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Citation: Finn, Robert (2011) Cytochrome P450 Monooxygenase Complex and Skin Development. In: Northumbria Research Conference, 5-6 May 2011, Northumbria University, Newcastle-upon-Tyne.

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Cytochrome P450 monooxygenase Complex and Skin Development

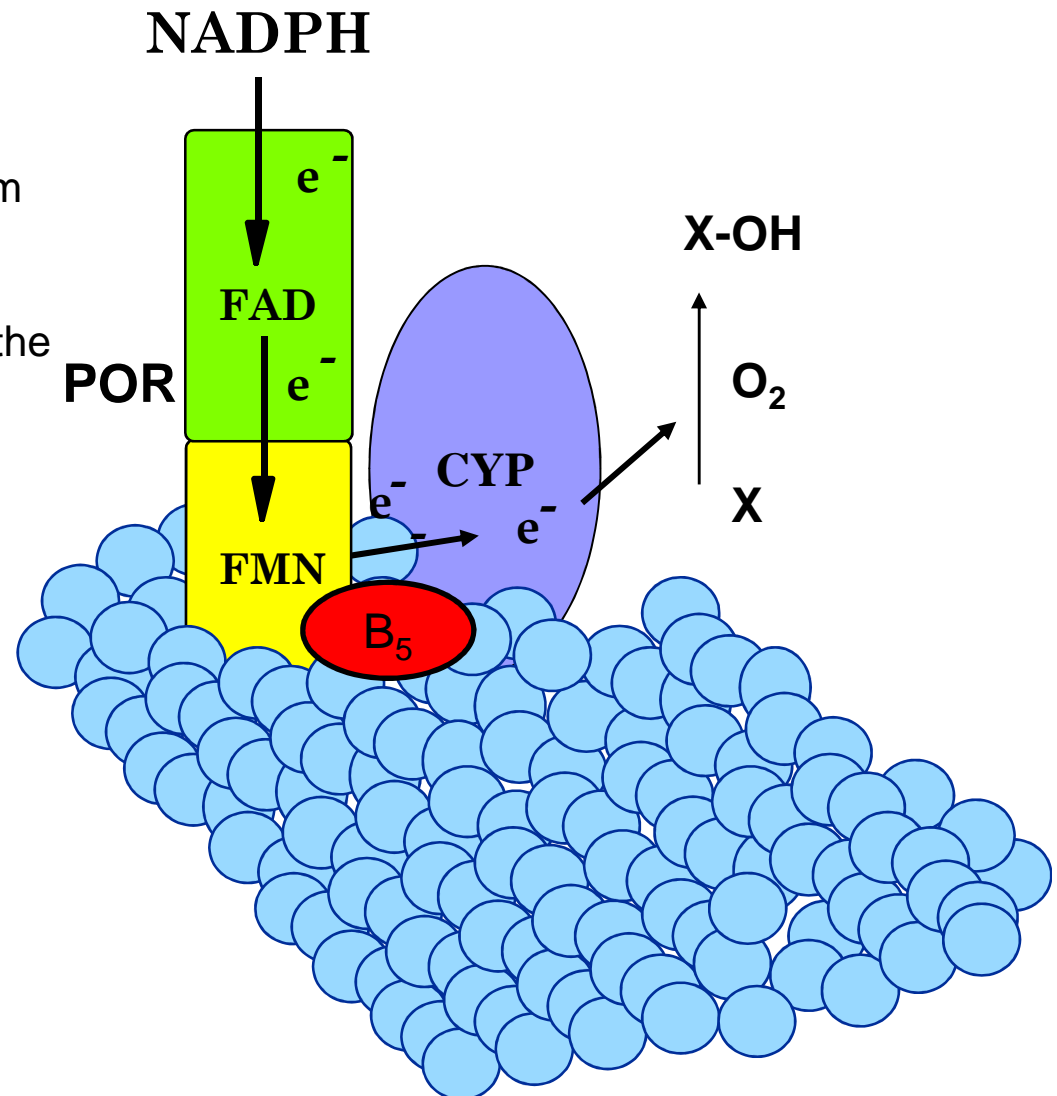
Dr Robert Finn

School of Life Sciences

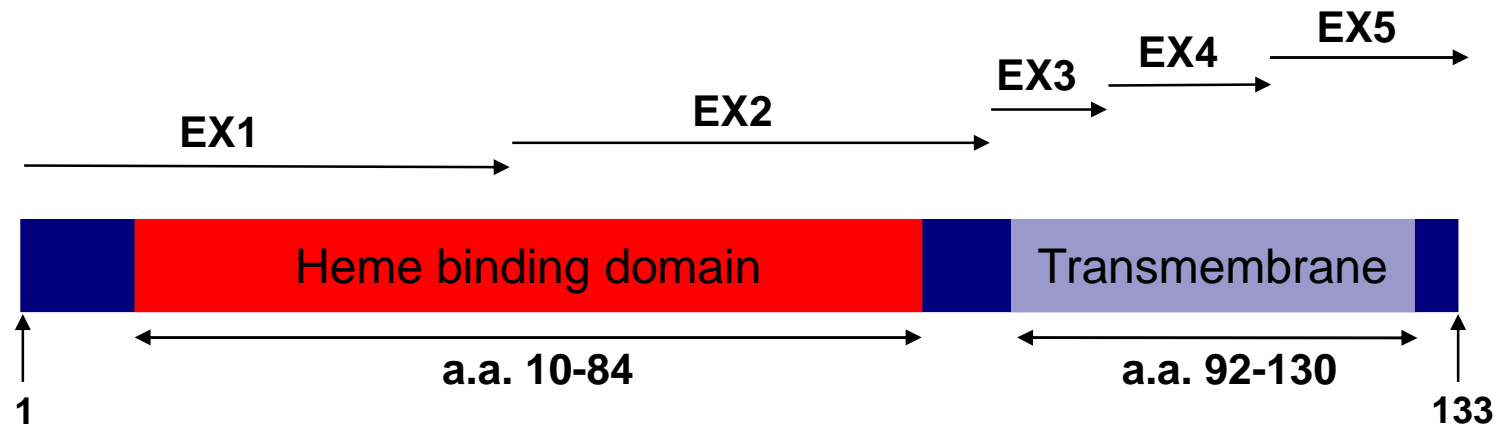
University Research Conference

6th May 2011

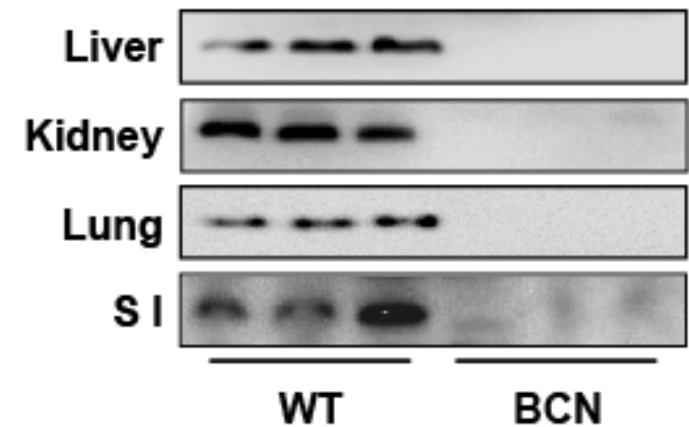
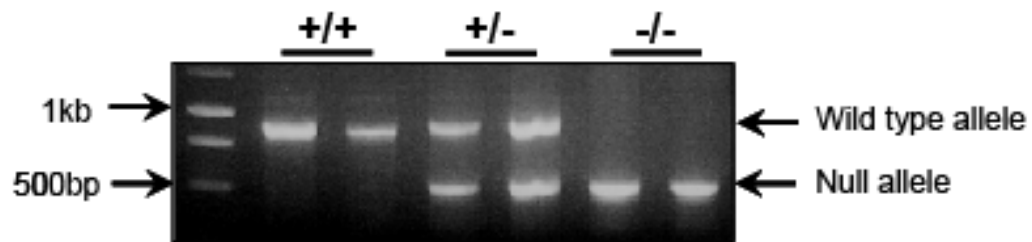
- Cytochrome P450 (CYPs) major Phase I drug metabolising enzymes.
- Several CYP genes have been deleted- conflicting and confusing results.
- All microsomal CYP receive electrons from Cytochrome P450 reductase (POR).
- Deletion of POR or Cyt b_5 would facilitate the study of *in vivo* CYP function.



Mouse Cytochrome *b*₅ peptide structure:

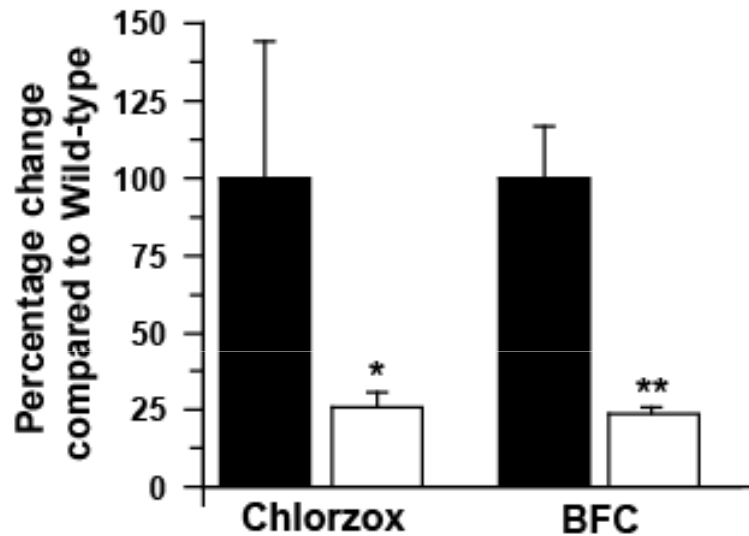


Delete a.a. 44-133 i.e. 70% of core heme binding domain and all transmembrane domain.

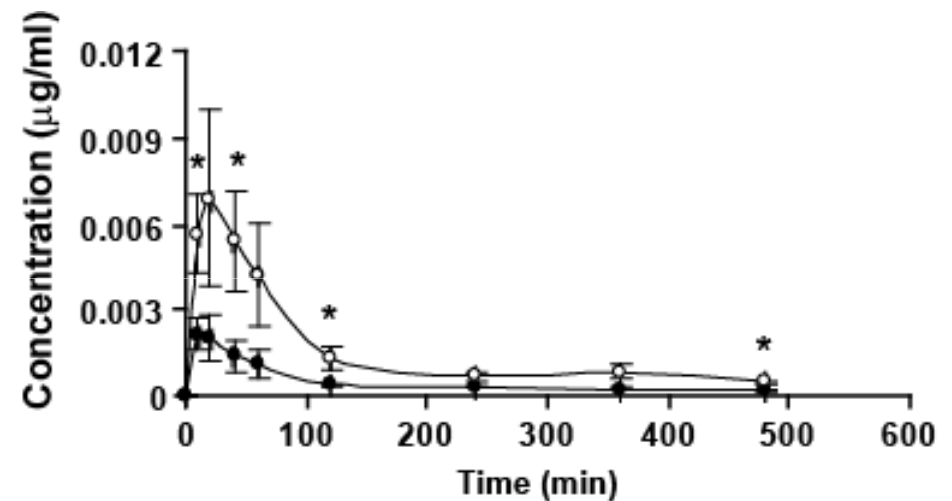


Cytochrome *b*₅ Complete Null – BCN mice

Cytochrome P450 mediated Drug metabolism:



Metoprolol Metabolism



<i>PK Parameter</i>	<i>Wild-Type</i>	<i>BCN</i>
AUC (min*µg/ml)	0.22 ± 0.05	0.76 ± 0.24 *
C _{max} (µg/ml)	0.002 ± 0.001	0.008 ± 0.003
Clearance (L/min/kg)	8.37 ± 0.95	2.36 ± 0.53 ***
Terminal half-life (min)	146 ± 30	350 ± 66 *

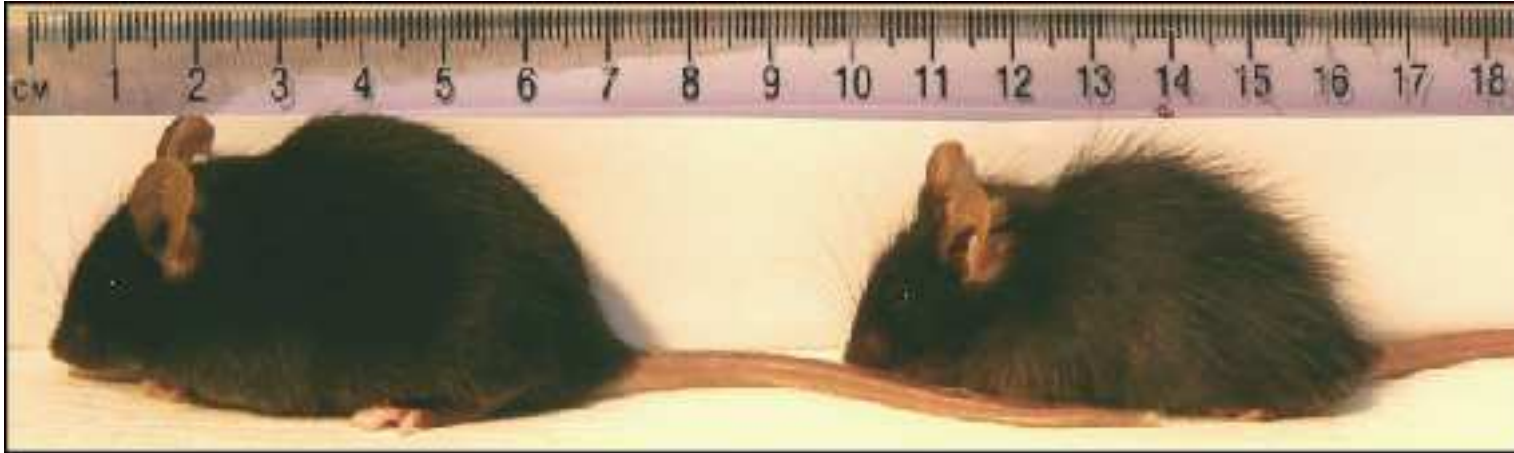
Values represent the mean ± S.E.M. where n = 5.

Confirms the in vitro findings and our previously published work in the HBN model.

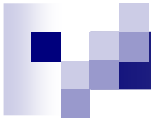
McLaughlin, et.al., (2010) Molecular Pharmacology. Vol. **78**, 269-278.



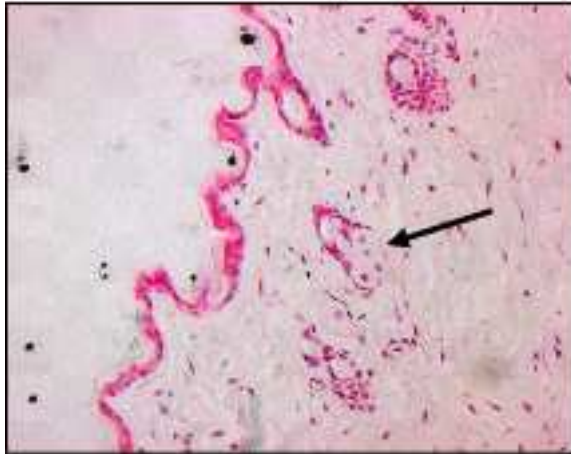
Skin & Hair Follicle Development:



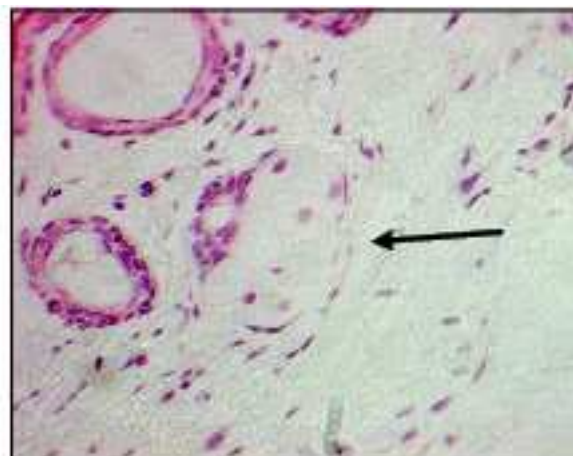
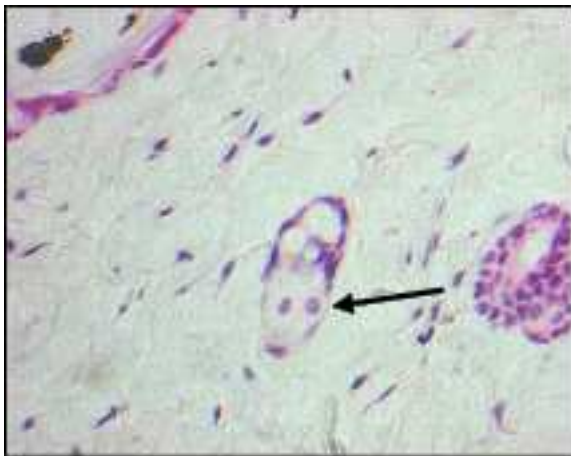
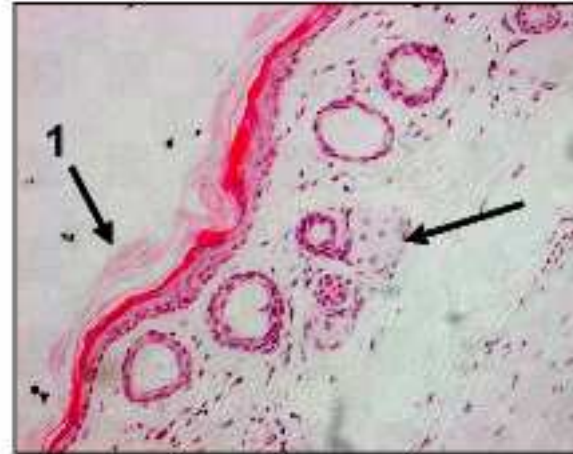
Finn, et.al., (2010) Transgenic Research.

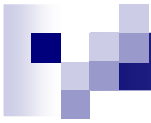


WT

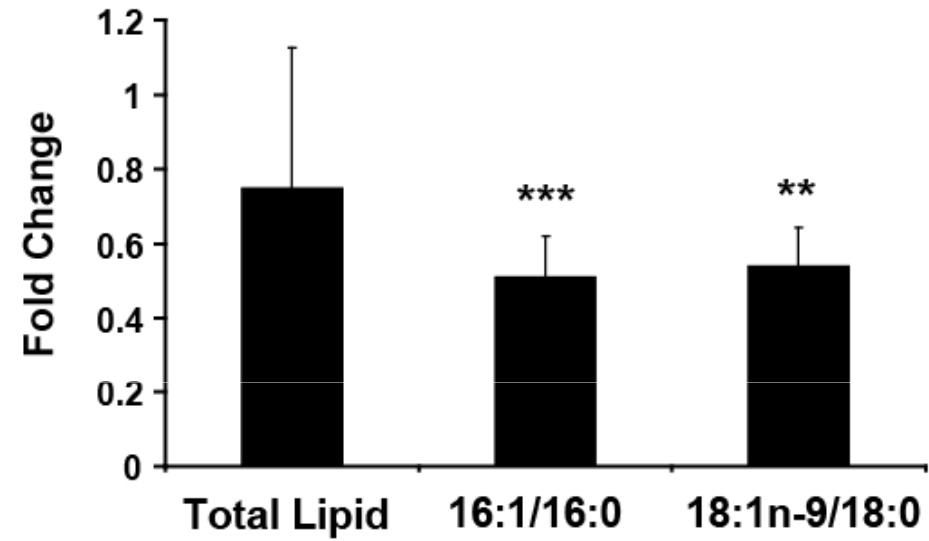
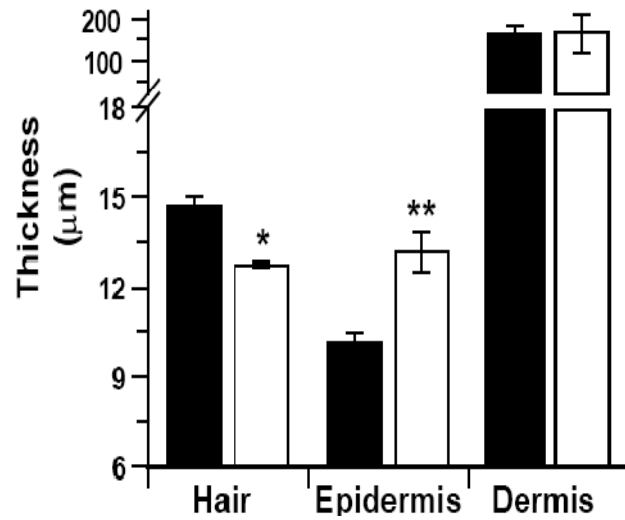


BCN





Black = WT, White = BCN



Disruption of Fatty acid desaturation! Or is it?

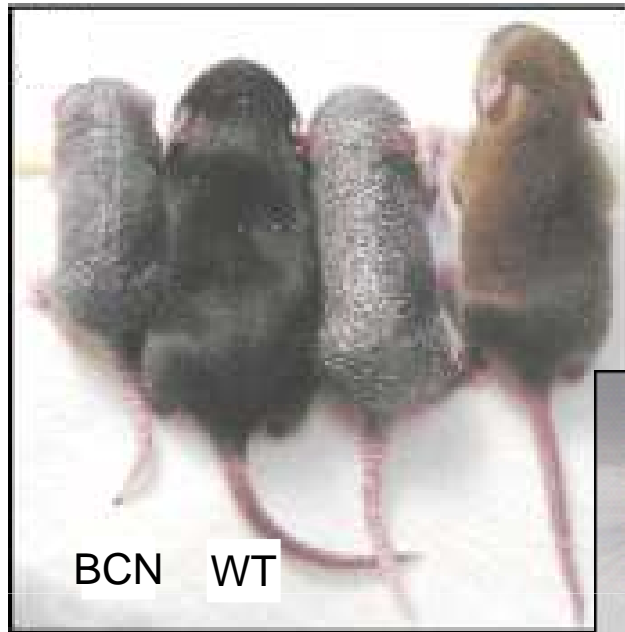
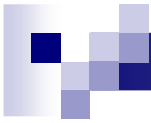
12R-Lipoxygenase deficient mice



+/+

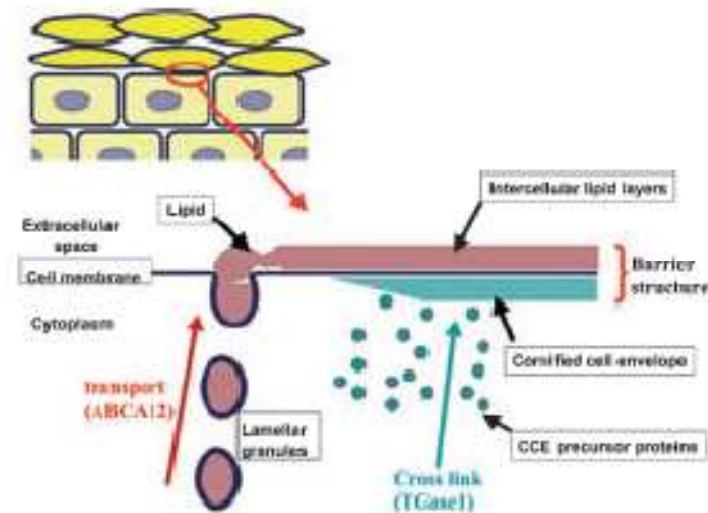
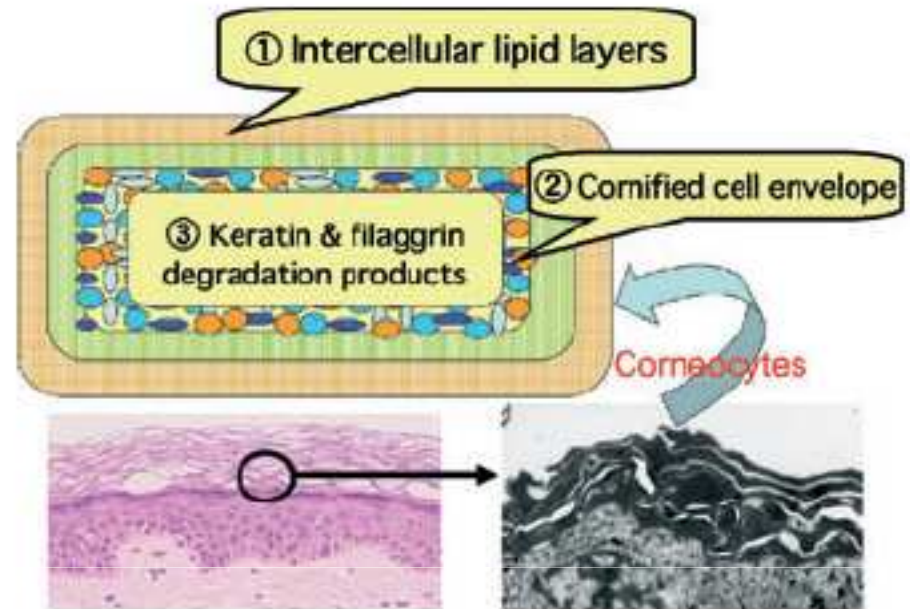
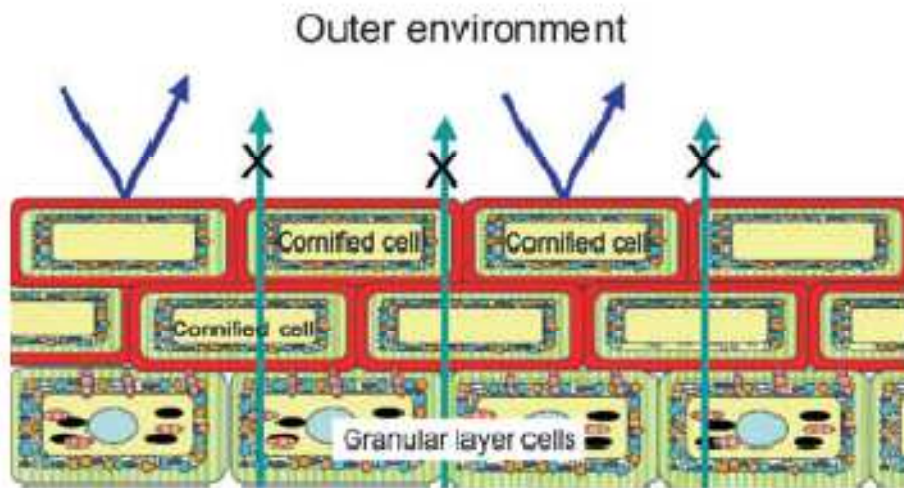


-/-

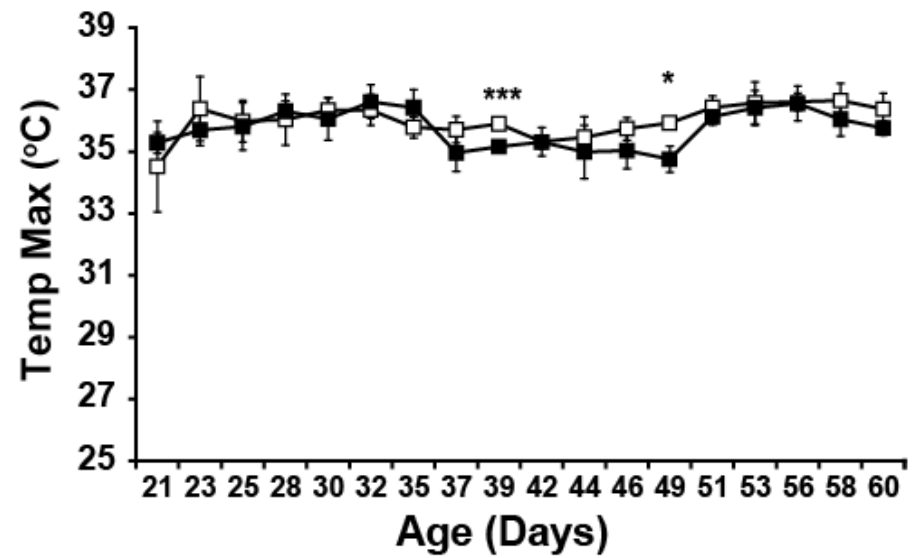
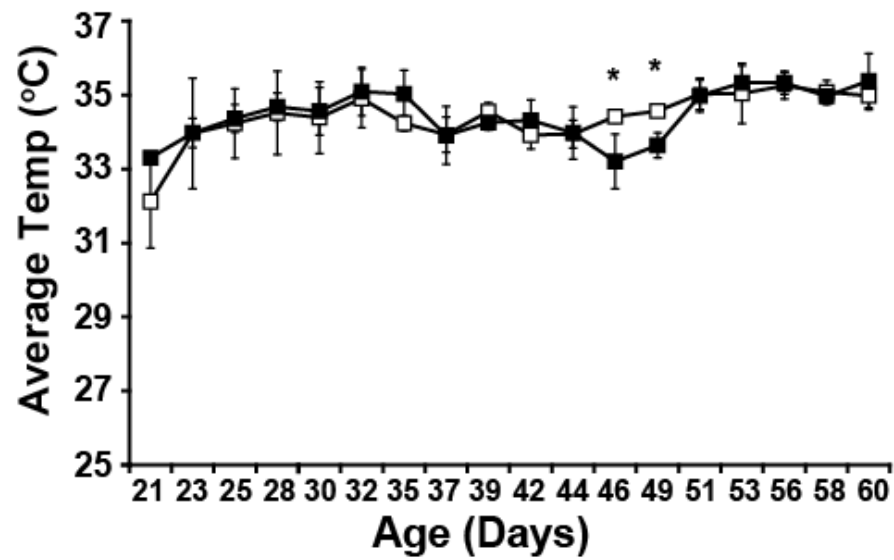
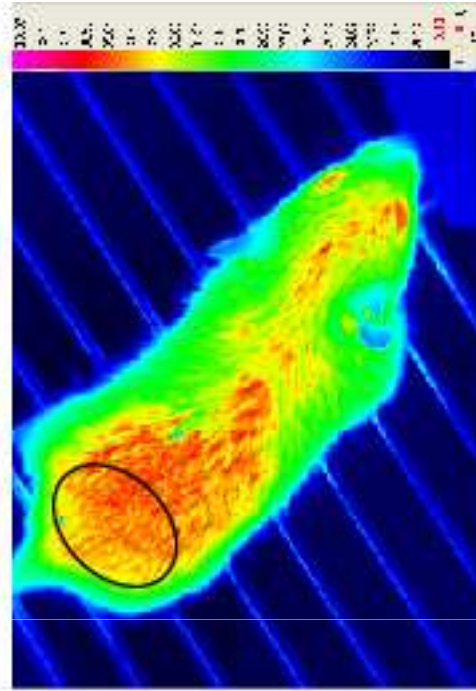
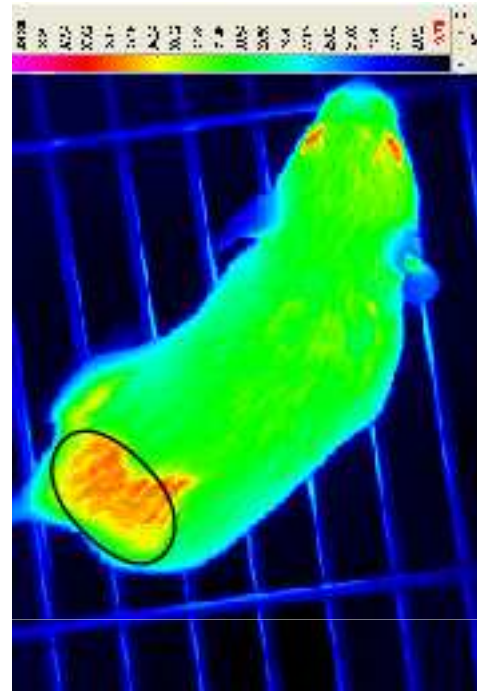
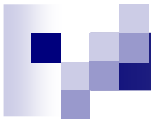


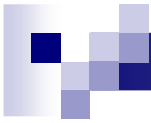
Suga, et.al., 2000 J. Cell Biology.
Loricrin null mice.



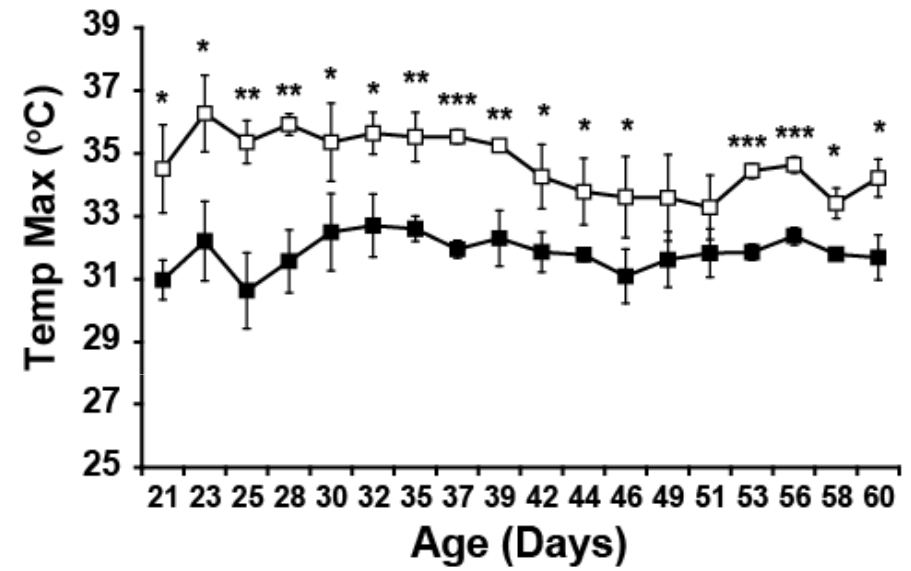
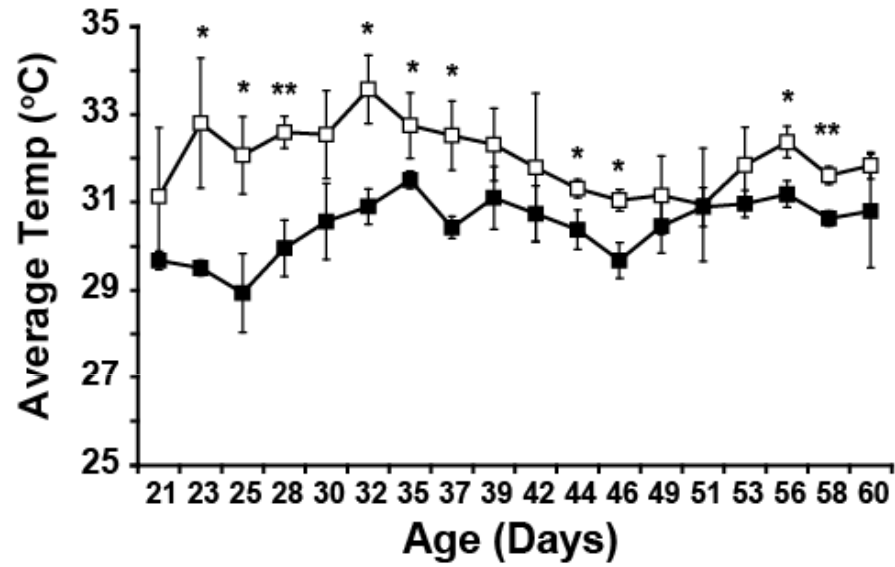


Akiyama & Shimizu, 2008 Expt Dermat





Haired area measurements



Lefèvre, 2006 Human Mol Genetics

Phospholipase

Lipoxygenase + FLAP

Epoxide isomerase

ABC protein / receptor

Epoxide hydrolase

ABC protein / receptor

Glutathione S-transferase

Cytochrome P450

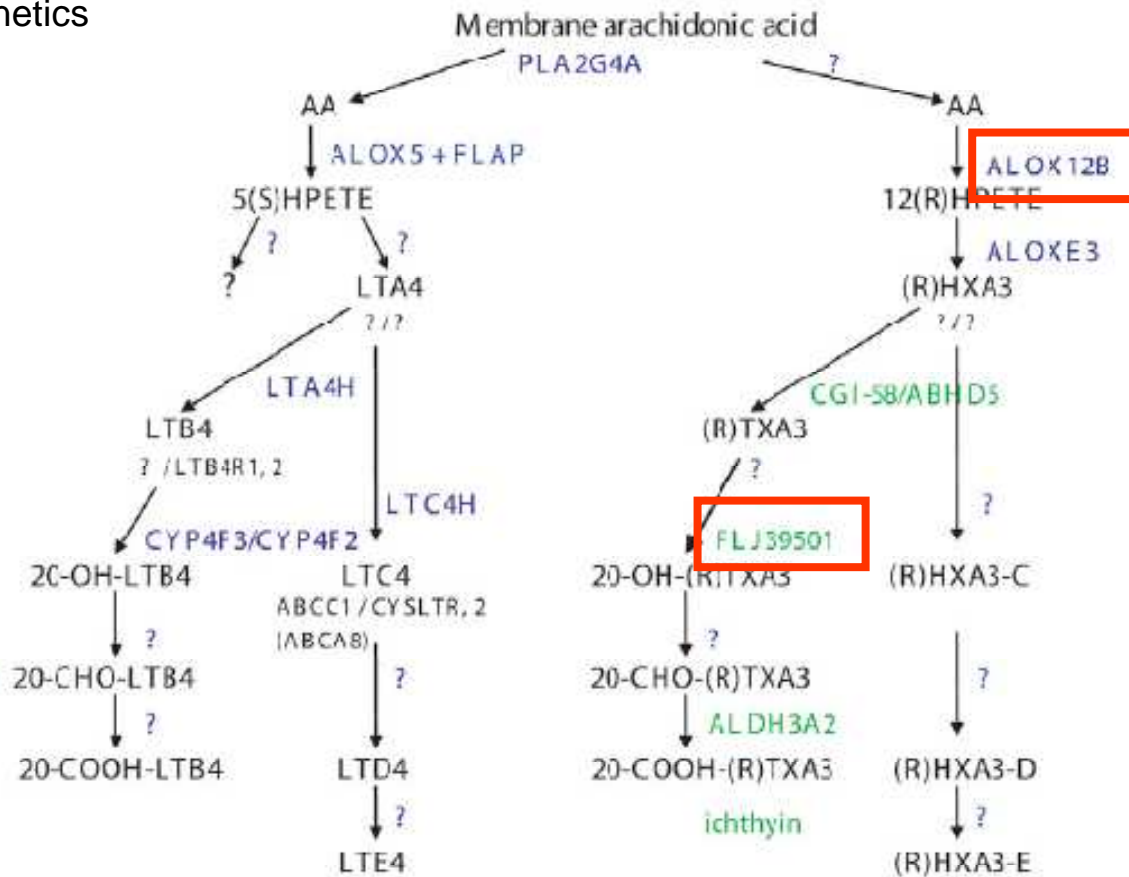
ABC protein / receptor

FADH

γ -glutamine-transpeptidase

FALDH

Dipeptidase / receptor



Leukotriene
5(S)-lipoxygenase

Hepoxilin 12(R)
12(R)-lipoxygenase

FJ39501 (CYP4F22) or Cyp4f39 in mice – no published characterisation, activity influenced by b_5 ?



Conclusion so far:

BCN mice develop an ichthyosis (scaly skin) phenotype resulting from:

Disruption of FA desaturation

Disruption of alternative pathway of AA metabolism.

Where to go next:

Clone human CYP4F22 and mouse Cyp4f39

Establish enzyme activity assay

Investigate effect of Cyt b_5 on activity – test skin samples obtained from KO mice

Investigate mechanism behind genetic disruption.



Acknowledgements

Roland Wolf
Colin Henderson

The b_5 Team:

Lesley McLaughlin
Sebastien Ronseaux
Catherine Hughes

CRUK Transgenic services:

Ian Rosewell.
Many others.

Charlie Song – University of Shanghai, China

Irwin McLean – University of Dundee

Hao Zhu – Kansas University Medical Centre, USA

CANCER RESEARCH UK

