

# CRT Licensing Opportunity



## Endothelial Specific Cre-ER(T2) Mice Strains

- Mouse models for temporal and spatial control of genes in endothelial cells
- Expression of Cre-ER(T2) driven by VECAD or BMX promoters
- Extensively validated using the ROSA26R reporter mouse
- Low background Cre-ER(T2) expression, highly inducible by tamoxifen

ENABLING TECHNOLOGY

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### Introduction

Transgenic mouse models have been used to elucidate much information about vascular development. However, studies of protein function in angiogenic processes in later stages of embryonic development, as well as neo-angiogenesis in adulthood are restricted by the fact that gene knockouts are often embryonic lethal. As such, mouse models that allow both temporal and spatial control of genes of interest are invaluable research tools for investigating protein function in these settings. Two mouse strains have been developed that express the inducible Cre-ER(T2) gene switch exclusively in endothelial cells.

### Background

Cre/LoxP is an established system for the silencing of specific genes in mouse models, utilizing the activity of the Cre recombinase to drive excision of the gene of interest, which is engineered with flanking LoxP target sites. In recent years, this system has been further improved through the use of fusions of Cre with the oestrogen receptor (ER), which are only active in the presence of tamoxifen, allowing temporal control of the tissue-specific recombination event. The improved ER(T2) version of the oestrogen receptor, developed by Metzger and Chambon shows increased sensitivity to tamoxifen, and lower response to endogenous steroids than the wildtype counterpart.

### The Technology

Varying problems can be encountered when using tissue specific Cre-ER systems, including mosaic induction and background leakiness of the Cre gene expression. These issues seem to depend both on the choice of promoter for driving Cre expression, as well as on the extent of characterization of the responder lines.

Researchers at Cancer Research UK's London Research Institute have developed and extensively validated two transgenic mouse lines that show exquisitely restricted expression of Cre-ER(T2) in endothelial tissues. The mice can be crossed with other strains carrying LoxP-flanked genes of interest to generate temporally controlled tissue-specific deletions upon tamoxifen treatment.

The inducible Cre transgenic strains express the Cre-ER(T2) gene switch using a phage artificial chromosome (PAC) containing the VECAD or BMX promoter. Specificity and efficiency of Cre induction was assessed by crossing the strains with the ROSA26R reporter mouse, in which a floxed-stop cassette has been placed upstream of the beta-galactosidase gene.

Tamoxifen treatment of the VECAD-Cre-ER(T2) embryos induces Cre activity in >90% of endothelial cells of all arteries, veins and in the lymphatic system (Figure 1). Tamoxifen treatment of adult mice induces Cre activity only in smaller vascular beds. As such, these mice will be excellent tools for the study of genes involved in vascular development and pathological angiogenesis in adult mice.

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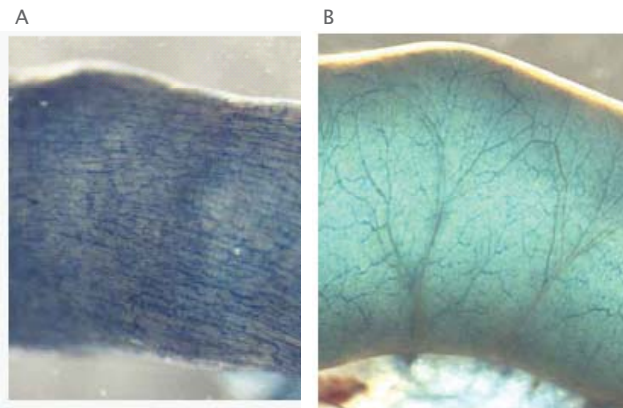


Figure 1. Expression of beta-galactosidase in uterus (A) and intestine (B) in VECAD-Cre-ER(T2) in the background of the ROSA26R reporter mouse, induced by subcutaneous implantation of tamoxifen slow-release pellets.

Tamoxifen treatment of the BMX-Cre-ER(T2) mice induces Cre activity in arterial but not venous endothelial cells (Figure 2). These mice are useful for study of genes involved in pathological arterial conditions, including arteriosclerosis.

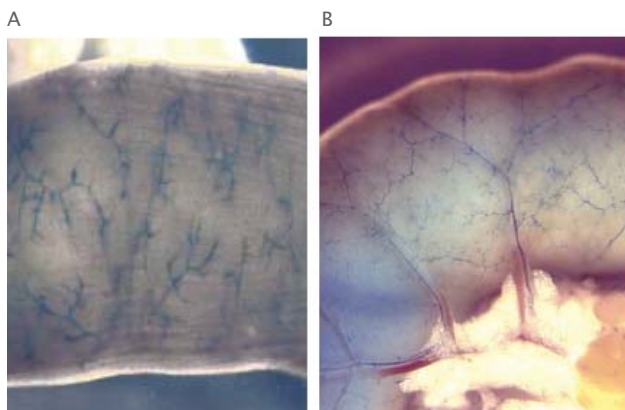


Figure 2. Expression of beta-galactosidase in uterus (A) and intestine (B) in BMX-Cre-ER(T2) in the background of the Rosa26R reporter mouse, induced by subcutaneous implantation of tamoxifen slow-release pellets.

## Commercial Opportunity

The VECAD-Cre-ER(T2) and BMX-Cre-ER(T2) deleter strains are available for non-exclusive licensing for internal research and development use.

Contact: Raj Mehta, [rmehta@CancerTechnology.com](mailto:rmehta@CancerTechnology.com)

Ph: +44 (0)207 269 3640