MONASH University

Production of recombinant human plasminogen

THERAPEUTIC: Inflammation & Immunity

Product Type	Recombinant protein therapeutic
Indication / ROA	Heterotopic ossification, wound healing (burns, diabetic wounds and musculoskeletal injuries) and other diseases where plasminogen is depleted
Target / MoA	Method of production of recombinant plasminogen in a mammalian expression system
Development Stage	Pre-clinical
Brief Description & Differentiation	Plasminogen is considered to be vital across multiple phases of the wound healing process – inflammation, proliferation and remodeling – and plasminogen supplementation can be used to treat a range of these conditions. Commercial human plasminogen is currently produced from human plasma but is limited by supply and risk of contamination. Alternative production of recombinant human plasminogen in both bacterial and mammalian systems also faces limitation with purity and yield for use as a therapeutic. In mammalian systems, plasminogen produced is converted intracellularly into plasmin, which causes issues with cytotoxicity, in turn limiting production. The Whisstock lab has developed methods of producing novel recombinant human plasminogen in a mammalian expression system which significantly improves the process. • Produces significant quantities of the recombinant plasminogen • Protein is stable, biologically active and has demonstrated superior efficacy compared to current commercial preparation of plasma-derived plasminogen • Simple methodology with an easy 3-step purification process
Research Team	Prof. James Whisstock, Dr. Ruby Law, Dr. Adam Quek and Dr. Paul Conroy
Intellectual Property	Australian Provisional 2019902468 filed in 2019
Key Publications	-
Future	Testing of the GMP-grade recombinant plasminogen in various animal models

Key Data

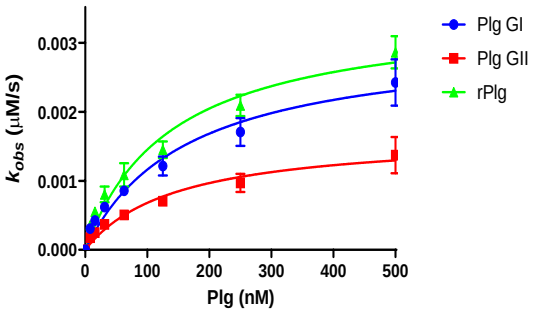
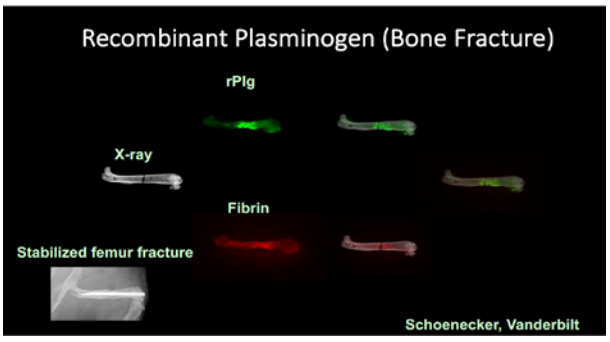


Fig. 1: rPlg is more activatable than native Plg. Michelis-Menten analysis of tPA activation of native Plg GI, GII and rPlg indicates that rPlg is the most readily-activatable (lowest K_M and highest V_{max})



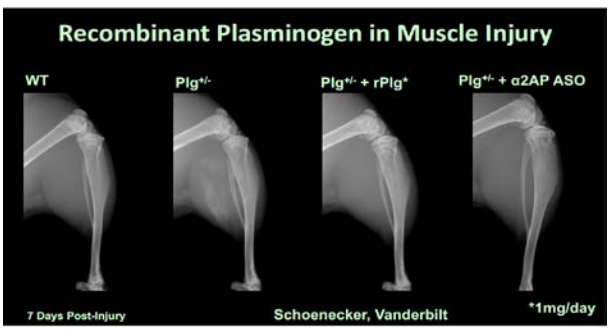


Fig. 2: rPlg (labelled with AlexaFluor790) accumulates at the site of bone and reduces dystrophic calcification following injury.
(Top): rPlg accumulates at the bone fracture site. IP injection of AlexaFluor-labelled fibrin and rPlg. (Bottom) rPlg accumulation at injury site (induced by cardiotoxin) prevents muscle calcification in Plg +/- animals. rPlg was injected IP at 1 mg/day and images were recorded at day 7 post-injury. Muscle calcification is evident in Plg+/- but not in WT animals, and can be rescued by using rPlg or inhibition of alpha2-5 antiplasmin (α2AP) expression using an α2AP antisense oligonucleotide.