \beta 6$ positive	USA + UK incidence	# of $\alpha v \beta 6$ +ve tumours
Cervix	92%	13,873	12,763
Head and Neck	64%	22,900	14,656
Breast	43%	227,960	98,023
Lung	35%	253,020	88,557

HIGH $\alpha v \beta 6$ EXPRESSION CORRELATES WITH POOR PROGNOSIS

Colon carcinoma

- Reduction in median survival from 16.5 years to 5 years (Bates et al, 2005)

Cervical carcinoma

- Reduction in 5yr survival from 91% to 54% (Hazelbag et al, 2007)

Lung cancer

- Prognostic in early and late-stage cancers, with an independent hazard ratio of 1.9 (Elayadi et al, 2007)

Oral squamous cell carcinoma

- Correlates with progression to malignant disease (Hamidi et al, 2000)

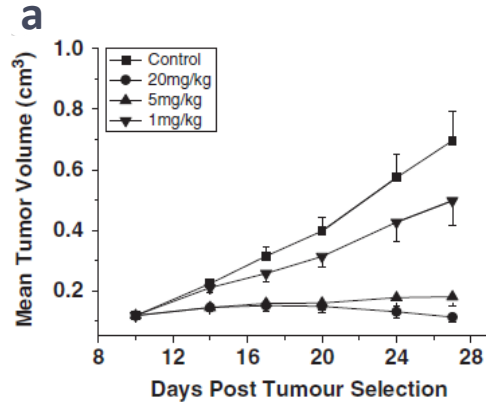
Increased $\alpha v \beta 6$ expression associated with pro-invasive and aggressive phenotype

- 77% of metastatic lesions overexpress $\alpha v \beta 6$

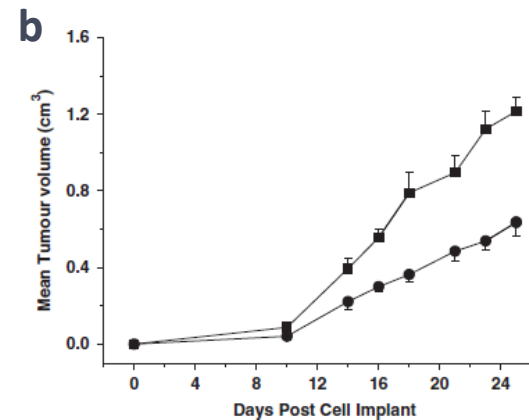


TARGETING $\alpha v \beta 6$ CAN REDUCE TUMOUR GROWTH *in vivo*

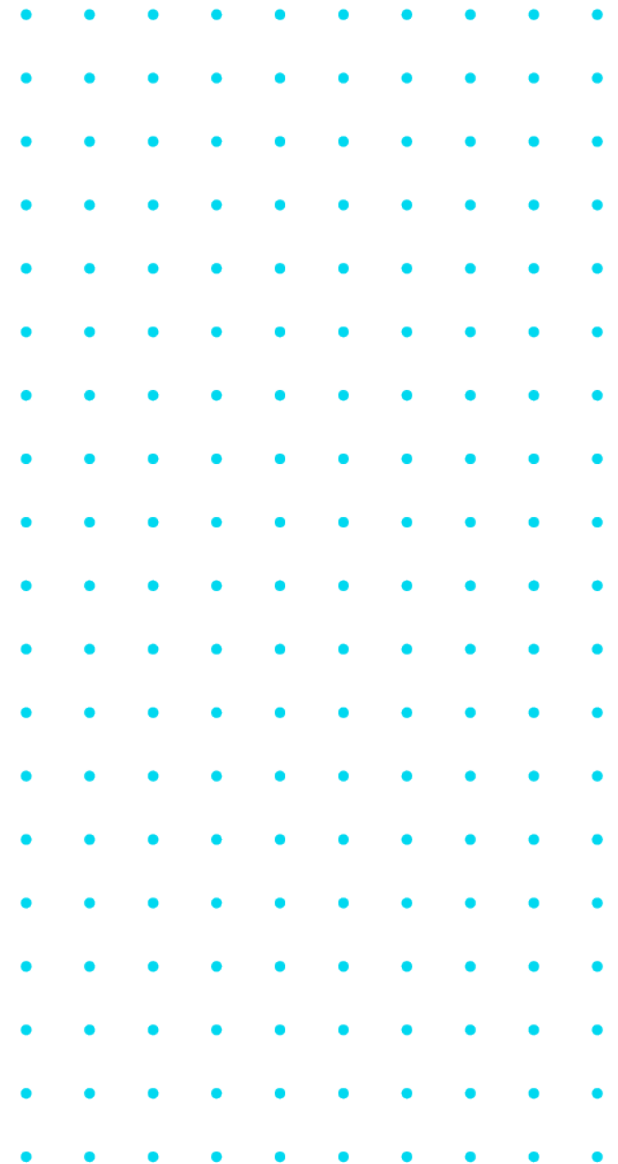
Proof of concept established by the $\alpha v \beta 6$ (and $\alpha v \beta 8$) blocking antibody (264RAD) reduces tumour growth and metastasis (Eberlein et al, Oncogene, 2012)



Inhibition of Detroit 562 tumour growth. Established tumours were treated with indicated doses of 264RAD twice weekly



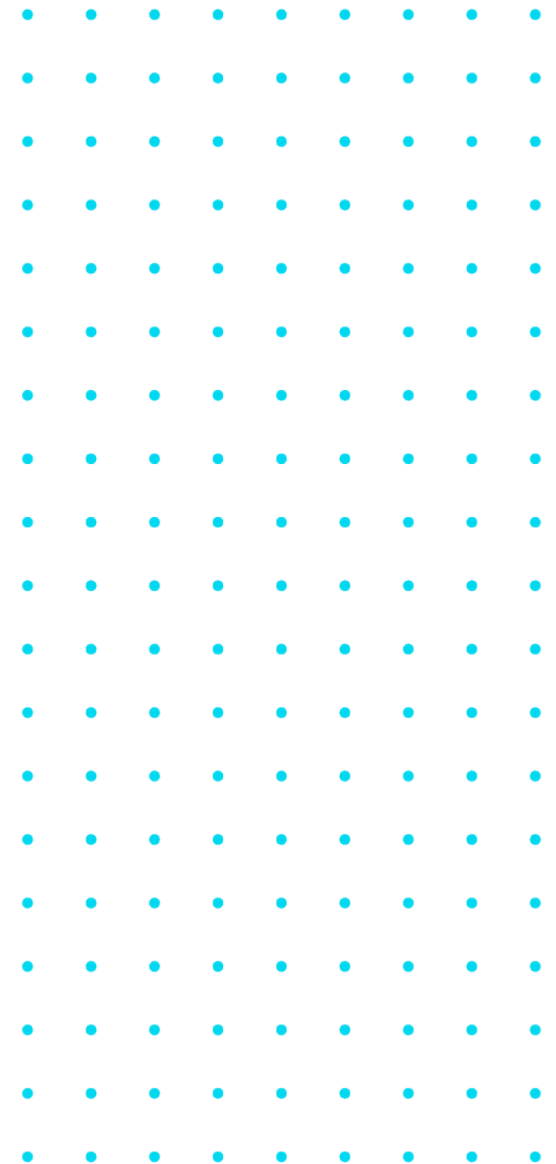
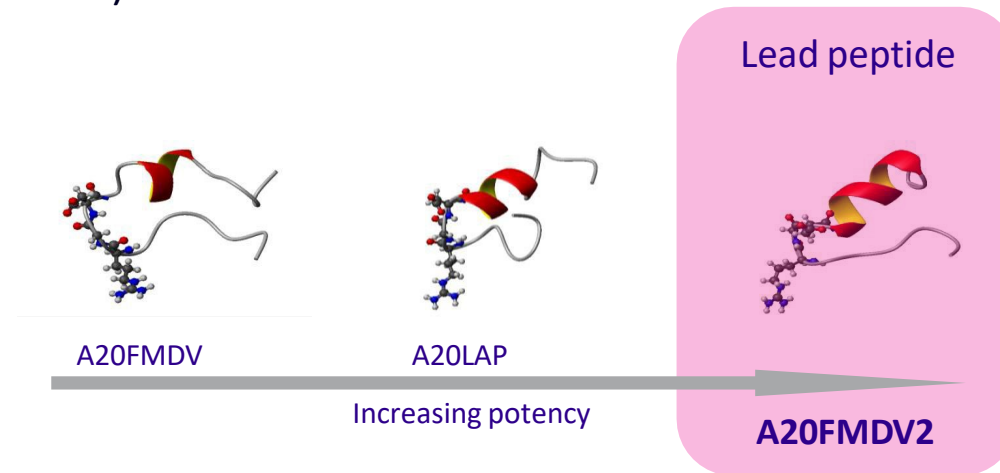
Inhibition of 4T1 tumour growth. Established tumours were treated with 20mg/kg 264RAD twice weekly



GENERATION OF HIGH AFFINITY $\alpha v \beta 6$ SPECIFIC PEPTIDES

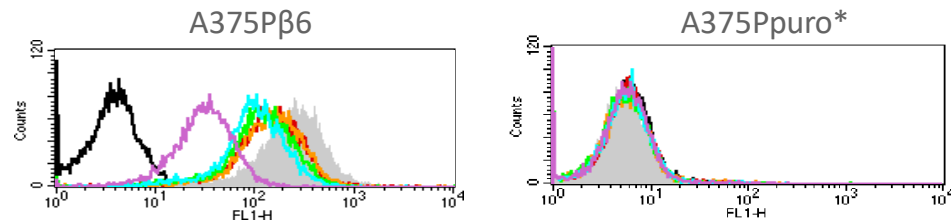
Used peptides derived from natural ligands (TGF β 1-LAP and Foot and Mouth Disease Virus) as a starting point

- Most potent peptides possessed RGDLXXL/I motif
- Discovered that affinity correlated with ability to form alpha-helical structure (DiCara et al., 2007)



In vitro PROPERTIES OF LEAD PEPTIDE A20FMDV2

Specificity



FACS analysis using A20FMDV2
1nM – 10uM

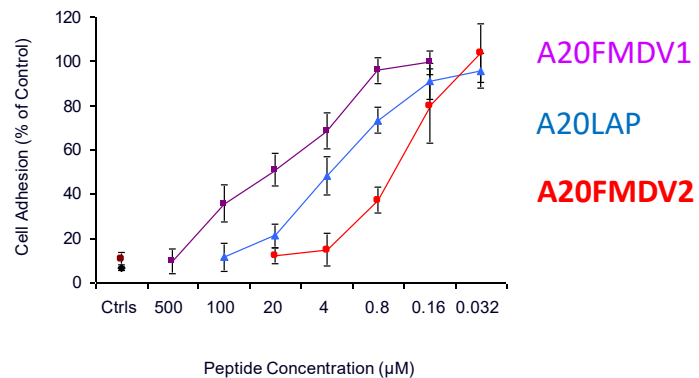
	$\alpha\nu\beta 6$	$\alpha\nu\beta 3$	$\alpha\nu\beta 5$	$\alpha 5\beta 1$
A20FMDV2	$3 \pm 1 \text{ nM}$	$>10 \mu\text{M}$	$>100 \mu\text{M}$	$>10 \mu\text{M}$

- A20FMDV2 is highly $\alpha\nu\beta 6$ -specific (>1000 fold versus other integrins)

*A375Ppuro –ve for $\alpha\nu\beta 6$; +ve for $\alpha\nu\beta 3$, $\alpha\nu\beta 5$, $\alpha 5\beta 1$

Inhibition of adhesion and migration

- A20FMDV2 potently inhibits $\alpha\nu\beta 6$ -dependent cell adhesion and migration



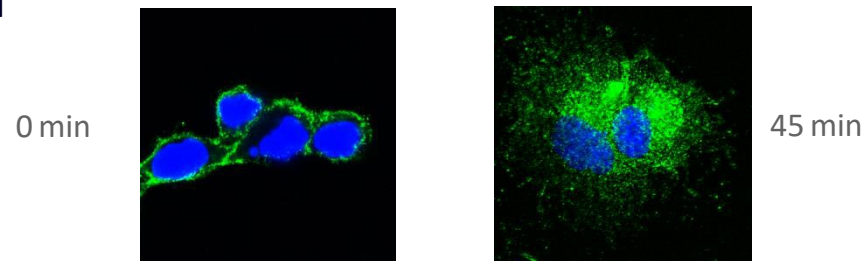
IN VITRO PROPERTIES OF LEAD PEPTIDE A20FMDV2

High affinity binding

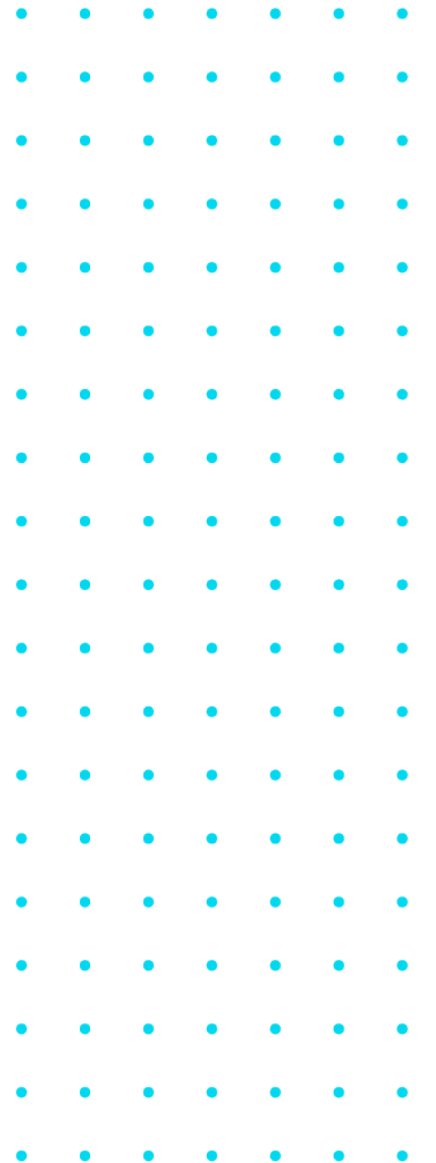
- Binding is highly stable
- A20FMDV2 binds to $\alpha v \beta 6$ with affinity constant of 1.73 ± 0.46 nM

Ligand internalisation

- A20FMDV2 is rapidly internalised into tumour cells



Saha et al, J Pathol, 2010



In vivo EFFICACY AS TOXIN-TARGETING THERAPEUTIC

High affinity binding

- Toxin-conjugated A20FMDV2 demonstrated control or clearance of distinct, in vivo, murine human xenograft pancreatic cancer models
- No signs of toxicity
- Toxin-conjugated A20FMDV2 demonstrated selective killing of numerous $\alpha v\beta 6+$ (vs $\alpha v\beta 6-$) tumour cell lines – with nM IC50s (in vivo and in vitro data available under CDA)



A20FMDV2 LABELS $\alpha v\beta 6+$ TUMOURS

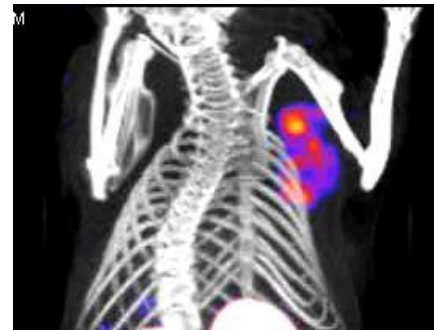
A20FMDV2 is able to target tumour cell lines that endogenously express $\alpha v\beta 6$ in murine models



DCIS Breast cancer cell line xenograft

NanoSPECT-CT imaging of $^{111}\text{Indium-A20FMDV2}$

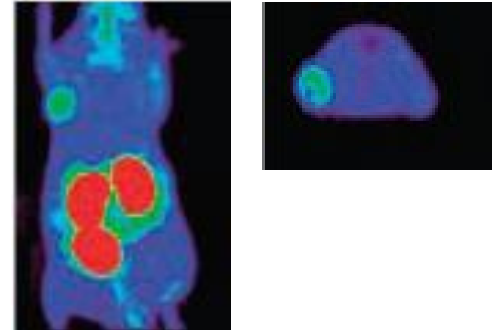
Saha et al, J Pathol, 2010



CA1a Breast cancer cell line xenograft

NanoSPECT-CT imaging of $^{111}\text{Indium-A20FMDV2}$

Saha et al, J Pathol, 2010



BxPC3 pancreatic cancer xenograft

microPET imaging of $^{18}\text{F}[\text{FBA}-(\text{PEG}28)_2\text{-A20FMDV2}]$

Hausner et al, Cancer Res, 2009



PATENT POSITION

First family:

PCT publication: WO2007/039728
Priority date: 03.10.2005
Filing date: 03.10.2006
EP grant date: 12.07.2017
EP grant no. EP1957522B1
Basic expiry date: 03.10.2026

Countries covered:

- Europe (Switzerland, Germany, Spain, France, United Kingdom and Italy)
- Canada
- United States
- Japan

This patent covers the A20 peptides called A20FMDV1, A20LAP and A20FMDV2, constructs in which one of these peptides is linked to a detectable moiety or a therapeutically active moiety, and uses for treatment or diagnosis of cancer. These are “natural” peptides with L-amino acids.

Second family:

PCT publication: WO2018/197490
Priority date: 24.04.2017
Filing date: 24.04.2018
EP grant date: 23.09.2020
EP grant no. EP3615563B1
Basic expiry date: 24.04.2038

Countries covered:

- Europe (Switzerland, Germany, Spain, France, United Kingdom and Italy)
- United States
- Australia
- China
- Canada
- Japan
- South Korea

This patent covers a broader class of peptides defined by the motif, provided that the N-terminal amino acid (X1) is D-Asn. The patent examples show that these variants of the original A20 peptides are stronger binders and are internalised more readily than the A20 peptides. The variant peptides also exhibited superior biodistribution towards avB6-positive tumour.

SUMMARY AND NEXT STEPS

- $\alpha\beta6$ expression is upregulated in cancer and correlates with poor prognosis
- High affinity $\alpha\beta6$ -specific lead peptide A20FMDV2
- Highly specific for $\alpha\beta6$ (>1000 fold versus other integrins)
- Selectively binds $\alpha\beta6$ +ve tumours in vivo
- Selective killing in vitro and in vivo with A20FMDV2-toxin conjugate
- Comprehensive, granted patent territory

- We are looking for commercial partners to enable further clinical validation and market access
- Collaborative development or straight licensing interests are welcome



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THANK YOU

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