Cancer, Cardiovascular, Inflammatory Disease
Drug Discovery and Development
New Treatments for Global Unmet Clinical Need

Vascular Biology and Translational Research

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Introduction

Cardiovascular disease (CVD) and cancer remain the most prevalent causes of morbidity and mortality. These diseases, together, accounts for over half of all global deaths. The pathogenesis of these and related inflammatory, proliferative, migratory diseases is underpinned by molecular and cellular changes in our blood vessels.

Our research is uncovering key networks of transcriptional control that lead to vascular disease. Building on these mechanistic insights, we are developing new drugs that have the potential to treat a myriad of health problems, from cancer and arthritis through to eye and heart disease.

Available Projects

1. **Novel cancer pharmacotherapeutics.** This project develops new small molecule inhibitors of immune checkpoints, notably the PD-1/PD-L1 system. Many different cancers use the PD-1/PD-L1 checkpoint to avoid being attacked by the immune system. This project involves work with cancer cells (focusing on melanoma), immune cells and animal models of cancer.
2. **Novel anti-inflammatory therapeutics for CVD.** Recent large scale clinical trials have established that CVD is a treatable inflammatory disease. This project develops potential new drugs for inflammatory CV conditions such as atherosclerosis, restenosis, unstable plaque causing a heart attack, and damage to heart after a heart attack, and involves work with vascular cells and animal models of CVD.
3. **Novel anti-inflammatory therapeutics for acute respiratory stress syndrome (ARDS).** ARDS is a type of respiratory failure typified by rapid onset widespread inflammation in the lungs. This project develops new treatments for ARDS and involves work with vascular cells and animal models.
4. **Novel therapeutics for diabetic retinopathy (DR).** DR is a complication of diabetes that affects blood vessels in the back of the eye (retina). Many patients with DR do not, or no longer respond to standard anti-VEGFA therapy. This project develops new treatments for DR and involves work with vascular cells and animal models of DR.

Several recent examples are provided below.

Example 1 – Control of Tumour Growth

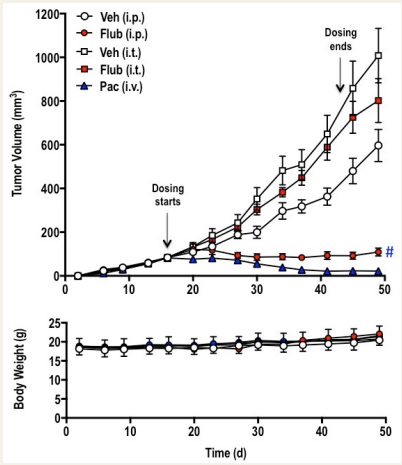


Fig. 1. Flubendazole (an anthelmintic), delivered intraperitoneally, abrogates human melanoma growth as solid tumors in mice.

Example 2 – Control of Metastatic Spread

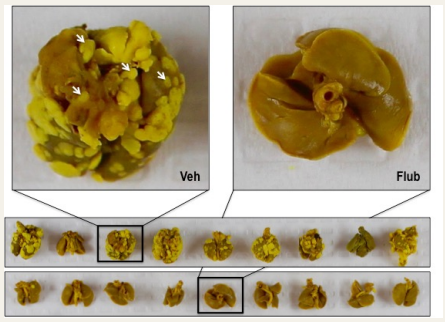
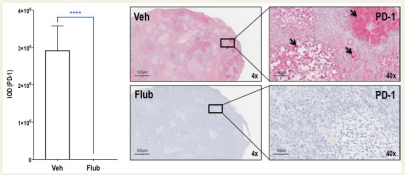
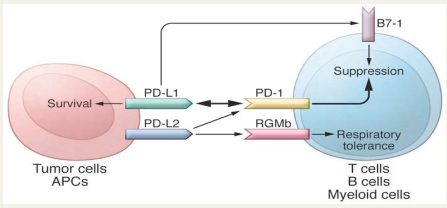


Fig. 2. Flub suppresses metastastic spread of melanoma to the lungs of mice. Tumours colonised in lungs stain yellow with Bouin's solution.

Example 3 – Definition of Mechanisms in Cancer



Figs. 3. Flub suppresses programmed cell death protein-1 (PD-1) within tumours *(above)*. PD-1 binds to PD-L1 and prevents tumor cell destruction (cytolysis) by immune cells (*below,* after Chen and Han, *J Clin Invest* 2015;125:3384-3391).



Example 4 – Engineering a Potential New Gene Therapeutic for CVD

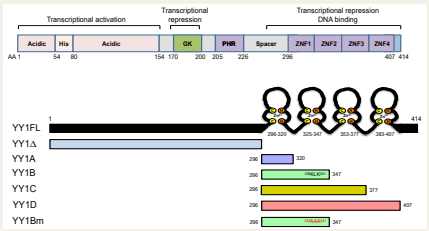
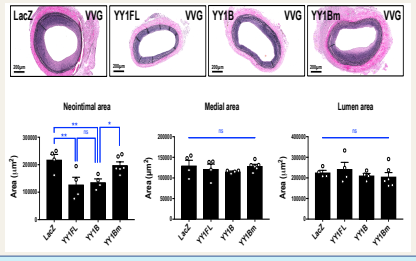


Fig. 4. YY1B (a truncated version of its parent protein YY1), delivered using an adenovirus, suppresses restenosis after balloon angioplasty of rat carotid arteries. Schematic representation f YY1, YY1B and other constructs *(upper)*. Cross section of carotid arteries treated with various constructs *(lower)* showing YY1B is as effective as full length YY1 in suppressing neointimal thickening.



Example 5 – Control of Inflammation in Arthritis

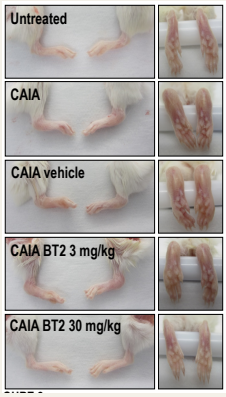
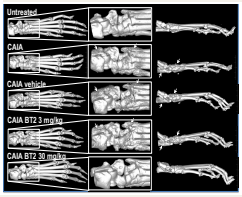


Fig. 5. BT2 inhibits hind footpad thickness in a mouse model of rheumatoid arthritis (collagen antibody-induced arthritis, CAIA) in a dose-dependent manner *(left)*. Micro-CT images of hind limbs showing BT2 inhibition of bone erosion *(below)*.



Example 6 – Control of a Key Biomarker of Retinal Pathology

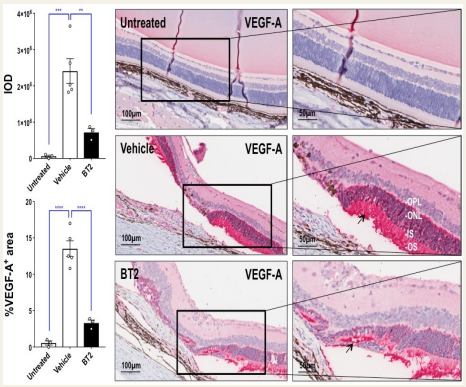


Fig. 6. BT2 inhibits VEGF-A expression in rat retina. Immunostaining for VEGF-A in rat retinal lesions induced by laser injury. Integrated optimal density (IOD) (upper histogram) or area stained (lower histogram) assessed with Image Pro-Plus. "Untreated" (first bar) denotes no injury or BT2 treatment. "Vehicle" (second bar) denotes injury and no BT2 treatment. BT2 given by intravitreal injection.

Recent References

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