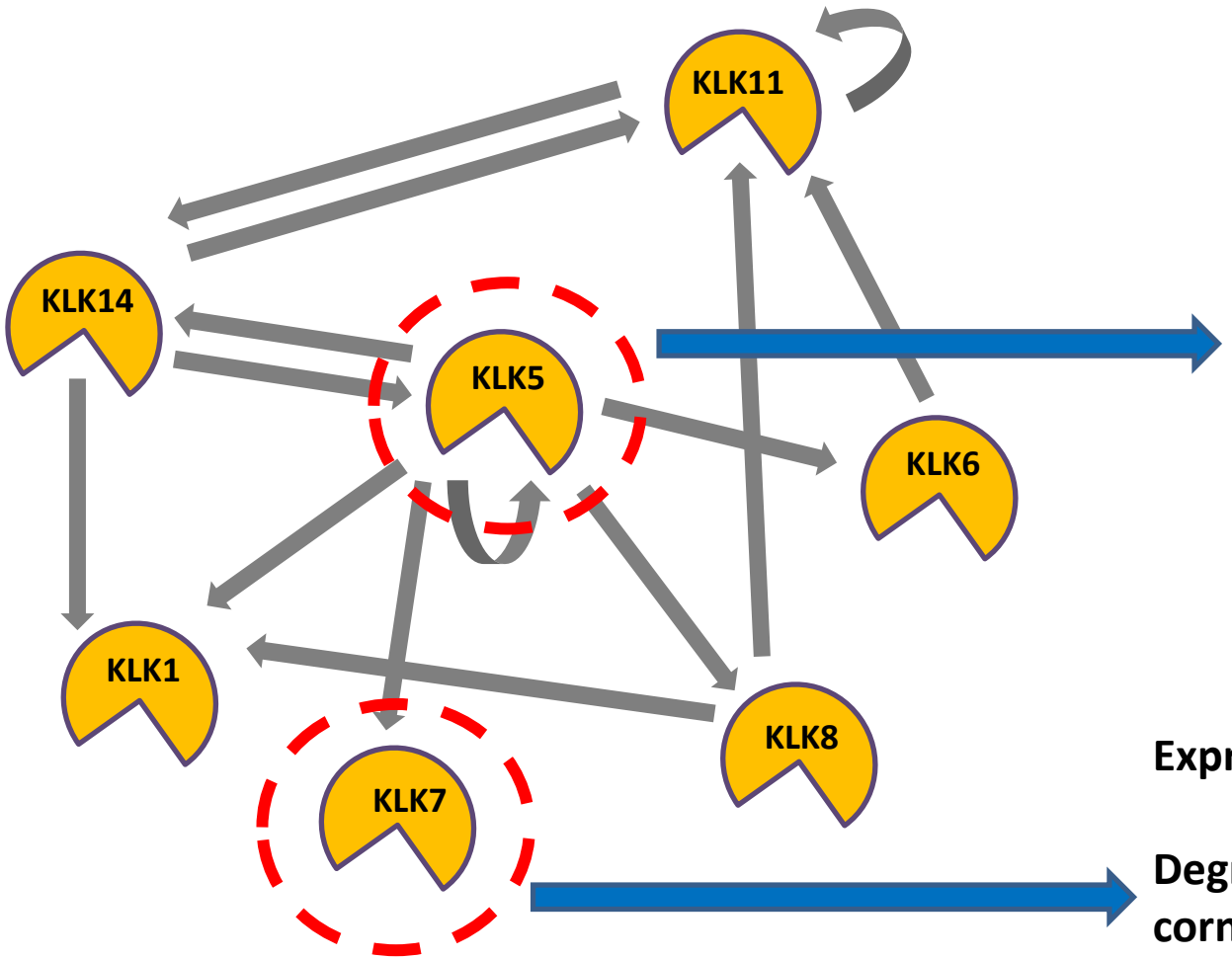
KLK5 and KLK7 ablation fully rescues lethality of Netherton syndrome-Like Phenotype

programmable nucleases help to reveal functional networks

Radislav Sedlacek

Czech Centre for Phenogenomics, Institute of Molecular Genetics
Czech Republic

Kallikrein-related peptidases (KLKs) in epidermis



Expressed in SC

Degradation of corneodesmosomal proteins (in vitro)

PAR-2 activation

Expressed in SC

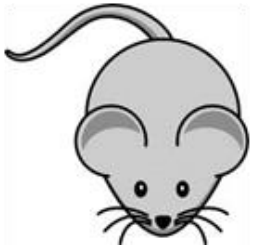
Degradation of corneodesmosomal proteins (in vitro)

What is the role of individual kallikreins in the epidermal-kallikrein network ?

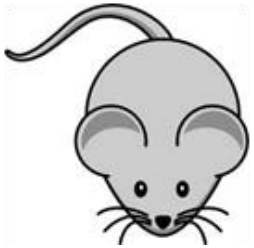
Cooperation, redundancy?

Generation of Klk-deficient models

Klk5 -/-



Klk7 -/-



Klk5/7 -/-

KLK5 and KLK7 single–deficient mice do not show any obvious skin phenotype

wt

Klk5$^{-/-}$

Klk7$^{-/-}$

Compansatory, redundancy, coopearation effects between KLK5 and KLK7?

=> **generation of Klk5/Klk7 DKO mice**

Klk5 deficient mice do not show any obvious phenotype

International Mouse Phenotyping Consortium: IMPC

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Gene: Klk5

Name	kallikrein related-peptidase 5	Login to register interest
Synonyms	1110030O19Rik	Order
Status	ES Cells, Mice tm2a, Mice tm2b, phenotype data available	
Links	MGI:1915918 Ensembl Gene Ensembl Orthologs ENU(7)	

All Phenotypes Summary

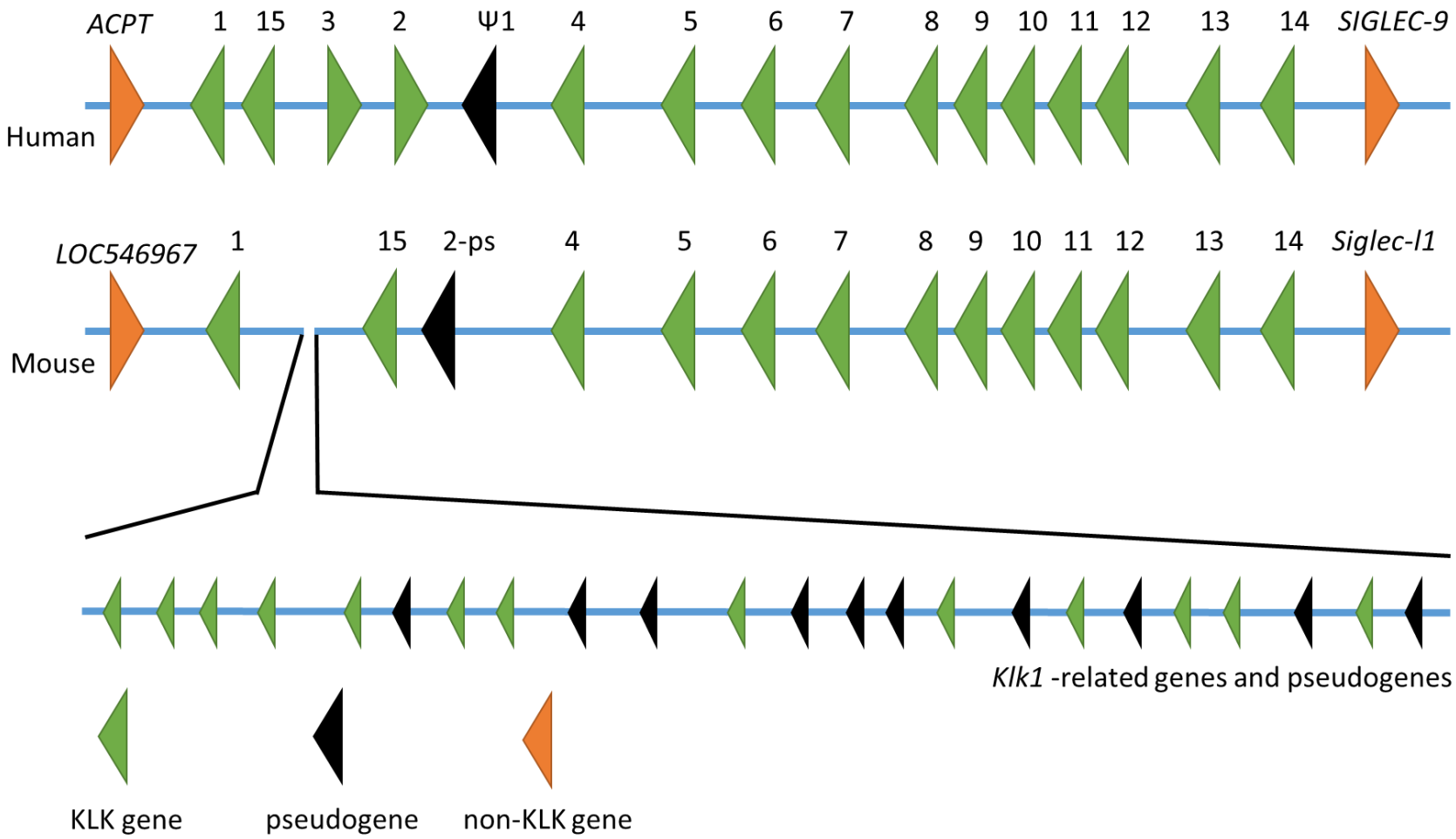
Based on automated MP annotations supported by experiments on knockout mouse models.
Click on icons to go to all Klk5 data for that phenotype.

All Data: Klk5 Measurements | Heatmap / Table

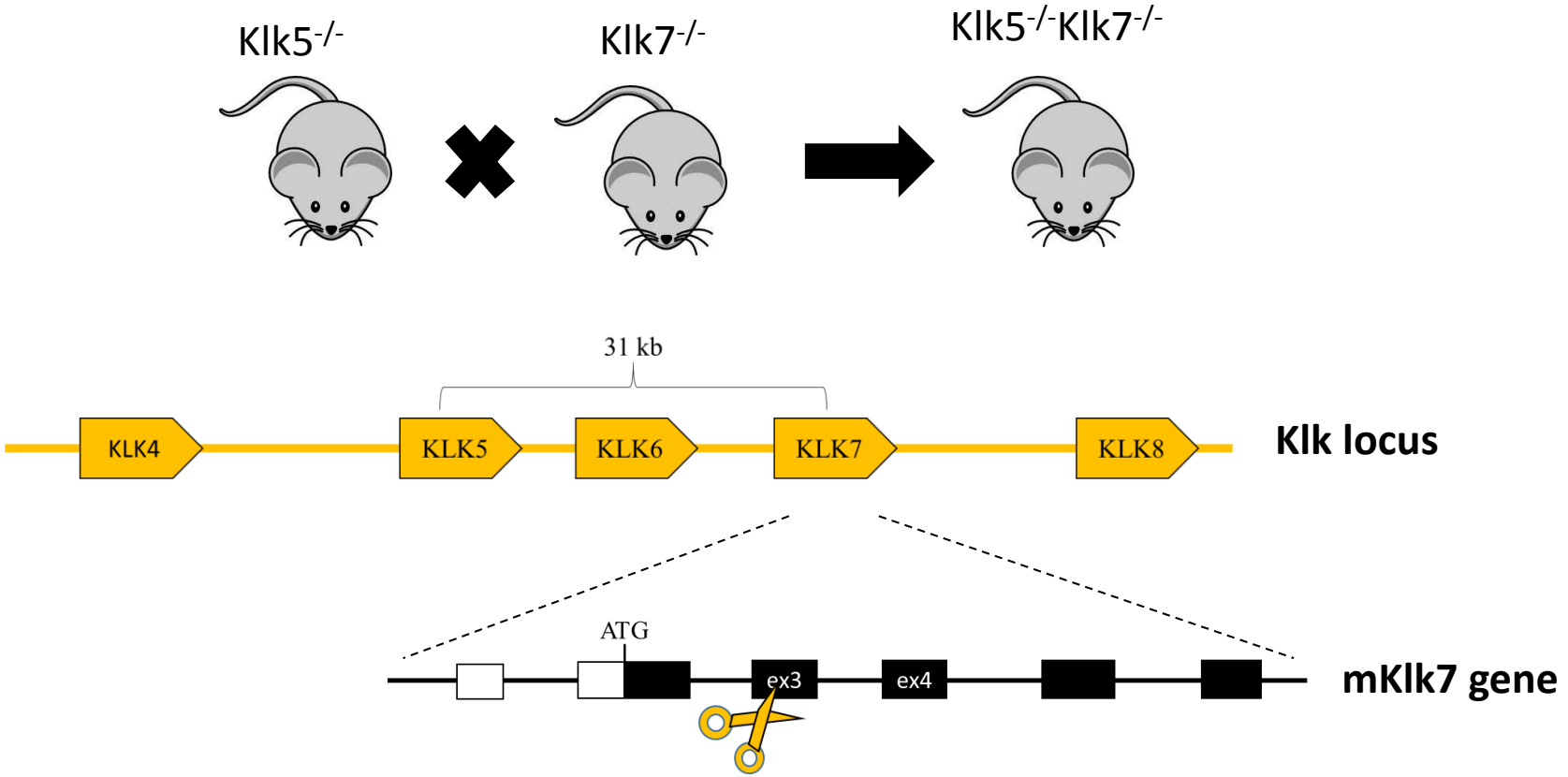
Significant Not Significant Not tested

No results meet the p-value threshold

Organization of Klk locus

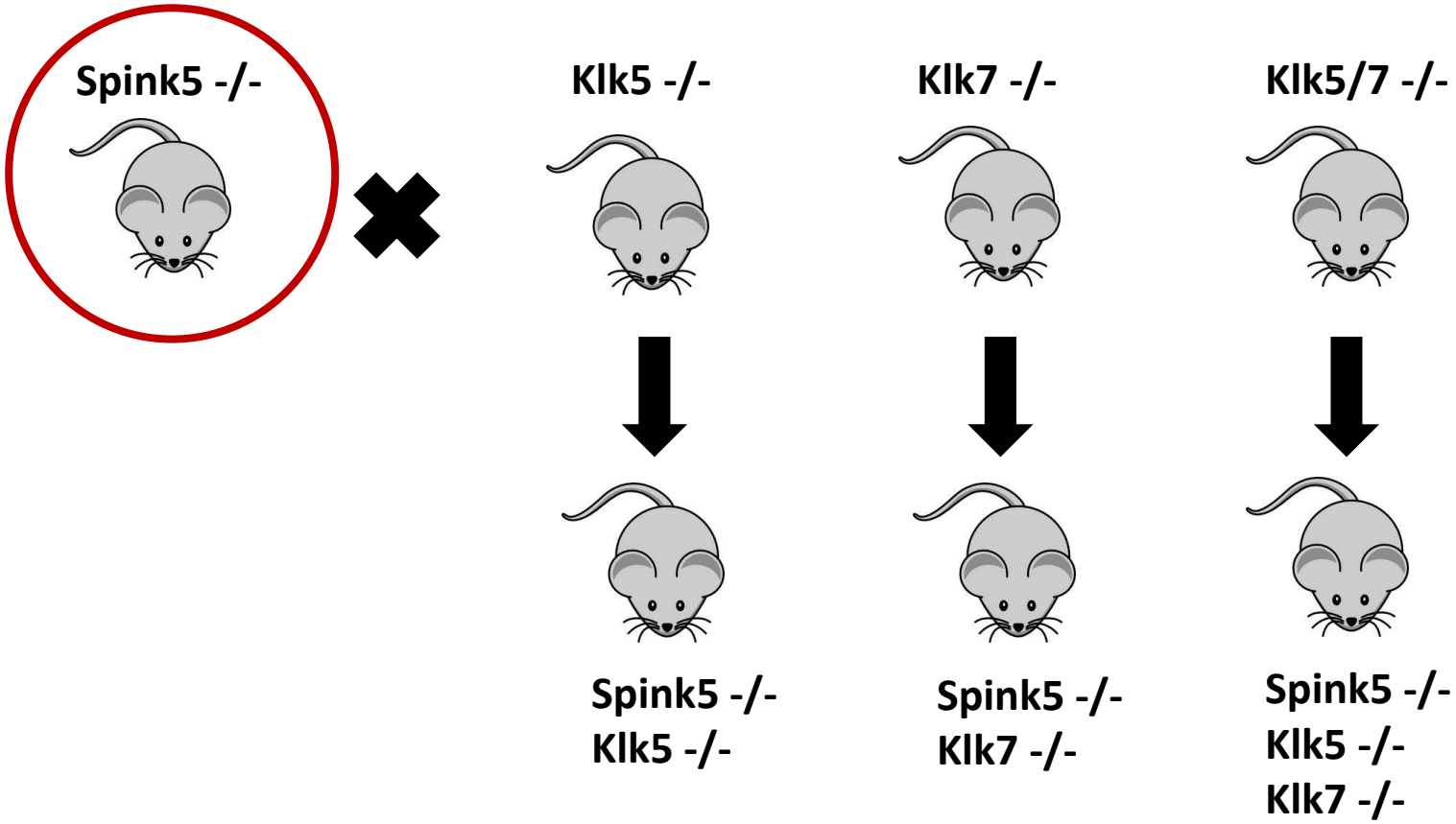


Generation of Klk5/Klk7 dKO mice using TALEN technology

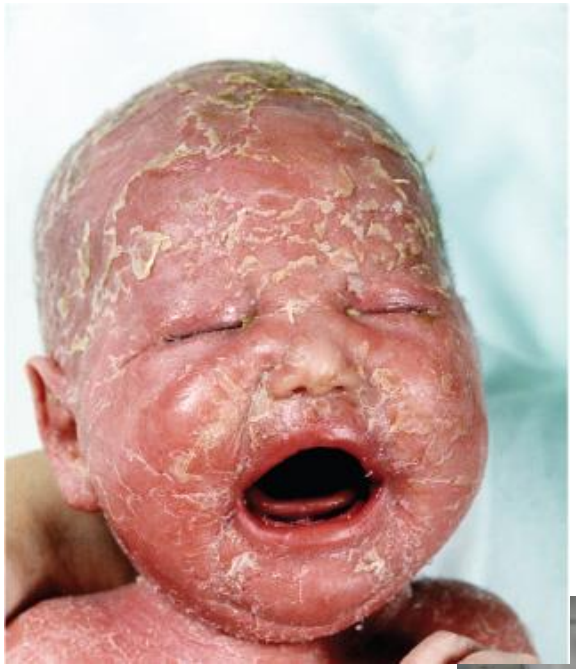


KLK-inhibitor network:

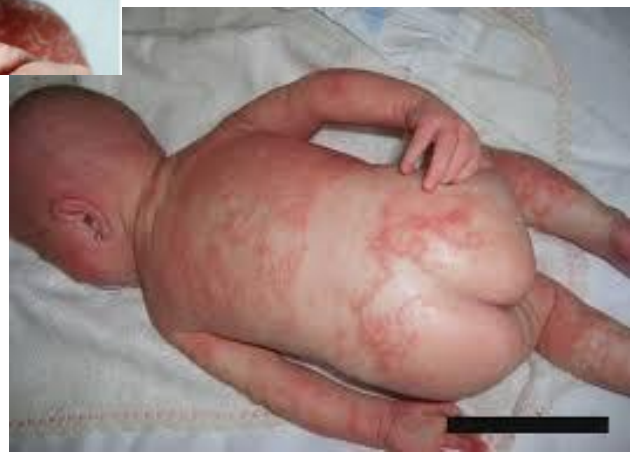
generation of Klk x Spink5 double and triple deficient mice



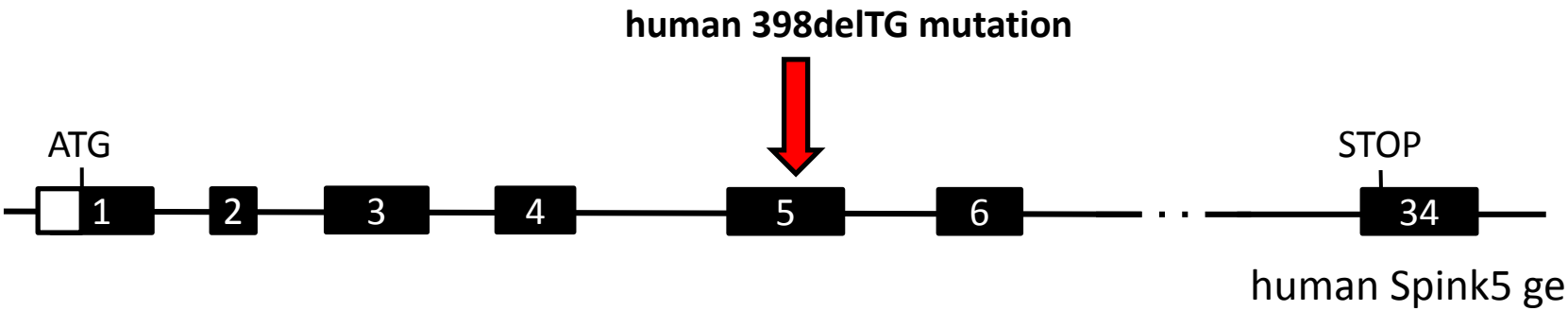
Netherton syndrome



- Autosomal recessive genetic diorder
- 1 in 200 000 newborn children
- Red, scaly, exfoliating epidermis
- Chronic skin inflammation
- Growth retardation
- Specific hair shaft defects (bamboo hair)
- Caused by mutation in Spink5 gene



Generation of a mouse model for Netherton syndrome



Raghunath et al., 2004

human wt: 5´CTG TGT GCT GAG AAT GCG 3´

human 398delTG: 5´CTG TGC TGA . . .3´

murine wt: 5´CTG TGT GCT GAG AAT GCG 3´

murine 402delTG: 5´CTG TGC TGA . . . 3´

Generation of a mouse model for Netherton syndrome

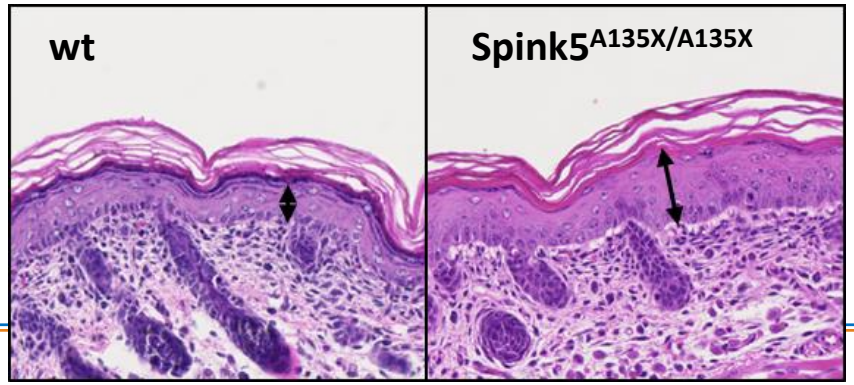
wt

TALEN mutagenesis

Spink5$^{A135X/A135X}$

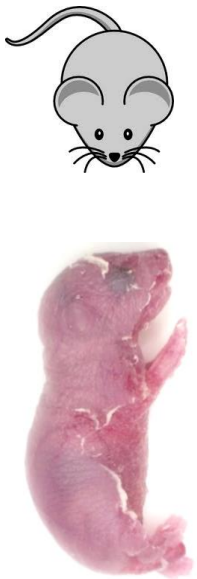
lethal

Abnormal diferentiation of epidermis:
Acanthosis
Parakeratosis



Generation of Klk x Spink5 double and triple deficient mice

Spink5 -/-



Klk5 -/-

Spink5 -/-
Klk5 -/-

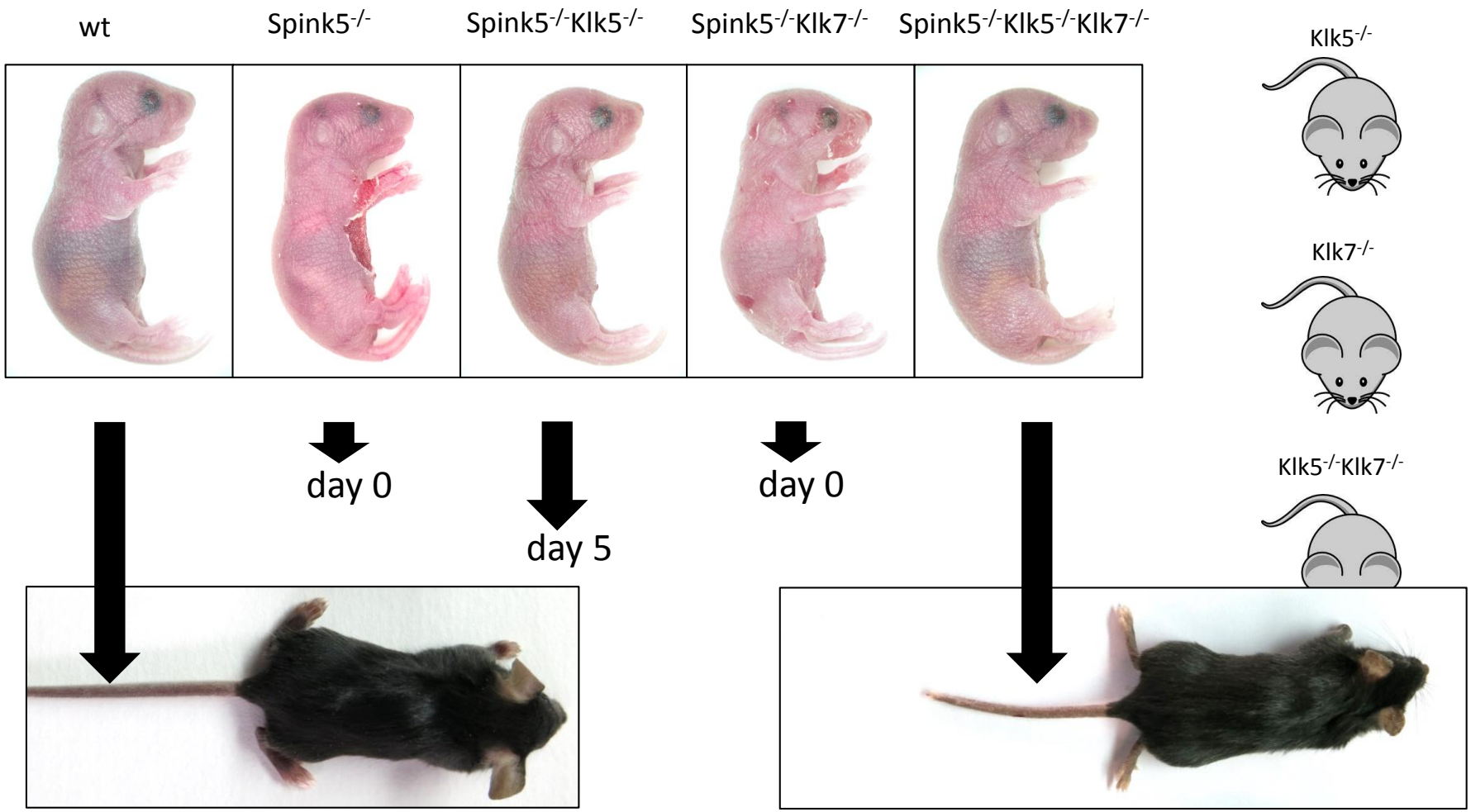
Klk7 -/-

Spink5 -/-
Klk7 -/-

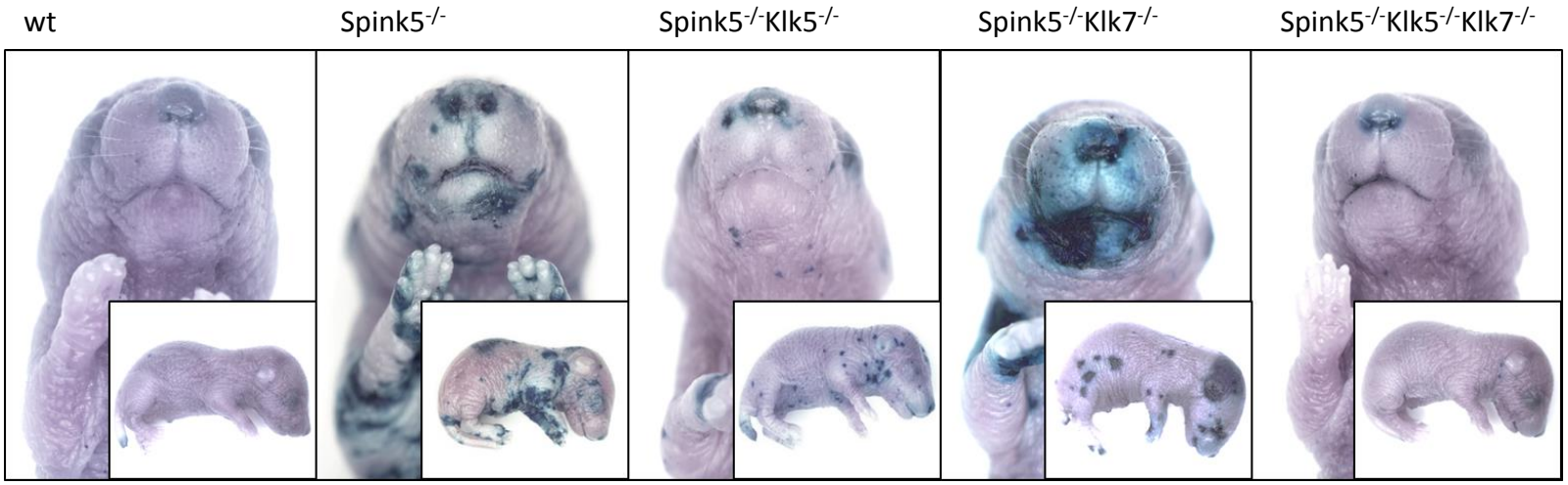
Klk5/7 -/-

Spink5 -/-
Klk5 -/-
Klk7 -/-

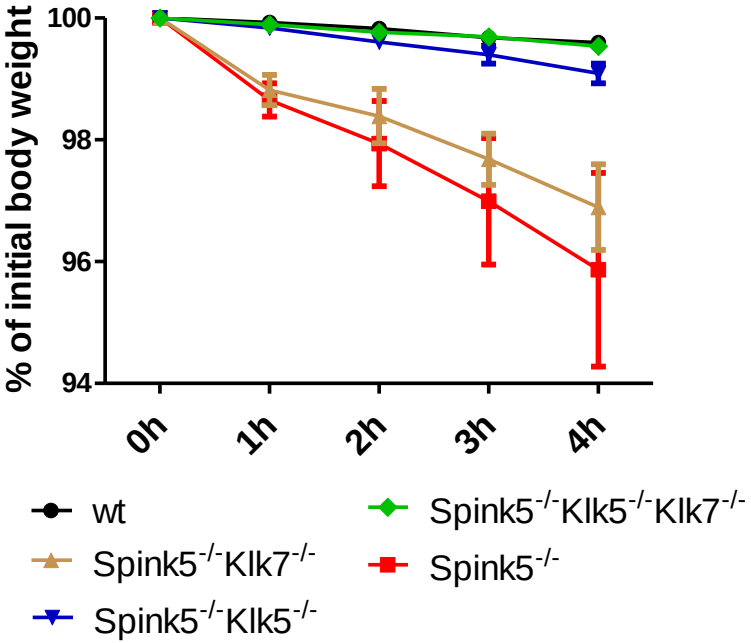
Simultaneous inactivation of KLK5 and KLK7 rescues lethal phenotype of NS mouse model



Both, KLK5 and KLK7 contribute to skin barrier defects



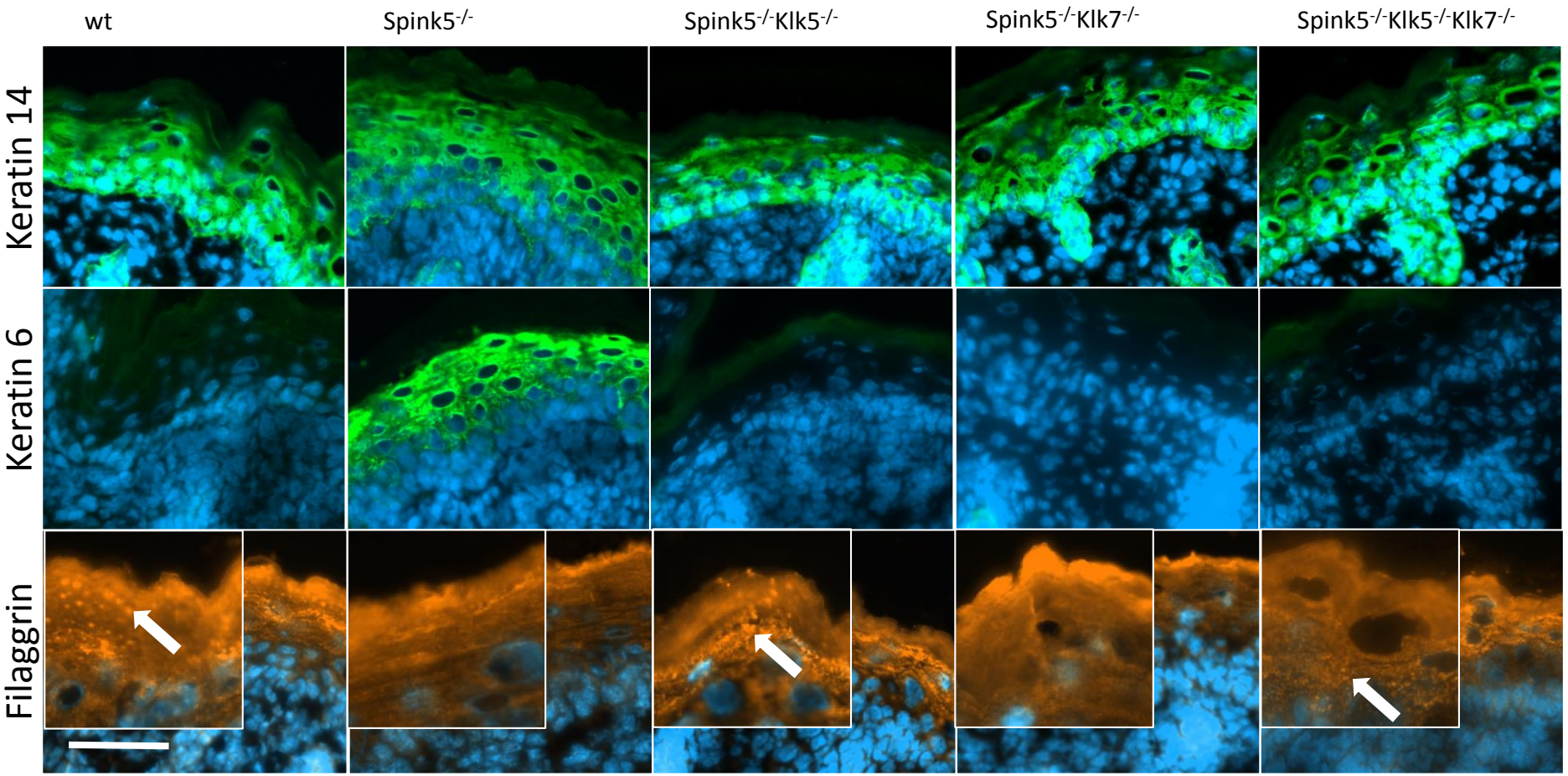
Toluidine blue penetration assay



Unregulated activity of KLK5 causes severe postnatal dehydration at P0

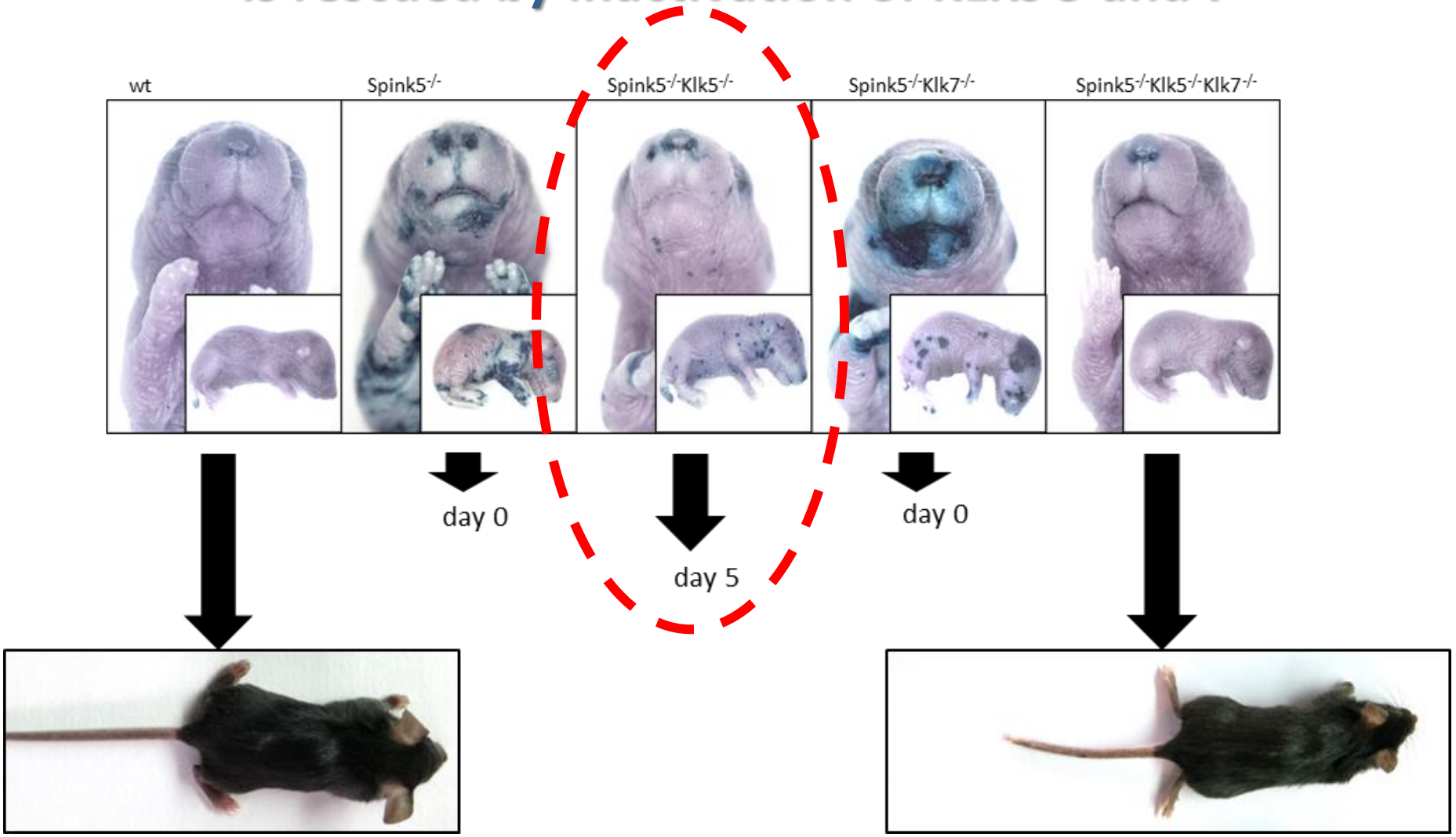
KLK7 causes damage of epidermal barrier independently of KLK5 activation

Abnormal differentiation of epidermis in Spink5-/- pups is rescued upon ablation of KLK5/KLK7



Abnormal processing of profilaggrin is associated with **KLK5** activity and may contribute to impaired water retention of **Spink5$^{-/-}$** and **Spink5$^{-/-}$KLK7$^{-/-}$** epidermis

Epidermal barrier disruption in NS mouse model is rescued by inactivation of KLKs 5 and 7

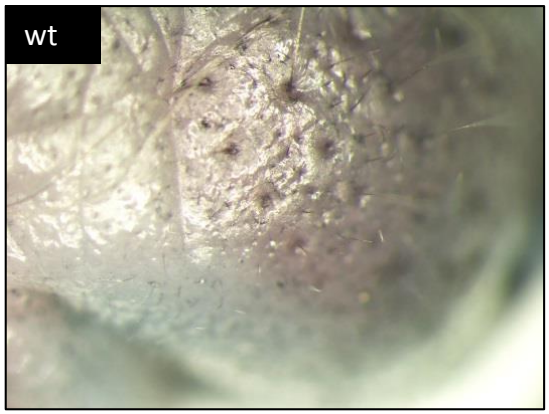


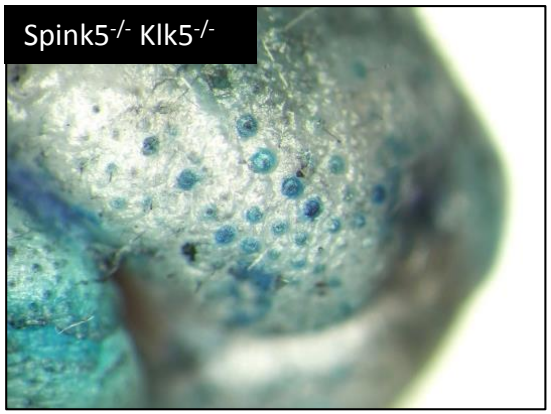
Kasparek et al., PLOS Genetics, 2017

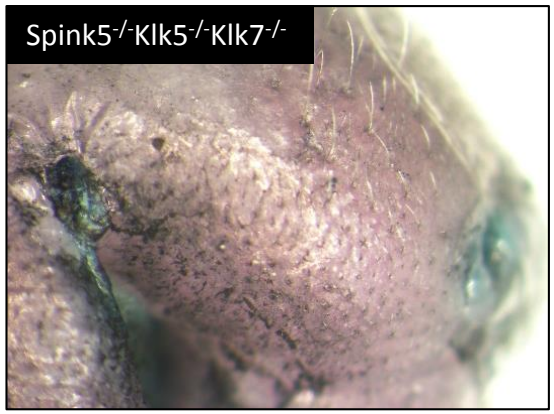
Unregulated activity of KLK7 causes severe epidermal barrier damage in time dependent manner

Spink5$^{-/-}$
Klk5$^{-/-}$

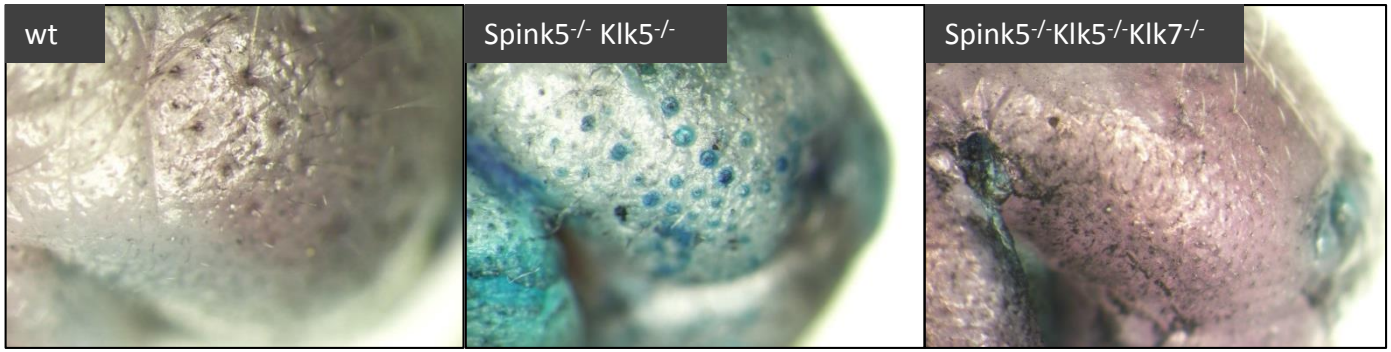
P0 → P5



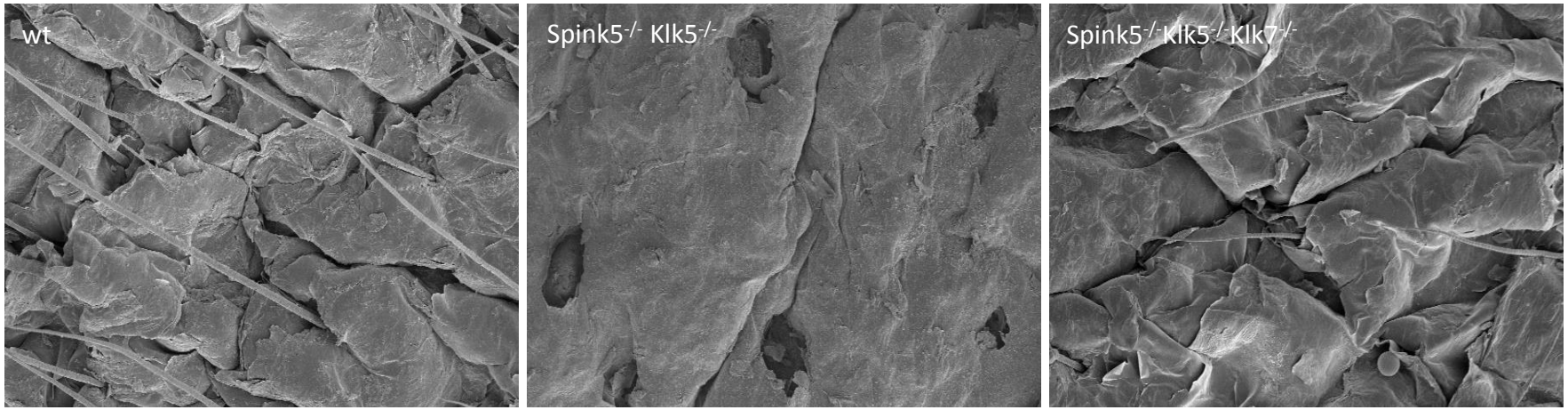




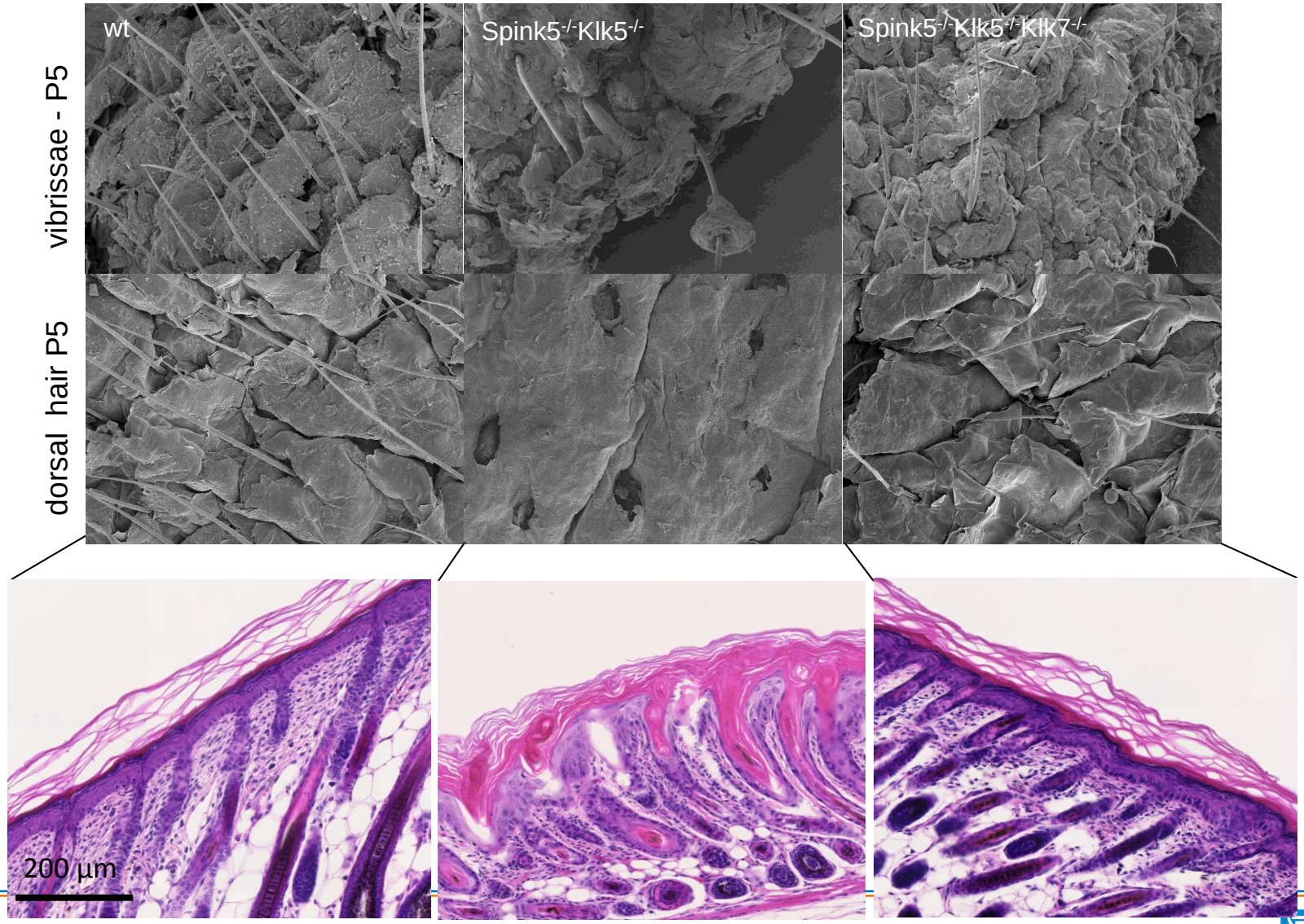
Unregulated activity of KLK7 causes severe epidermal barrier damage in time dependent manner



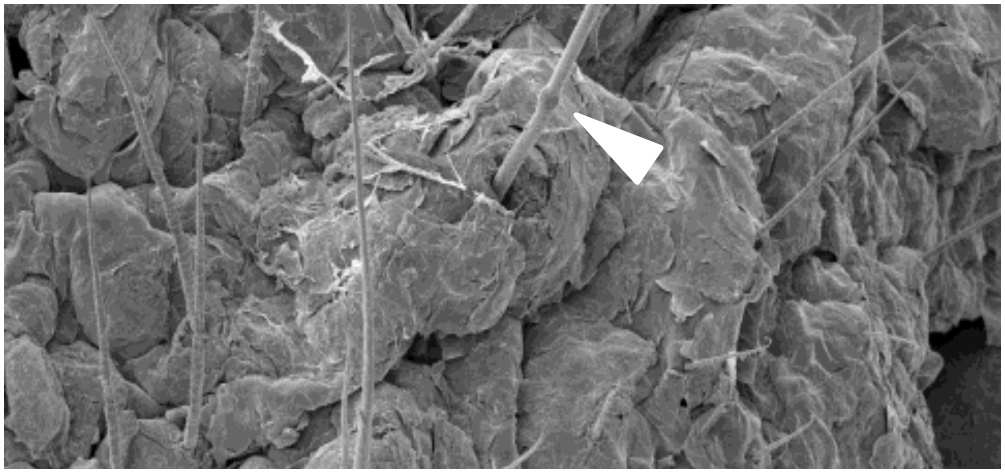
SEM



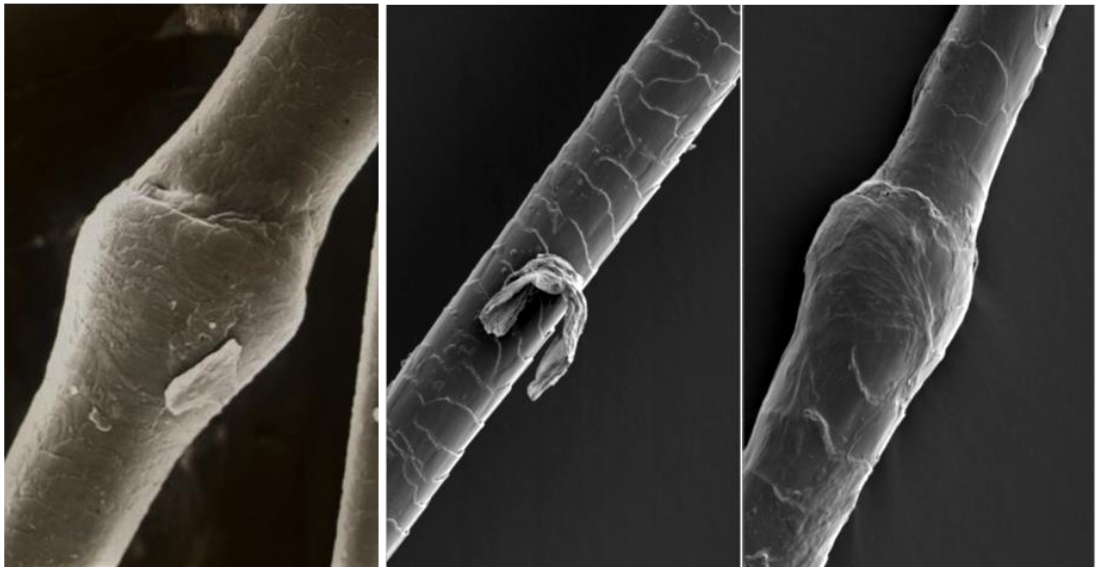
Unregulated activity of KLK7 causes severe damage of epidermis in time dependent manner



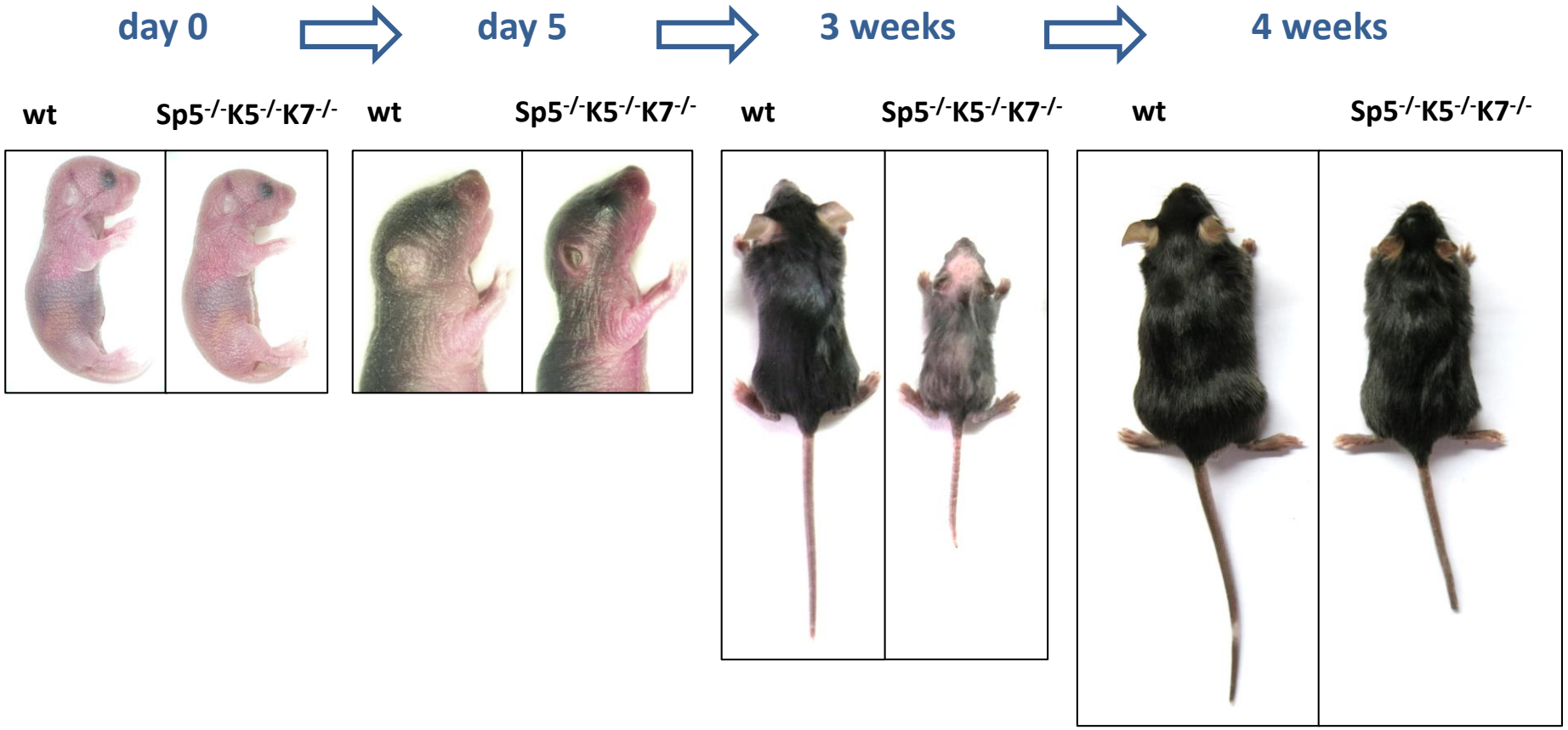
Bamboo hair in Spink5$^{-/-}$Klk5$^{-/-}$Klk7$^{-/-}$ mice are not found after 3 weeks of age



NS-patient (taken from keratin.com) **WT** **Spink5$^{-/-}$Klk5$^{-/-}$Klk7$^{-/-}$**



Adult Spink5$^{-/-}$Klk5$^{-/-}$Klk7$^{-/-}$ mice do not show any major skin defects



Summary

- Novel mouse model for NS was generated by mimicking the mutation from NS patients

- KLK5 and KLK7 are responsible for skin barrier disruption of Spink5$^{-/-}$ skin
- KLK7 causes severe skin-barrier defects in the proximity of hair follicles independently of KLK5 activation

- Bamboo hair defect does not depend on KLK5 or KLK7

- KLK5 and KLK7 together are required for inflammation and differentiation of Spink5 deficient epidermis

- Only simultaneous inactivation of KLK5 and KLK7 fully rescues lethality of NS-mouse model

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