CANCER RESEARCH HORIZONS

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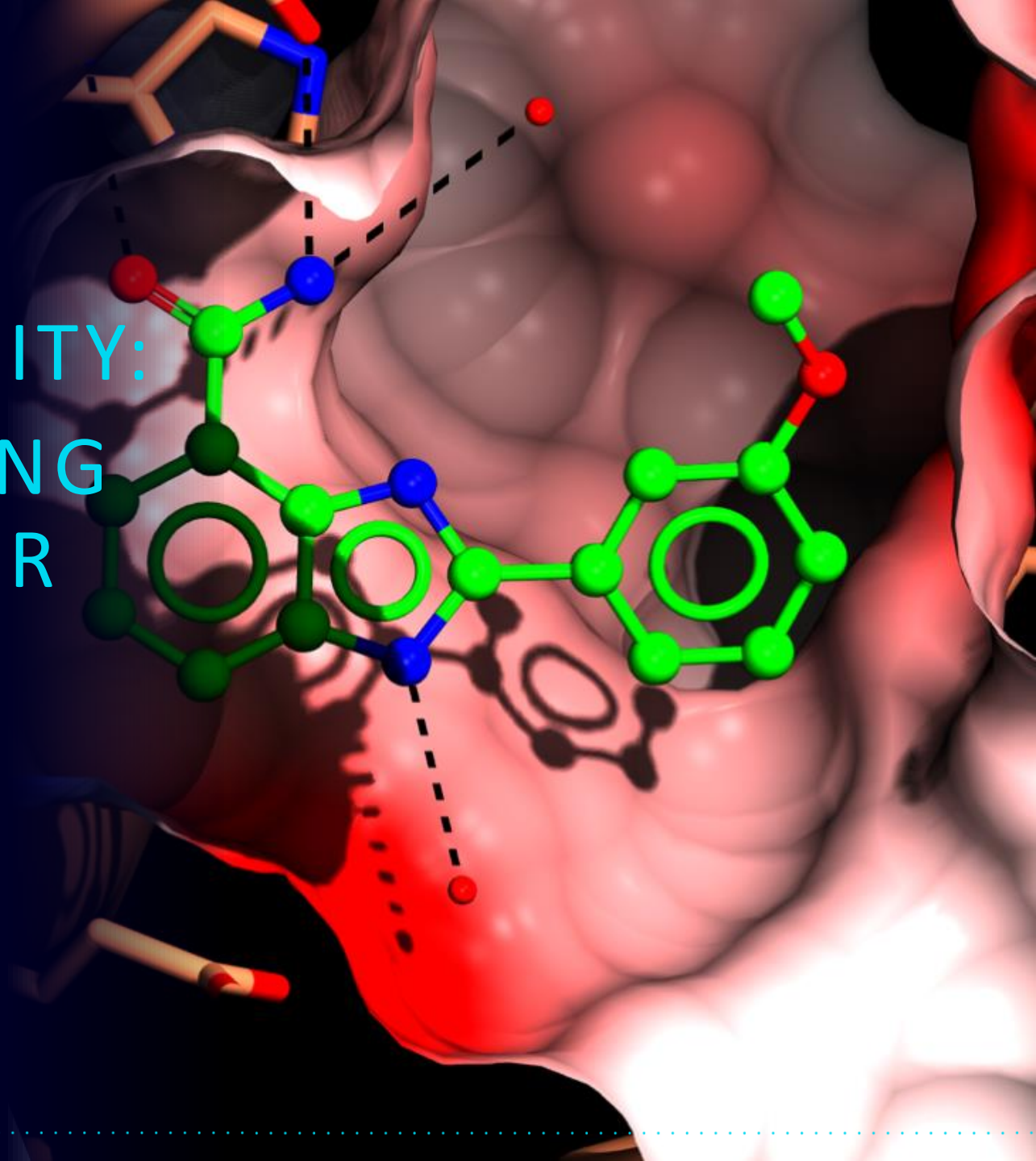
# LICENSING OPPORTUNITY: INTEGRIN AVB6-BINDING PEPTIDES FOR TUMOUR TARGETING & IMAGING



MAY 2022

# OPPORTUNITY OVERVIEW

Lead inventor: Prof John Marshall (QMUL)

High affinity αvβ6-specific lead peptide A20FMDV2

- Novel and proprietary peptides with high affinity and selectivity for integrin αvβ6
- Lead peptide selectively targets αvβ6+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 avB6-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

# αvβ6 - SELECTIVE TARGET IN CANCER

## αvβ6 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 αvβ6+ve tumours diagnosed each year in UK and US combined (excluding melanoma)

| Tumour site | % αvβ6 positive | USA + UK incidence | # of αvβ6+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 αvβ6 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

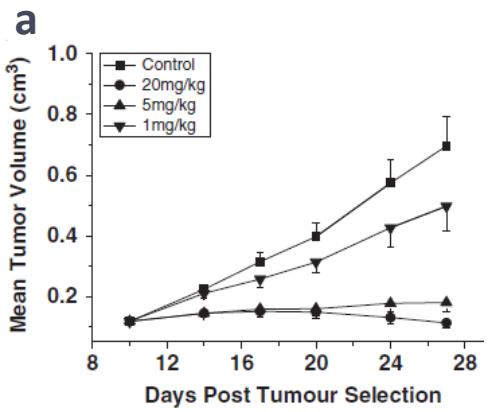
- Correlates with progression to malignant disease (Hamidi et al, 2000)

Increased αvβ6 expression associated with pro-invasive and aggressive phenotype

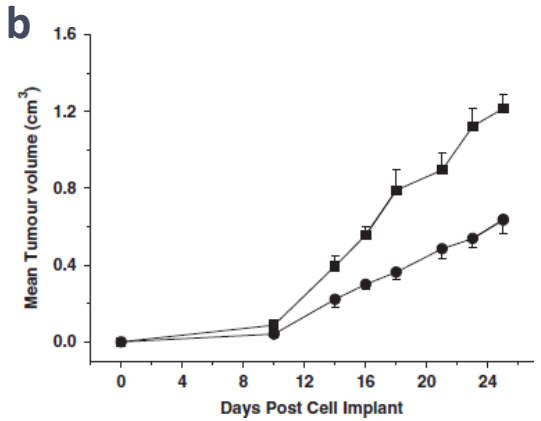
- 77% of metastatic lesions overexpress αvβ6

# TARGETING αvβ6 CAN REDUCE TUMOUR GROWTH *in vivo*

Proof of concept established by the αvβ6 (and αvβ8) 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

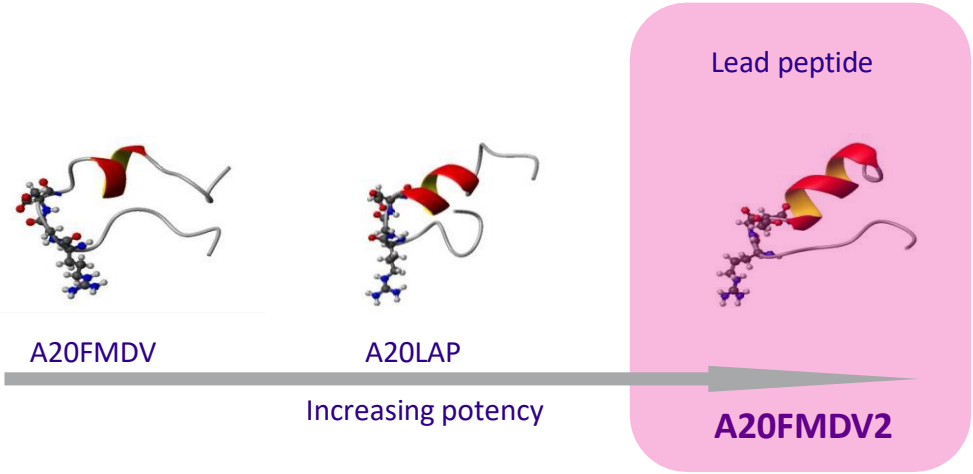



Inhibition of 4T1 tumour growth. Established tumours were treated with 20mg/kg 264RAD twice weekly

# GENERATION OF HIGH AFFINITY αvβ6 SPECIFIC PEPTIDES

Used peptides derived from natural ligands (TGFβ1-LAP and Foot and Mouth Disease Virus) as a starting point

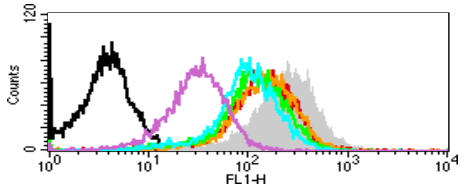
- Most potent peptides possessed RGDLXXL/I motif
- Discovered that affinity correlated with ability to form alpha-helical structure (DiCara et al., 2007)



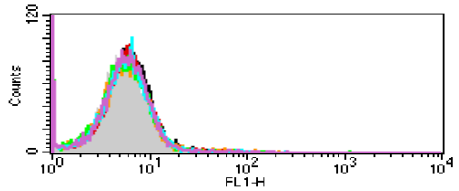
# *In vitro* PROPERTIES OF LEAD PEPTIDE A20FMDV2

## Specificity

A375Pβ6




A375Ppuro*




FACS analysis using A20FMDV2

1nM – 10mM

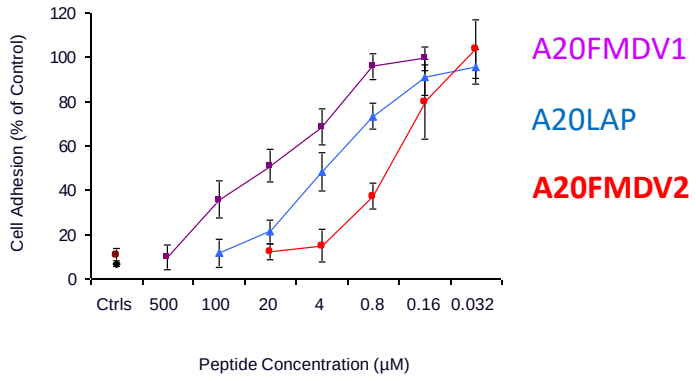
| | αvβ6 | αvβ3 | αvβ5 | α5β1 |
|---|---|---|---|---|
| A20FMDV2 | 3 ± 1 nM | >10 µM | >100 µM | >10 µM |

- A20FMDV2 is highly αvβ6-specific (>1000 fold versus other integrins)

*A375Ppuro –ve for αvβ6; **+ve** for αvβ3, αvβ5, α5β1

## Inhibition of migration

- A20FMDV2 potently inhibits αvβ6-dependent cell adhesion and migration



# *In vitro* PROPERTIES OF LEAD PEPTIDE A20FMDV2

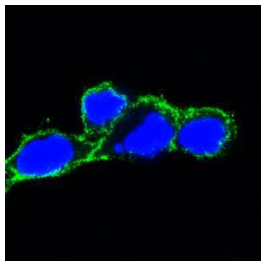
## High affinity binding

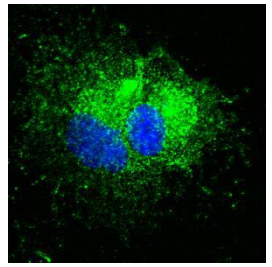
- Binding is highly stable
- A20FMDV2 binds to αvβ6 with affinity constant of 1.73 +/- 0.46 nM

## Ligand internalisation

- A20FMDV2 is rapidly internalised into tumour cells

0 min





45 min

Saha et al, J Pathol, 2010

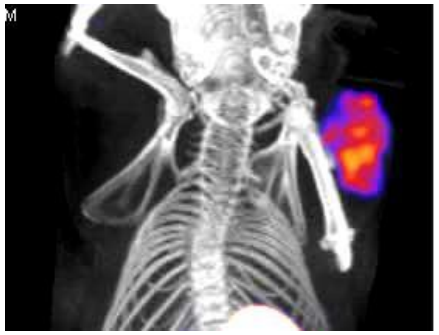
# *In vivo* EFFICACY AS TOXIN-TARGETING THERAPEUTIC

## 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 αvβ6+ (vs αvβ6-) tumour cell lines – with nM IC50s (in vivo and in vitro data available under CDA)

# A20FMDV2 LABELS αvβ6+ TUMOURS

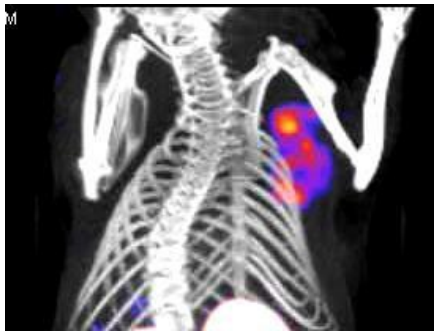
A20FMDV2 is able to target tumour cell lines that endogenously express αvβ6 in murine models



DCIS Breast cancer cell line xenograft

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

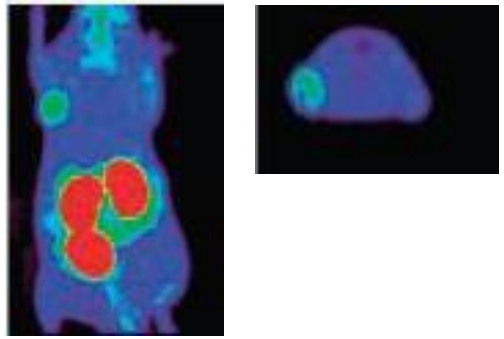
Saha et al, J Pathol, 2010



CA1a Breast cancer cell line xenograft

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

Saha et al, J Pathol, 2010



BxPC3 pancreatic cancer xenograft

microPET imaging of [$^{18}$F]FBA-$(PEG28)_2$-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 the A20 peptides. The variant peptides also exhibited superior biodistribution towards avB6-positive tumour.

# SUMMARY AND NEXT STEPS

- αvβ6 expression is upregulated in cancer and correlates with poor prognosis
- High affinity αvβ6-specific lead peptide A20FMDV2
- Highly specific for αvβ6 (>1000 fold versus other integrins)
- Selectively binds αvβ6+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

CANCER RESEARCH HORIZONS

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# THANK YOU

For further information, please contact:

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