CANCER RESEARCH HORIZONS

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ANTIBODY-DRUG CONJUGATES TARGETING CLEC14A: THERAPIES FOR SOLID TUMOURS

March 2023

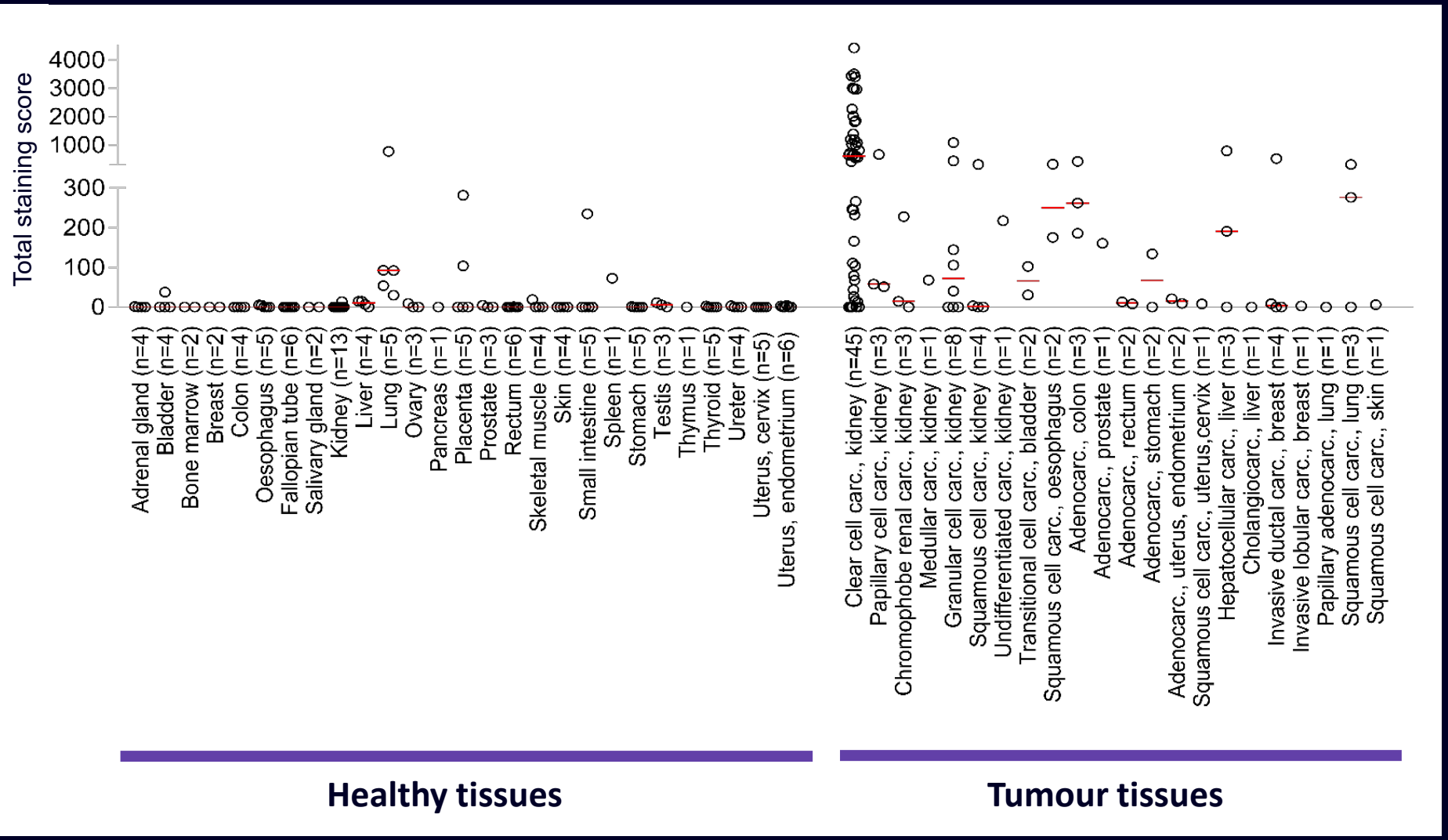
OPPORTUNITY OVERVIEW: CLEC14A ADCs

- CLEC14A is a C-type lectin transmembrane protein expressed on the surface of tumour endothelial cells but not on normal cells.
- Five antibodies selectively targeting CLEC14A have been generated. Two of them (CRT3 (C3) and CRT4 (C4)) were developed as antibody drug conjugates (ADCs) linked to SG3249, a pyrrolobenzodiazepine dimer-based DNA crosslinking agent.
- Whilst angiogenesis-targeting agents block tumour neo-angiogenesis, ADCs against CLEC14A disrupt already established tumour vasculature.
- CLEC14A ADCs show in vitro cytotoxicity in endothelial cells, and a reduced tumour vascularisation in a murine model of Lewis lung carcinoma, correlating with reduced tumour burden.
- This work was developed in the lab of Professor Roy Bicknell at the Institute of Cardiovascular Sciences, University of Birmingham, and is protected by three granted or pending patents.
- A commercial partner for collaboration and/or licensing, to enable further clinical validation and commercialisation of the CLEC14A ADC programs.

CLEC14A IS A COMPELLING TUMOUR TARGET

- CLEC14A is a C-type lectin transmembrane protein that is specifically expressed on the surface of tumour endothelial cells.
- CLEC14A expression is downregulated by shear stress, and as a result, expression is absent in healthy perfused tissue and occurs only in poorly perfused tissue such as tumour tissue.
- CLEC14 is expresses in 30% of human solid tumours and is exceptionally highly expressed in 50% of human renal tumours.
- CLEC14A-targeted therapy has great promise in the treatment of renal tumours. This would address a true unmet medical need since, other than surgery, the only treatment currently available is antiangiogenic chemotherapy, which shows limited efficacy.

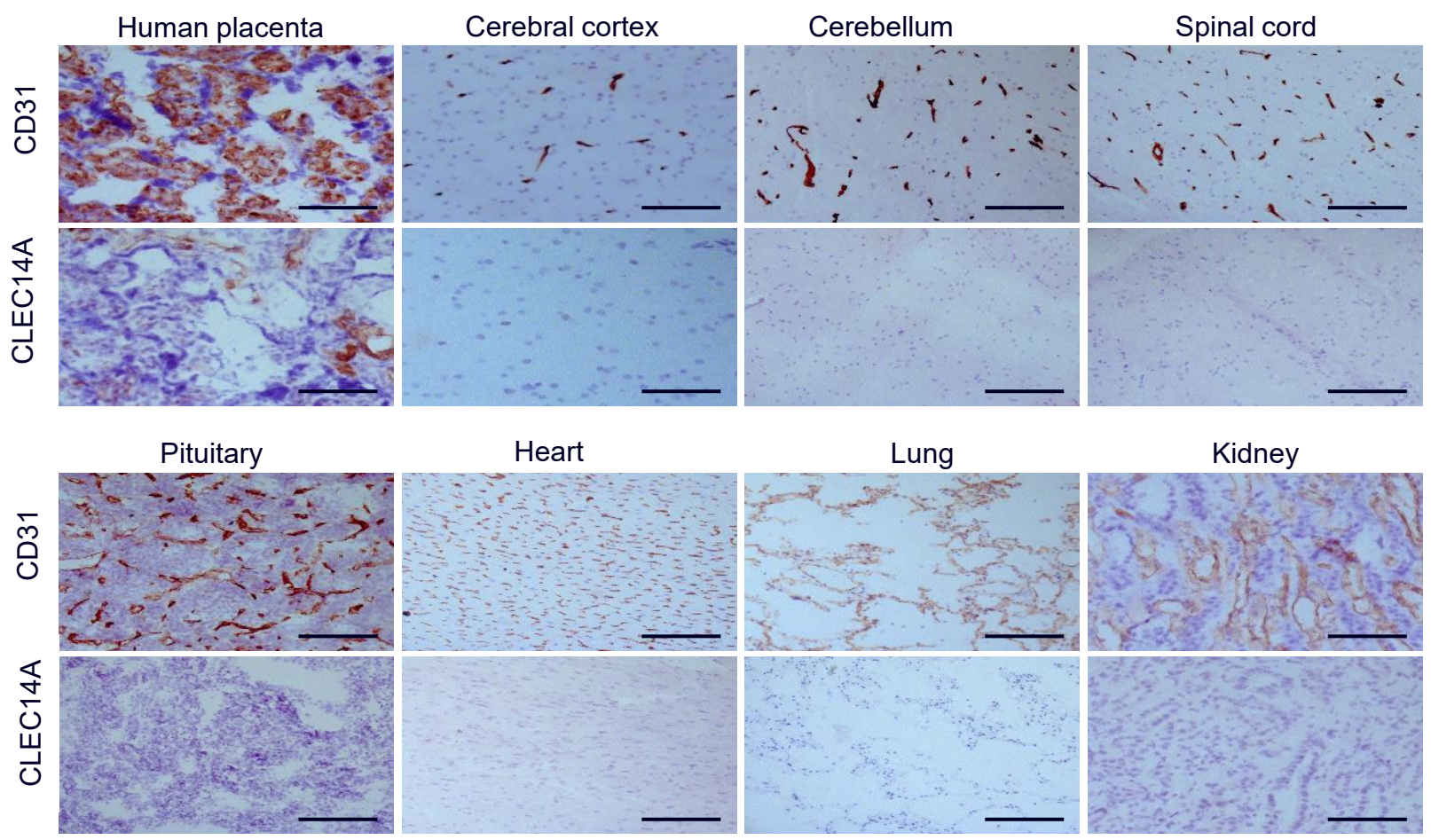
CLEC14A IS SPECIFICALLY EXPRESSED IN VESSELS OF TUMOUR TISSUES IN HUMANS



- Human healthy and tumour tissues were analysed for CLEC14A and CD31 (a vascular marker) expression using immunohistochemistry.
- Data are shown as the intensity of CLEC14A staining multiplied by the % of vessels stained, multiplied again by the density of vasculature within the tissue (“total staining score”).

Red line = median score

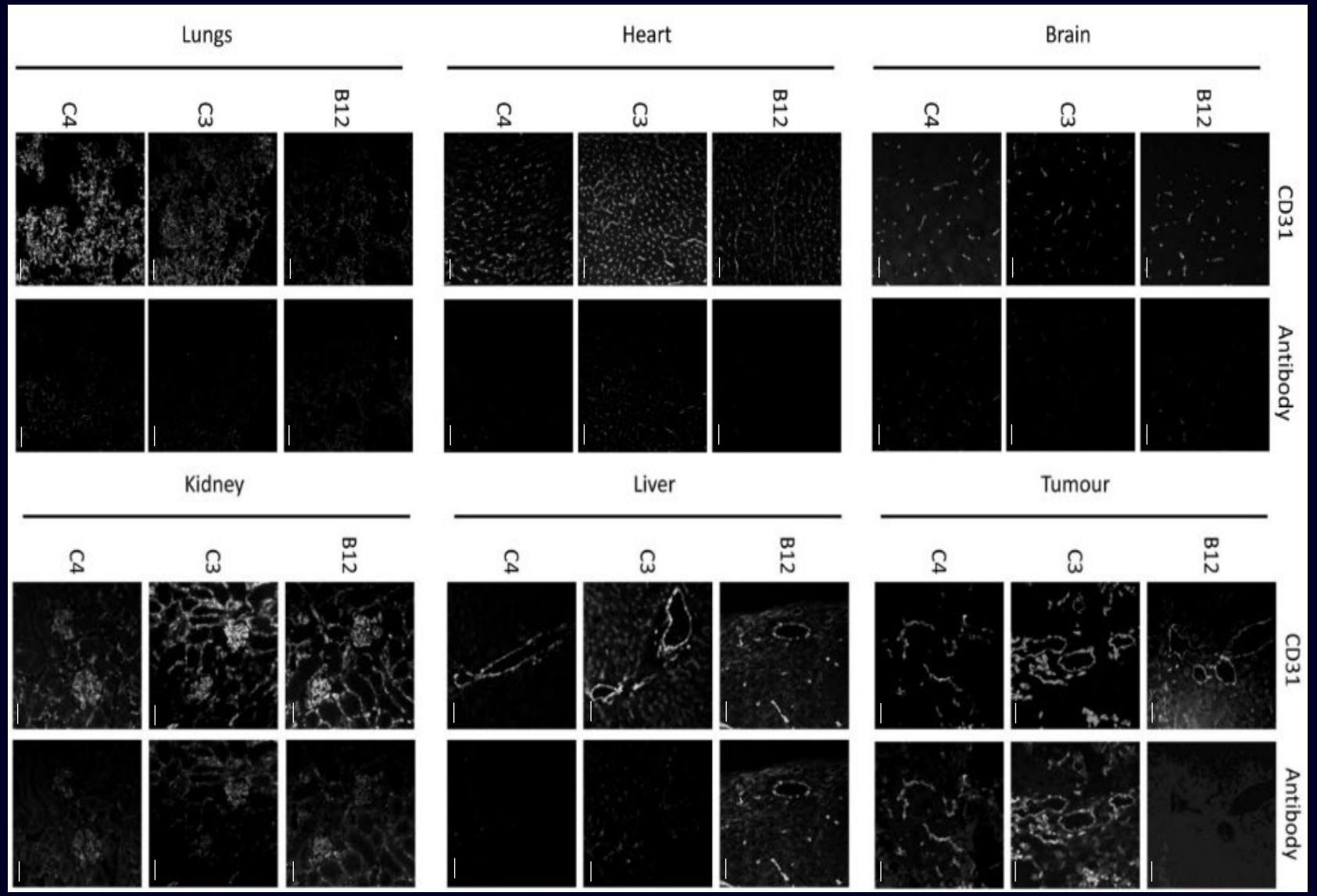
CLEC14A IS NOT EXPRESSED IN HEALTHY BRAIN, HEART, LUNG OR KIDNEY TISSUES IN PRIMATES



Frozen sections of human placenta and cynomolgus macaque tissues were stained with Clec14A and CD31 (a vascular marker). Concentration-matched isotype control antibody staining was negative.

All scale bars = 100 µm.

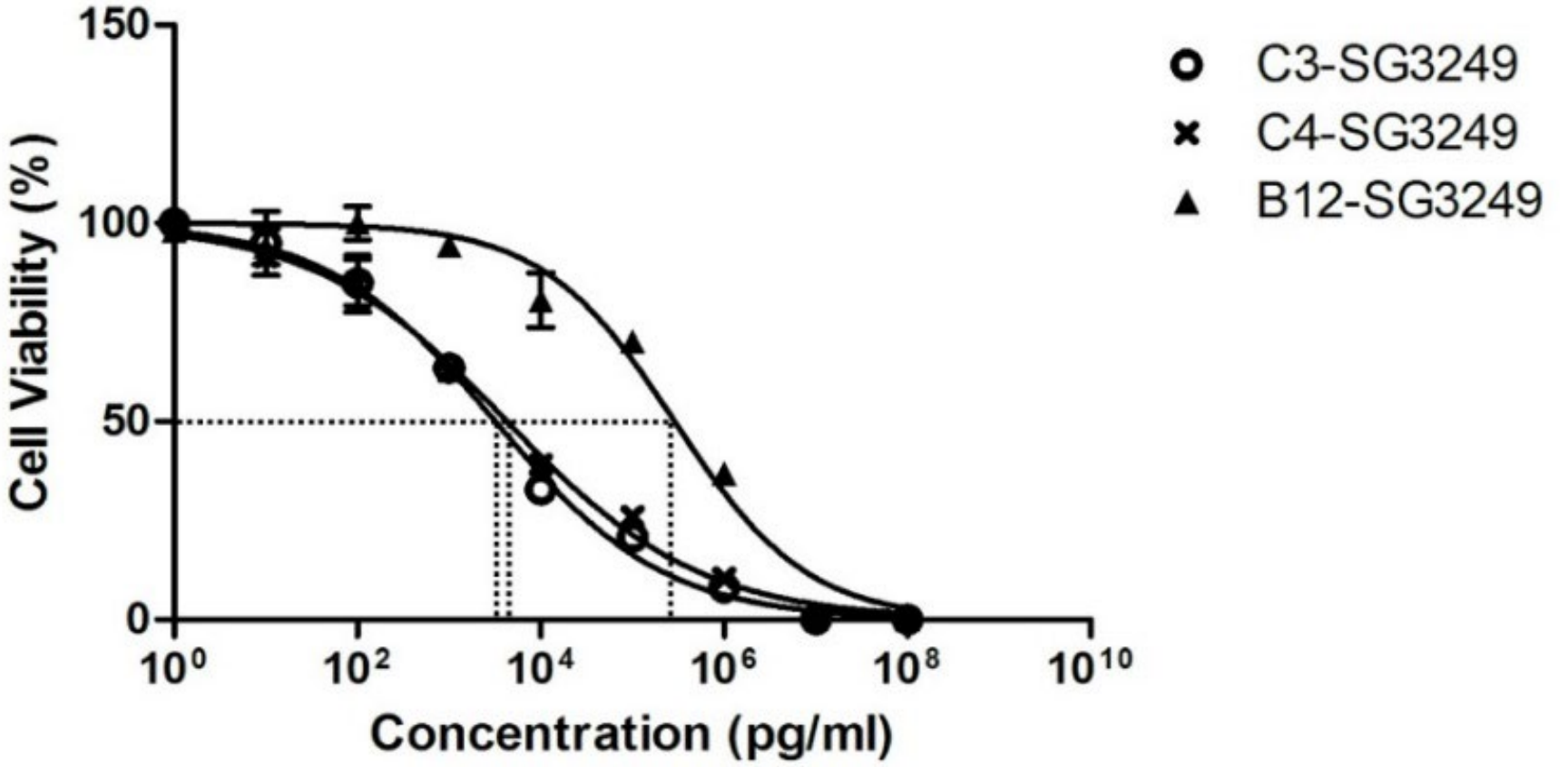
ANTIBODIES AGAINST CLEC14A LOCALISE MAINLY TO TUMOUR VESSELS IN TUMOUR-BEARING MICE



- To characterise CLEC14A antibody distribution *in vivo*, CRT3 (C3), CRT4 (C4) or B12 (control) antibodies were administered intravenously to tumour-bearing C57BL6 mice. Mice were culled after 90 minutes and tissues were harvested and immunostained to visualise antibody localisation.
- Images show Clec14A (“Antibody”) and CD31 (a vascular marker) staining.
- Antibodies C3 and C4 showed strong staining within tumour sections and showed no staining in key organs (lungs, heart, brain, liver) and low staining in the kidney, a known major route for antibody clearance.

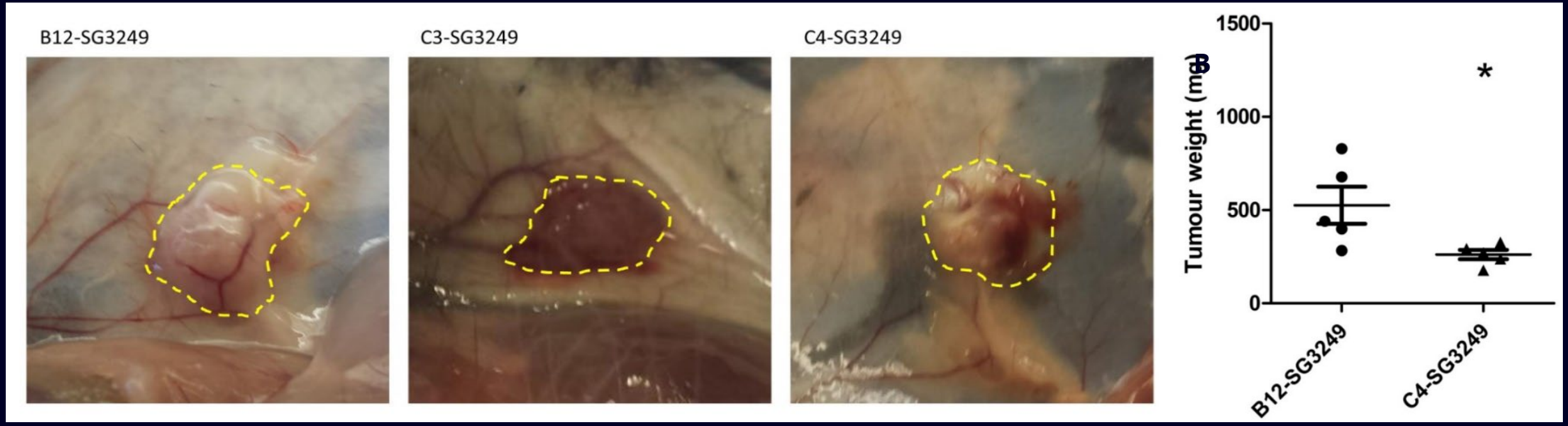
Scale bar = 10 µm

ANTIBODY-DRUG CONJUGATES AGAINST CLEC14A CAUSE ENDOTHELIAL CYTOTOXICITY *IN VITRO*



- The investigators generated ADCs with two anti-CLEC14A antibodies conjugated to SG3249, a pyrrolobenzodiazepine dimer-based DNA crosslinking agent which induces cell death by causing DNA damage.
- The graph shows the viability of HUVECs cells treated with CLEC14A-targeting ADCs with increasing concentrations of C3-SG3249, C4-SG3249 or B12-SG3249 (control) for 96 hours.

ANTI-CLEC14A ADCs REDUCE VASCULARISATION AND TUMOUR BURDEN



A) C57BL6 mice with Lewis lung carcinoma were treated with 1mg/kg of C3-SG3249, C4-SG3249 or B12-SG3249 (control) and culled after 24 hours. Leakage of blood into surrounding tissues was observed with C3-SG3249 and C4-SG3249 treatment, indicating vascular damage. Yellow dashes delineate tumour boundaries.

B) Endpoint weights of Lewis lung carcinoma tumours in C57BL6 mice after two weekly treatments with C4-SG3249 or B12-SG3249. n=5.

Mice showed no adverse effects after administration of ADCs, and histopathology showed no change in healthy tissues.

CLEC14A TECHNOLOGIES PATENT PORTFOLIO

Patent family	Priority	PCT	Status
Inhibitors targeting CLEC14A (Title: CLEC14A inhibitors)	US23958409P 03/09/2009	WO2011/027132 03/09/2010	Granted in: UK, Germany, France, and US.
Antibodies CRT1-4-5 against CLEC14A (Title: Inhibitors)	GB201501004D0 21/01/2015	WO2016/116760 21/01/2016	Granted in: Japan, Australia, Canada, UK, Germany, France, US.
Antibodies CRT2-3 against CLEC14A (Title: Antibodies and related molecules and uses thereof)	GB201604378A 15/03/2016 GB201612534A 19/07/2016	WO2017/158339 14/03/2017	Granted/pending in: Australia, Canada, Europe, Japan, China, US.

PARTNERING OBJECTIVES

We are seeking a commercial partner for collaboration and/or licensing, to enable further clinical validation and commercialisation of the CLEC14A ADC programs.

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