# IMMUNO-ONCOLOGY PARTNERING OPPORTUNITIES

*Cytokine-fusion agent*:

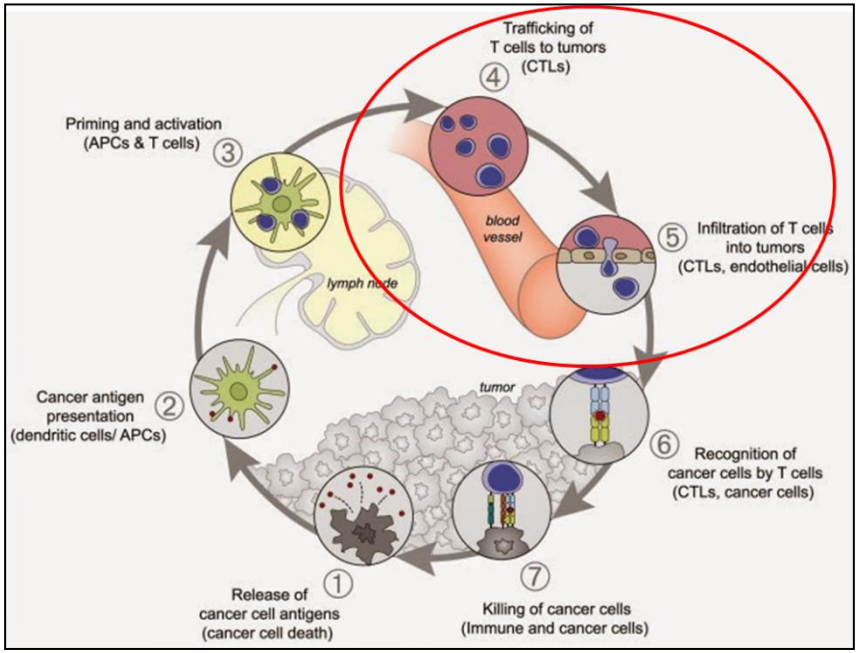
1. *LIGHT-RGR*

NOT FOR EXTERNAL DISTRIBUTION

# 1. LIGHT-RGR

# Introduction: Clinical need

- Stages 4/5 of the cancer-immunity cycle; immune cell trafficking/ 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.
- 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.

# Introduction: LIGHT-RGR

- A peptide-conjugated cytokine LIGHT/TNFSF14.
- Targeted to tumor vasculature by homing peptide 'RGR'.
- Dual dose-dependent effects within the TME:
  - Normalization of the angiogenic tumor vasculature
  - Induction of intratumoral tertiary lymphoid structures (TLS)

- Combination treatment with checkpoint blockade stimulates endogenous effector T cell trafficking and intratumoral activation and overcomes tumor-intrinsic resistance mechanisms.
- Further potential as a CAR-T adjunct to enhance trafficking and infiltration of engineered T cells into solid tumors.

# LIGHT-RGR:

- 'Low' dose is 0.2ng (6-7ng/kg) biweekly by IV injection.
- 'High' dose is 20ng (600-700ng/kg) biweekly by IV injection.
- No observed toxicity evidenced by weight loss, no pro-inflammatory side effects on vasculature or in organ systems in mouse models.
- Expected half-life of approx. 30 mins.
- Effective at extremely low doses (0.2ng *and* 20ng) – tumor targeting initiates a locally restricted amplification effect.

# LIGHT-RGR: Vessel normalization

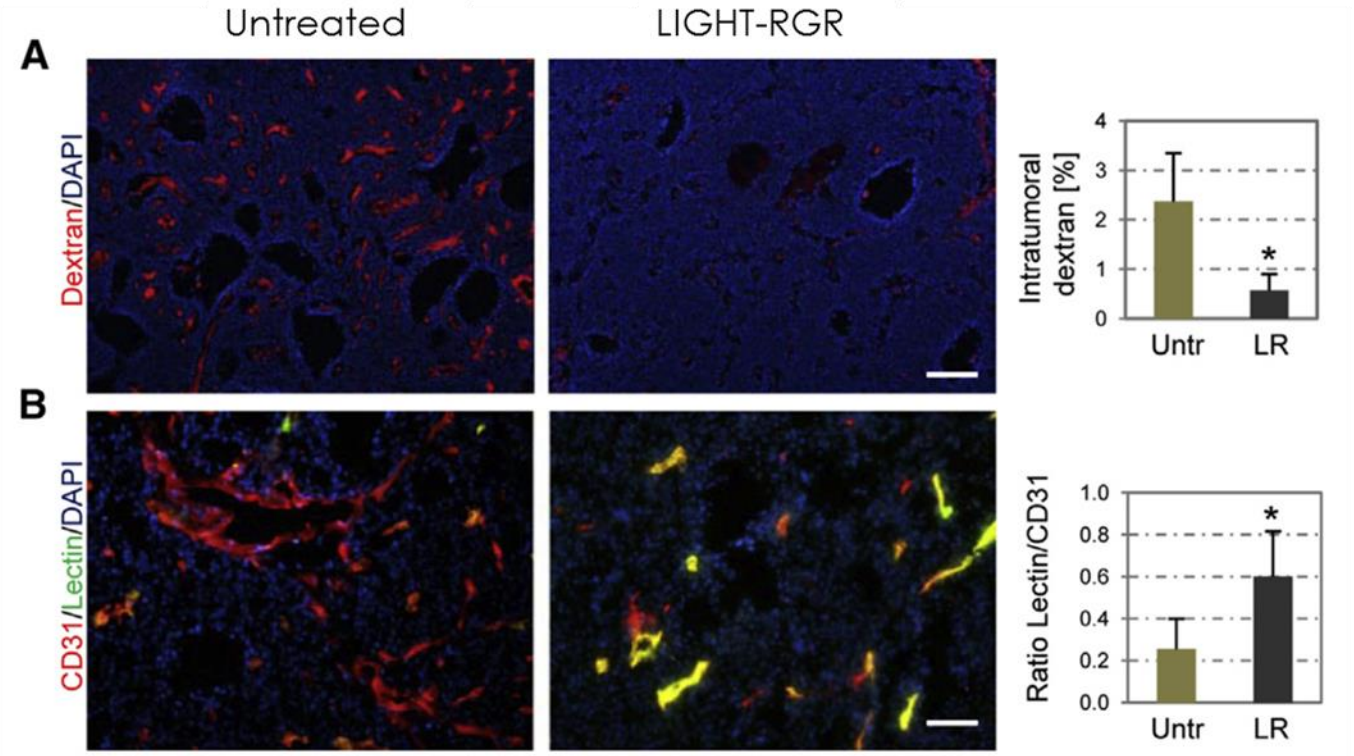
- LIGHT-RGR treatment induces tumor vasculature normalization:
  - reduced vascular leakiness
  - increased tumor perfusion
- Johansson *et al.,* Dec 2015; Cell Reports; 'Intratumoral LIGHT Restores Pericyte Contractile Properties and Vessel Integrity'
- Transient vessel normalization by use of low-dose anti-angiogenic drugs has been clinically investigated in IO combination regimens by others.
- LIGHT-RGR induces sustained vessel normalization and by a distinct pericyte-driven mechanism.

# LIGHT-RGR: Vessel normalization

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

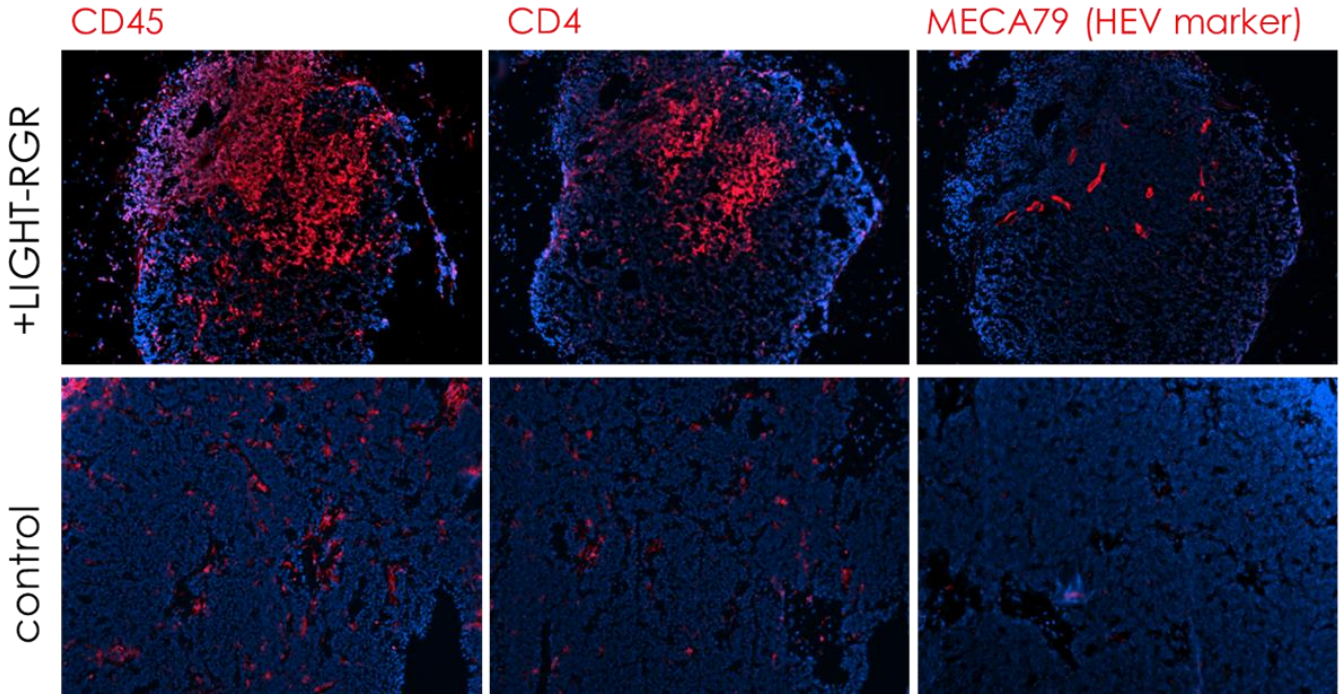


# LIGHT-RGR: Induction of TLS

- LIGHT-RGR induces formation of intratumoral ectopic lymph nodes containing high endothelial venules (HEVs).
- HEVs are 'portals' for the mass transit of immune cells into and out of lymph nodes and inflamed tissues; spontaneously arising TLS are indicative of positive patient outcomes.
- Cold-to-hot: this observation is remarkable in autochthonous tumor models (RIP1-Tag and LLC) which are devoid of lymphocytic infiltration and resistant to immunotherapy.
- LIGHT-RGR co-treatment gave a highly significant survival advantage ($P>0.0001$) versus combination anti-CTLA4 plus anti-PD1 over 45 weeks in the RIP-Tag insulinoma model.
- Characterisation of the immune infiltrate after LIGHT-RGR treatment shows highly enriched activated immune cell populations in tumors with TLS.

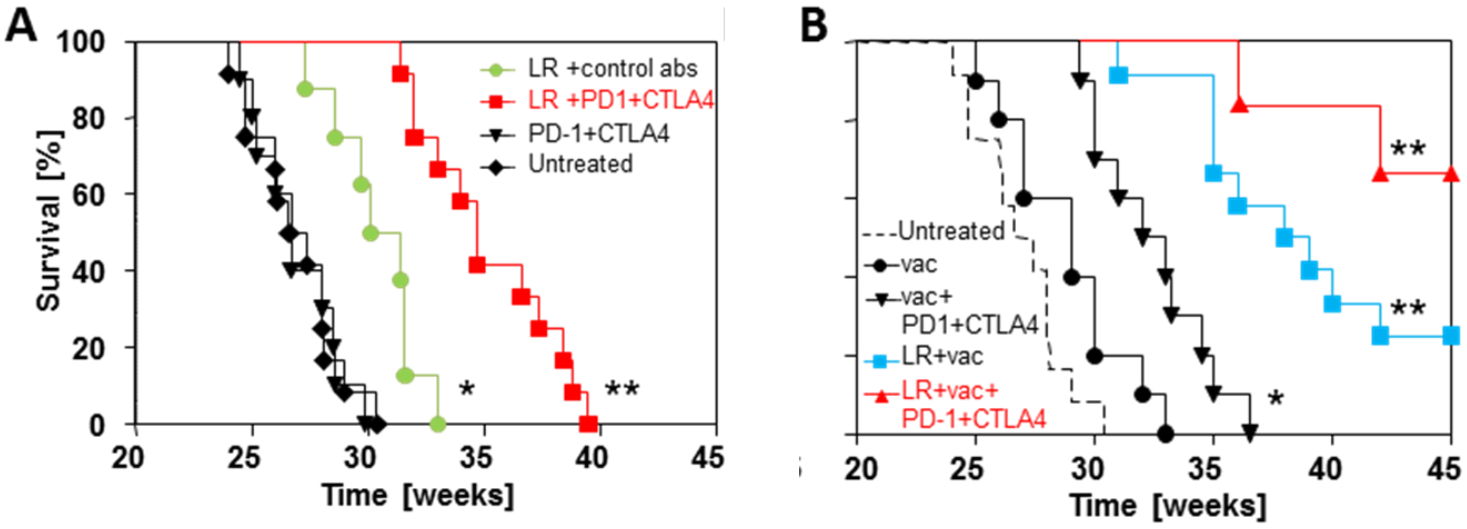
# LIGHT-RGR: Induction of TLS

- 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



# LIGHT-RGR:

- 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



# LIGHT-RGR: IP

- Priority application filed September 2014.
- Claims drawn to a peptide-protein conjugate and to methods of treatment.
- Assigned to the University of Western Australia.
- Inventors: Prof Ruth Ganss and Dr Anna Johansson.
- National phase applications filed in US and EP (and in China, Malaysia, Korea, Japan, Singapore and Hong Kong; rights in these territories are currently under Option).

# LIGHT-RGR: Comparators

- 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.
- Both are tumor vessel-targeted TNF's which are fundamentally anti-angiogenic – LIGHT-RGR does not cause vessel death.
- 'Low-dose normalization effects' described of vessel-targeted TNF's are mediated via endothelial cells – LIGHT-RGR acts via pericytes.
- Targeted TNF's do not induce formation of TLS.
- In head-to-head studies LIGHT-RGR is shown to have greater potency and longer lasting effects, even in long term treatment (over 20 weeks) than TNF-RGR (Johansson PNAS 2012).

# LIGHT-RGR: Differentiation

- 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.
- LIGHT-RGR 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.

# LIGHT-RGR: Next objectives

- We seek interest of biopharma partners to develop LIGHT-RGR in IO combination therapy regimens.
- Studies now underway will show utility in additional tumor types incl. glioma, pancreatic adenocarcinoma, lung and breast.

- CMC manufacturing to GMP(like).
- Formal preclinical safety & toxicology.
- Phase Ib/IIa clinical trial under the Australian TGA Clinical Trial Notification (CTN) scheme; standard 3+3 dose escalation design with an expansion cohort of (n) to be determined at MTD.

# END

Enquiries to:
Dr Louis Pymar
Project Manager Commercialisation, Research Development and Innovation

Office of Research Enterprise
The University of Western Australia
35 Stirling Highway
Crawley WA 6009

E: louis.pymar@uwa.edu.au
T: +61 8 6488 4363

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

THE UNIVERSITY OF WESTERN AUSTRALIA