215 LIGHT-RGR, Peptide-conjugated Cytokine

Asset Overview

Product Type	Protein
Indication	Oncology
Current Stage	Preclinical
Target(MoA)	Immune cell stimulation and effector T-cell expansion
Brief Description	• A peptide-conjugated cytokine LIGHT/TNFSF14 • Targeted to tumor vasculature by homing peptide 'RGR' • LIGHT-RGR is a novel biologic agent which induces de novo intratumoral lymph nodes and vessel normalization and potentiates immunotherapy by enhancement of tumor perfusion and trafficking/ infiltration of immune cells.
Organization	University of Western Australia

Differentiation

□ **Unmet need**

- Immune cell trafficking and infiltration need urgent attention.
- Emerging immunotherapy drugs suffer from limited response rates.
- Tumor immunity and T cell activation necessarily need for tumor infiltration.
- All IO drugs will potentially benefit from enhanced immune cell priming/ activation within the tumor.
- CAR-T has shown positive results in blood cancers, however solid tumors pose a significant accessibility challenge due to the complexity of the tumor stroma.

□ **Pipelines**

- MolMed: TNF-NGR (phase III mesothelioma)
- Philogen: TNF-L19 (phase II STS, phase III melanoma); L19 is a single-chain variable fragment which binds fibronectin

□ **Differentiated profiles of LIGHT-RGR**

- Induces angiogenic tumor vessel normalization: Increases tumor perfusion, access of circulatory chemo, IO drugs and immune cells
- Induces tertiary lymphoid structures in solid tumors:
  - Stimulates infiltration of anti-tumor immune cells and intratumoral effector priming → immuno-permissive TME.
  - Cold-to-hot transition of immuno-resistant tumor types.
  - Highly significant increase in efficacy of anti-CTLA4 plus anti-PD1 by LIGHT-RGR combo treatment.
- Potentiates activity of tumor vaccines and adoptive T cell therapies.
- CAR-T adjunct potential by enabling infiltration and priming of engineered T cells – and for ex vivo T cell activation.

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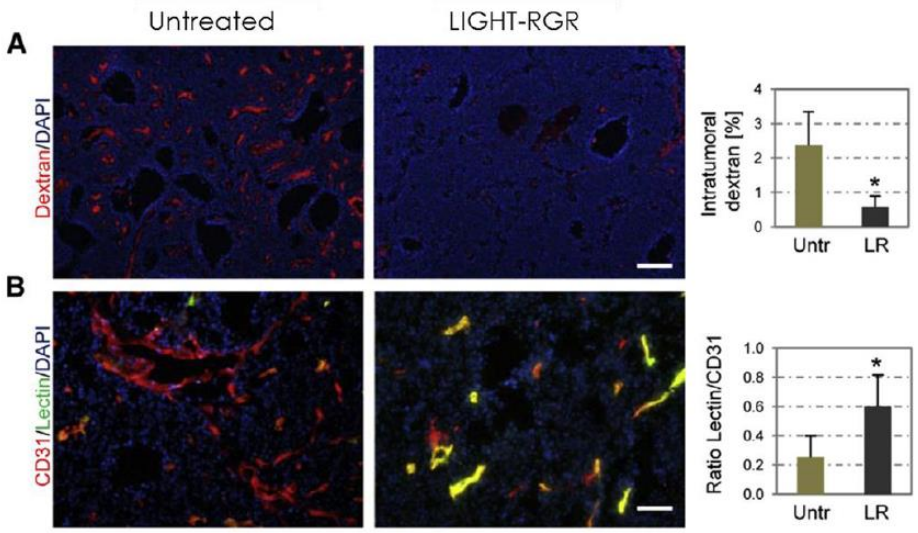
Key Data

Vessel normalization in tumors in RIP1-Tag5 transgenic mice

A. LIGHT-RGR normalises tumour vessels and reduces leakiness demonstrated by reduced extravasation of labelled dextran

B. LIGHT-RGR enhances tumour perfusion indicated by increased FITC-lectin binding to tumour vessels

Representative of at least three independent experiments. Data are presented as mean ± SD. n = 4–7 mice, *p < 0.05



Vascular changes in RIP1-Tag5 tumors, analyzed after 2 weeks of treatment with 0.2 ng LIGHT or LIGHT-RGR (LR) in comparison to untreated tumors (Untr).
(A) Histology image of intratumoral dextran (red) following injection with 70 kDa Texas Red dextran and quantification of extravasated **dextran as surrogate marker for vascular leakiness** in untreated (Untr) and LIGHT-RGR (LR)-treated tumors. Scale bar, 100 mm.
(B) Overlay of **CD31+ vessels with FITC-lectin** delineates **perfused (yellow)** and non-perfused (red) **tumor vessels** in untreated and LR-treated groups. *p < 0.05, Student's t test. Scale bar, 50 mm.

Spontaneously arising pancreatic neuroendocrine tumors (insulinomas) in RIP1-Tag5 mice, which express the SV40 large T antigen (Tag) under control of the promoter of the gene encoding rat insulin ('rat insulin promoter' (RIP))

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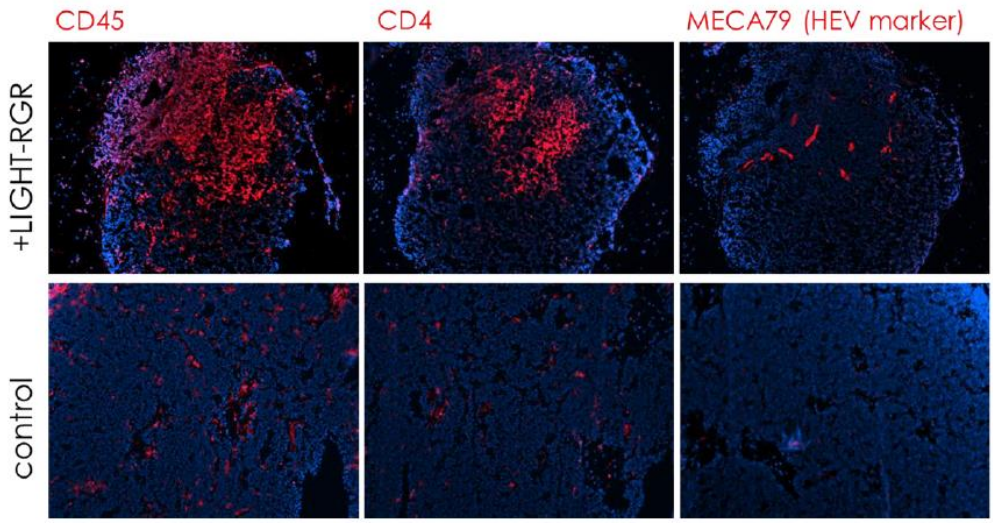
Key Data

Induction of intratumoral TLS (tertiary lymphoid structures)

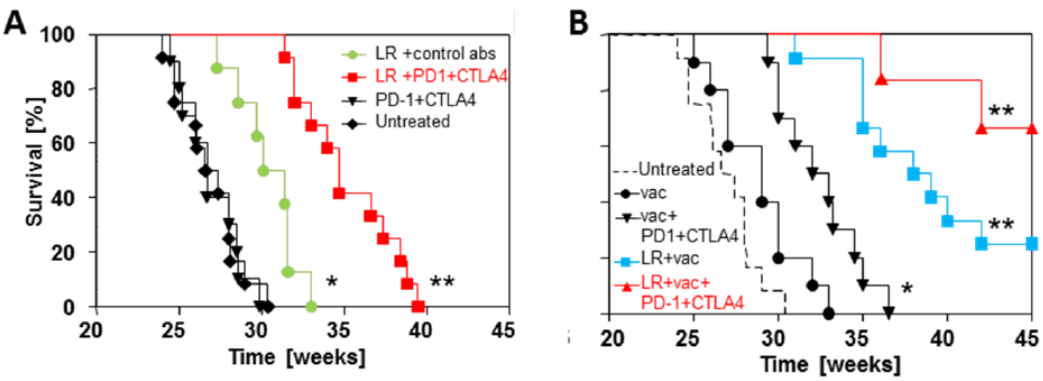
- High endothelial venules (HEVs) in tumours of RIP-Tag mice treated for two weeks with biweekly IV injections of 20ng LIGHT-RGR
- ELNs containing HEVs and heavily infiltrated with B and T cells were observed in 80% of treated tumours



Intratumoral TLSs were histologically defined on the basis of the presence of MECA79+ HEVs associated with lymphocyte clusters identified by staining with CD45+ & CD4 staining.

In vivo efficacy in the RIP1-Tag5 insulinoma model
highly significant survival advantage over 45 weeks

- RIP-Tag mouse survival following high dose (20ng) LIGHT-RGR treatment in combination with checkpoint blockade and anti-tumour vaccination (administered from week 23 to 45)
  A. LIGHT-RGR +/- anti-PD1/CTLA4
  B. LIGHT-RGR +/- anti-PD1/CTLA4 +/- anti-Tag vaccine
- For A and B, n=10-12; *P<0.001, **P<0.0001 to untreated



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Intellectual Property

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Application Date	
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Country	US, EP, JP, CN, SG, KR

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