

**Supplemental Figure 2.** Breeding schedule to generate ‘rescued’ cystatin M/E deficient mice. First, the transgenic founder mice (Tg (INV-*Cst6*-IRES-eGFP)) are crossbred with heterozygous *Cst6+/-* mice to generate F1 Tg(INV-*Cst6*)*Cst6+/ichq* mice.Subsequently, the offspring of two Tg(INV-*Cst6*)*Cst6+/ichq* mice (F1) resulted in Tg(INV-*Cst6*)*Cst6ichq/ichq* mice. These mice are completely deficient for *Cst6* expression, except for the tissues where the INV promoter is active, such as interfollicular epidermis. Expression of *Cst6* ’rescued’ the lethal phenotype of cystatin M/E deficient mice.