Czech Centre for Phenogenomics

Martin Gregor

Czech Centre for Phenogenomics (CCP)

basic facts

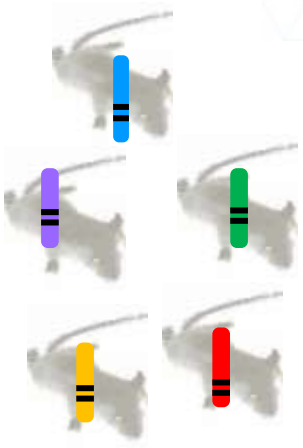
- unique in the Czech Republic, large national infrastructure
- 7200 m2, 24 mil. €, 30 000 cages
- one of the largest in Europe
- open acces - international centre

September 2014

Phenogenomics:

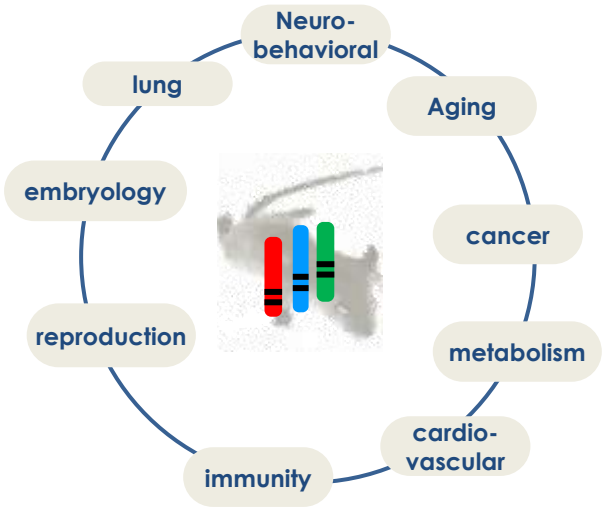
Systematic phenotyping analysis of animal models for annotation of gene function

genes to knock-out
(informative mutation)



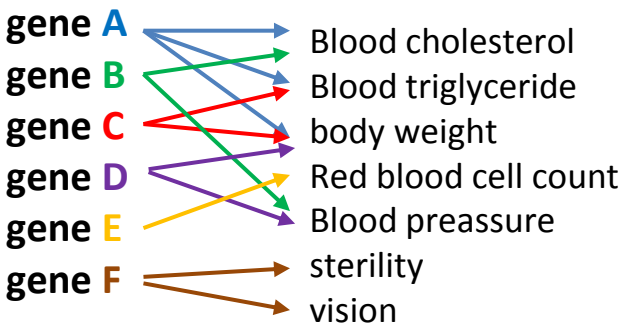
potential relevance to human diseases

comprehensive & large-scale phenotyping



more then 400 standardized parameters

Phenotype:
deciphering functions of individual genes



Encyclopaedic database on gene function

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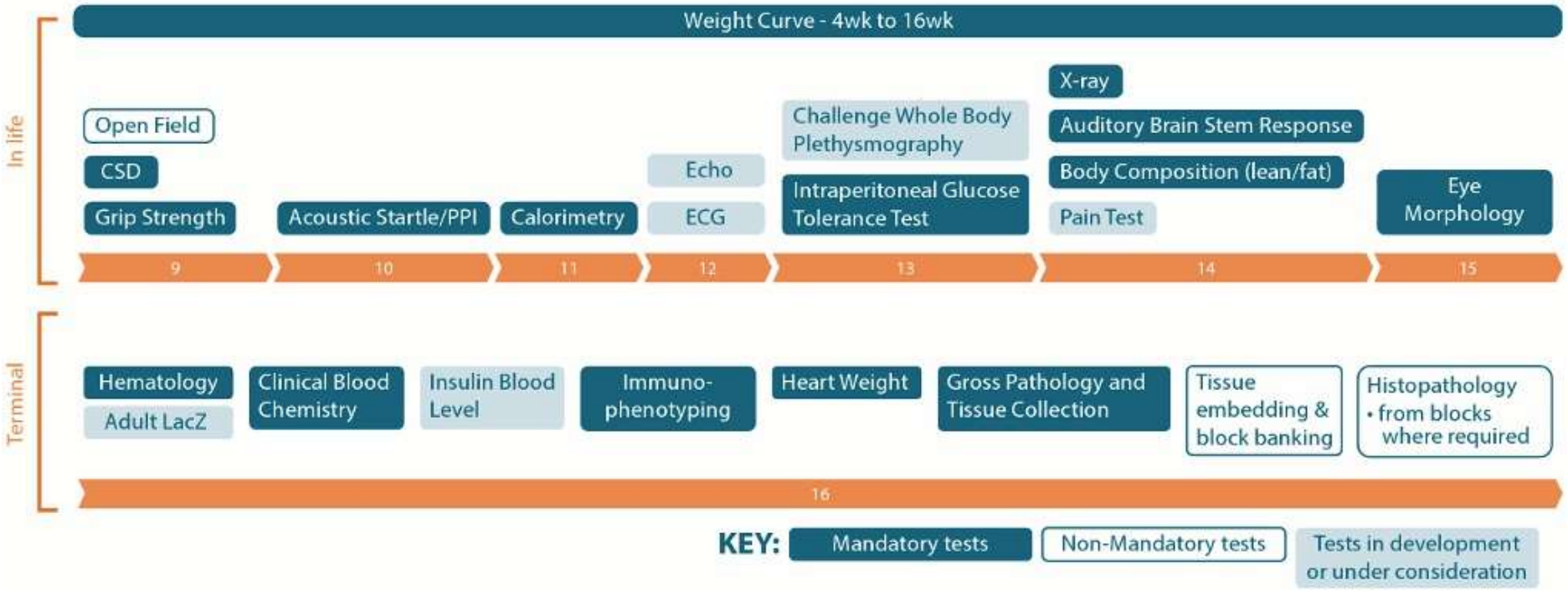
Phenotyping screens & pipeline



http://www.mousephenotype.org/

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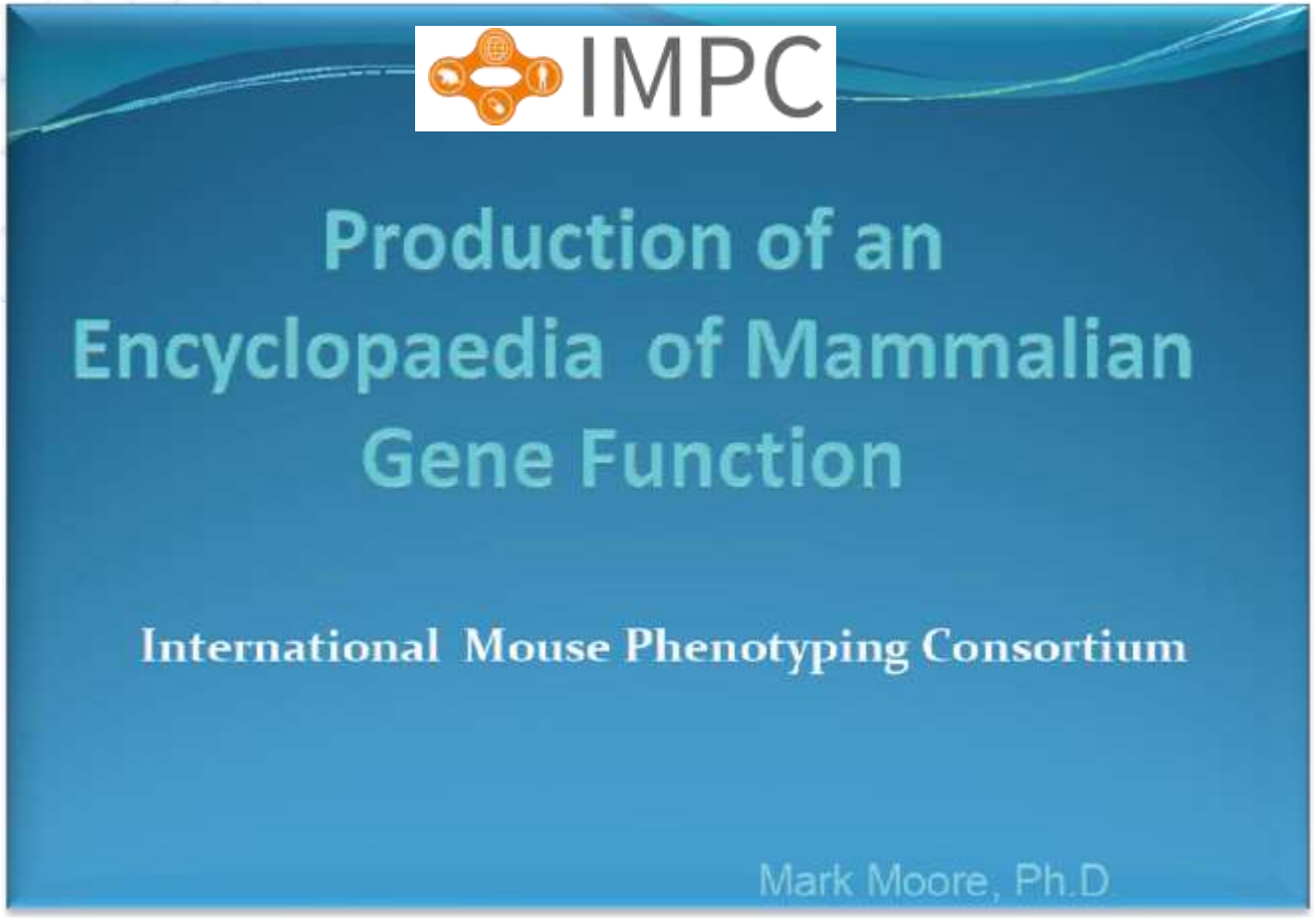
IMPC: global cooperation



http://www.mousephenotype.org/

Czech Centre for Phenogenomics
activities


production


Transgenic core


Cryo-archiving unit

Targeting:
design and generation of tools

Generation, archiving and distribution of transgenic models

Animal husbandry
& administration of the projects

Phenotyping
- systemic primary
- individual & secondary

Biomedical community

Top-down
Large scale projects:

IMPC & INFRAFRONTIER

Bottom-up

Individual user research projects

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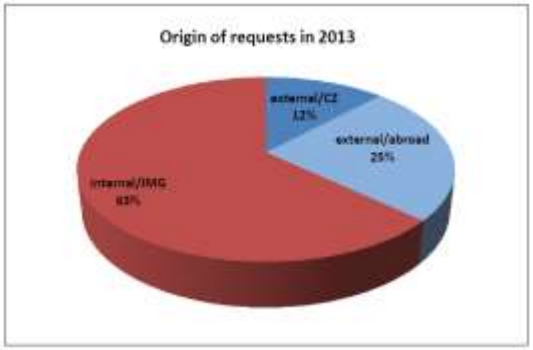
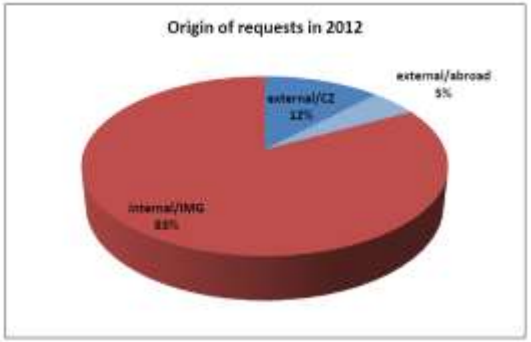
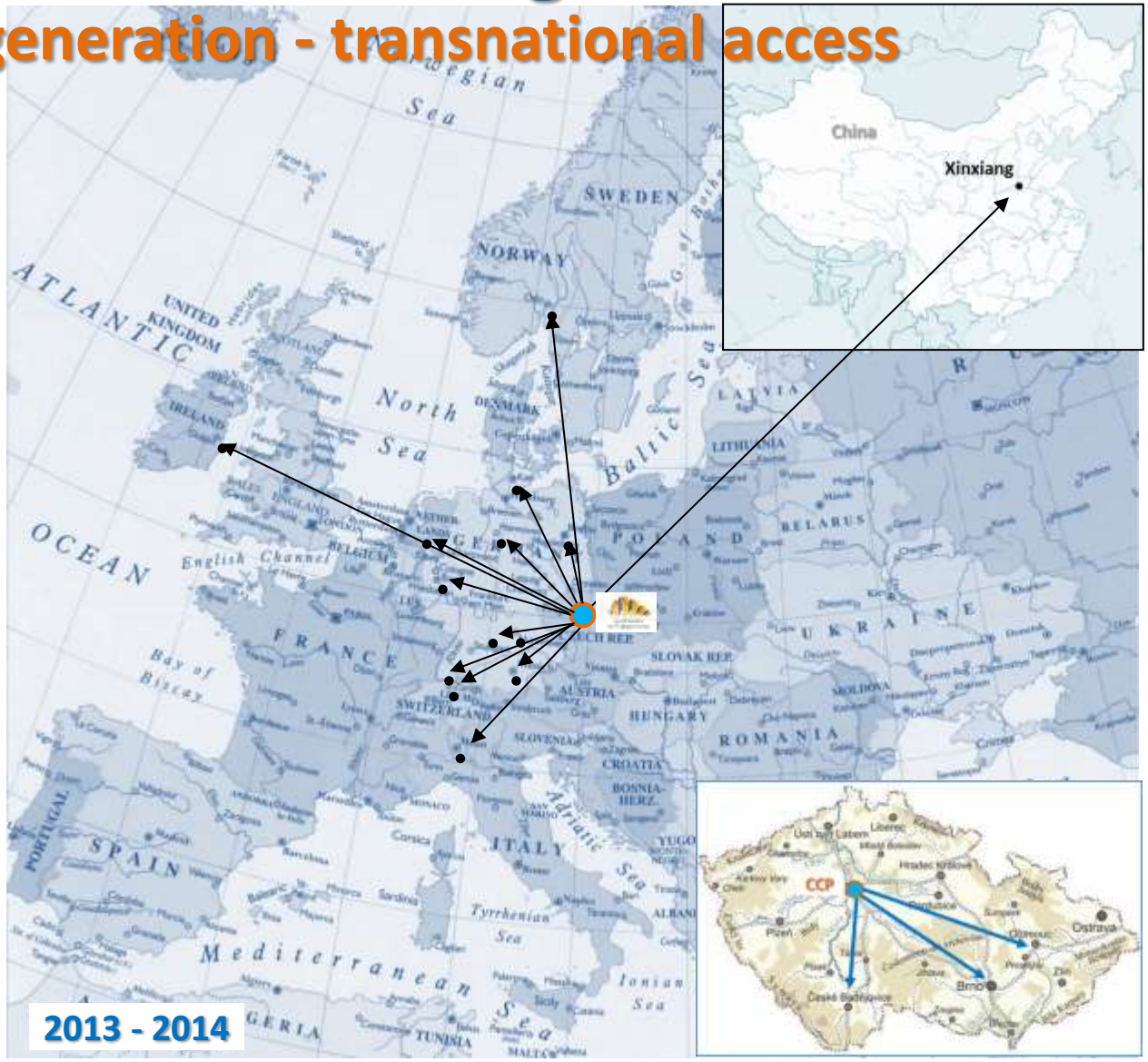
tg model generation - transnational access





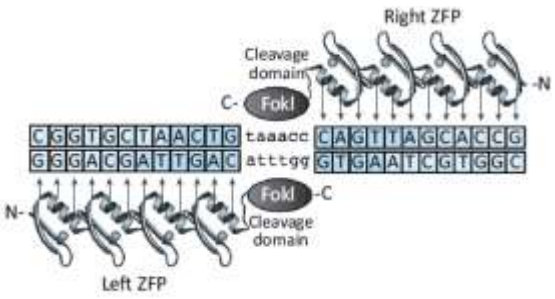


programmable nucleases

- mediated gene/genome modifications

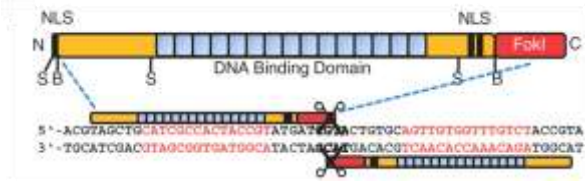
Zinc Finger Nucleases

- Cys2-His2 zinc finger domain
- Artificial arrays of 3-6 Zinc Fingers (9 – 18 bp)
- C-terminal fusion with endonuclease (FokI) – ZFN



Transcription Activator-Like Effectors nucleases (TALENs)

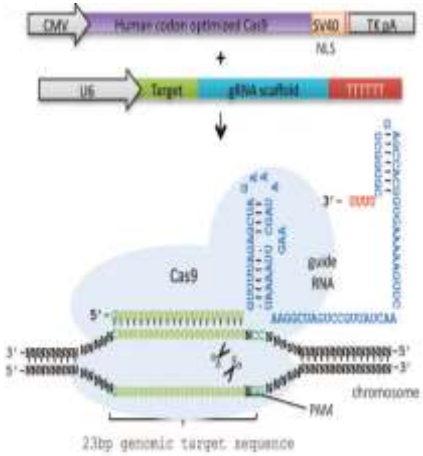
- Central Repeat Domain (CRD) responsible for DNA binding
- CRD consisting of 34aa highly homologous repeat modules
- DNA specifity determined by aminoacids 12 and 13 of each repeat
  – repeat variable diresidues (RVDs)



Modular assembly allows efficient and low-cost generation of TALEN vectors

CRISPR/Cas9 system

- interspaced short palindromic repeats (CRISPR) systems
- CRISPR RNAs (crRNAs) in complex with CRISPR-associated (Cas) proteins

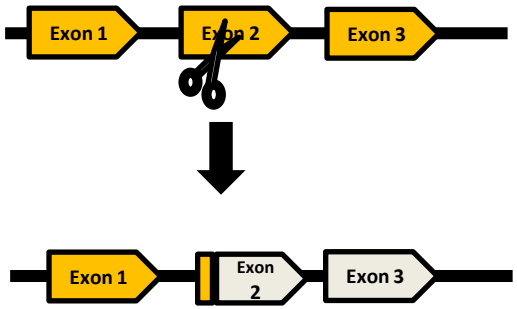


Mali et al., Science 2013

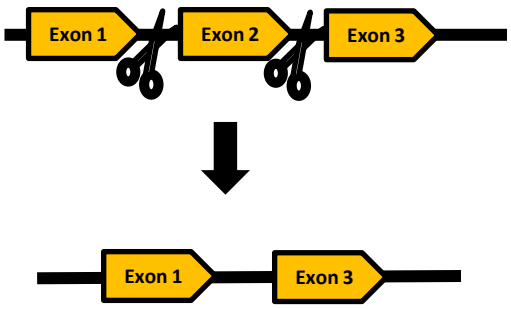
programmable nucleases

application

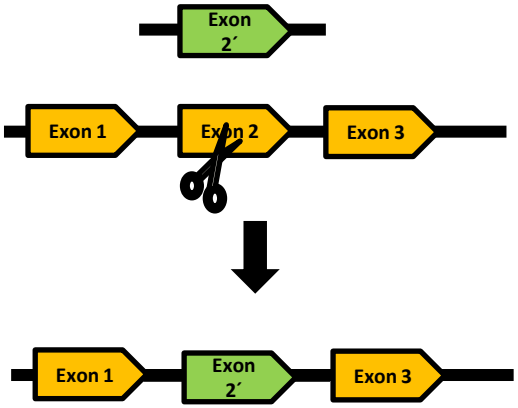
Generation of indel mutations



Excision of DNA fragment



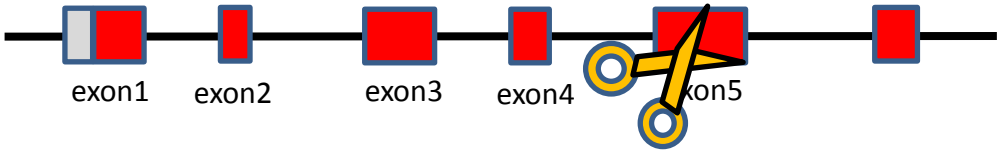
Site-specific integration

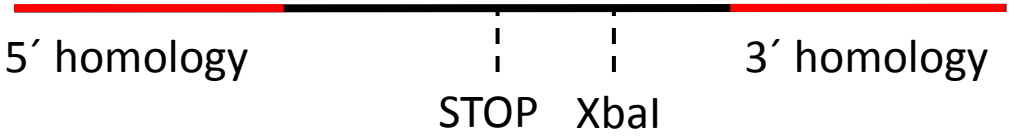


Netherton syndrome

mouse model

- Autosomal resccesive skin disorder
- Chronic inflammation, peeling skin, abnormal desquamation, abnormal hair growth
- Point mutation in exon5 of Spink5 (-> STOP codon)





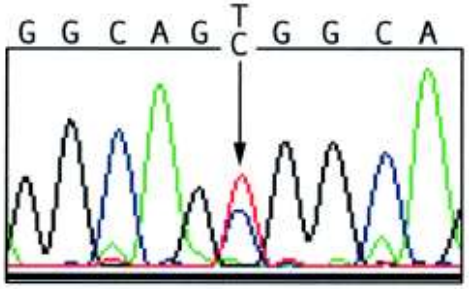
P. Kasparek, unpublished

Plectin deficiency

muscle dystrophy example

- tvorba puchýřů
- svalová dystrofie
- dystrofické nehty a zuby
- respirační obtíže
- poruchy vedení nervových vzruchů
- atrofie mozku
- poruchy gastrointestinálního traktu

Bodová mutace



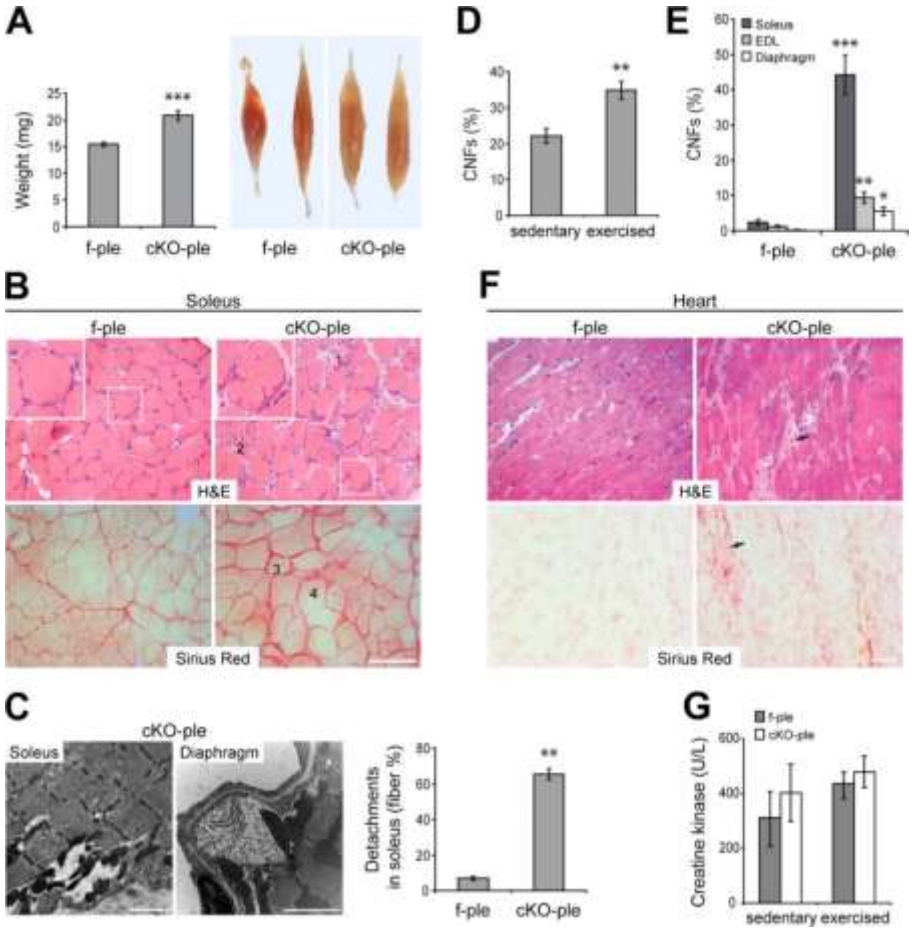
Plectin deficiency

deep drilling phenotyping

Skin deficiency

Ackerl R et al. J Cell Sci 2007;120:2435-2443

Muscle deficiency



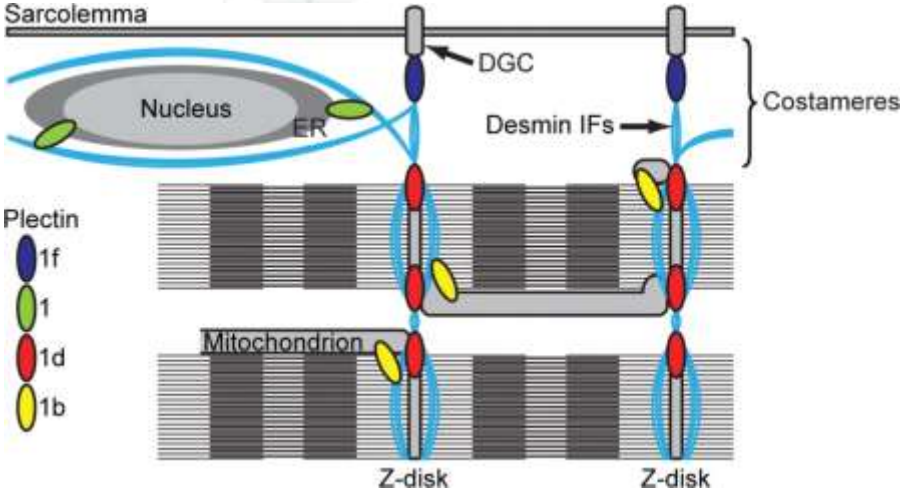
Konieczny P et al. J Cell Biol 2008;181:667-681

Plectin deficiency

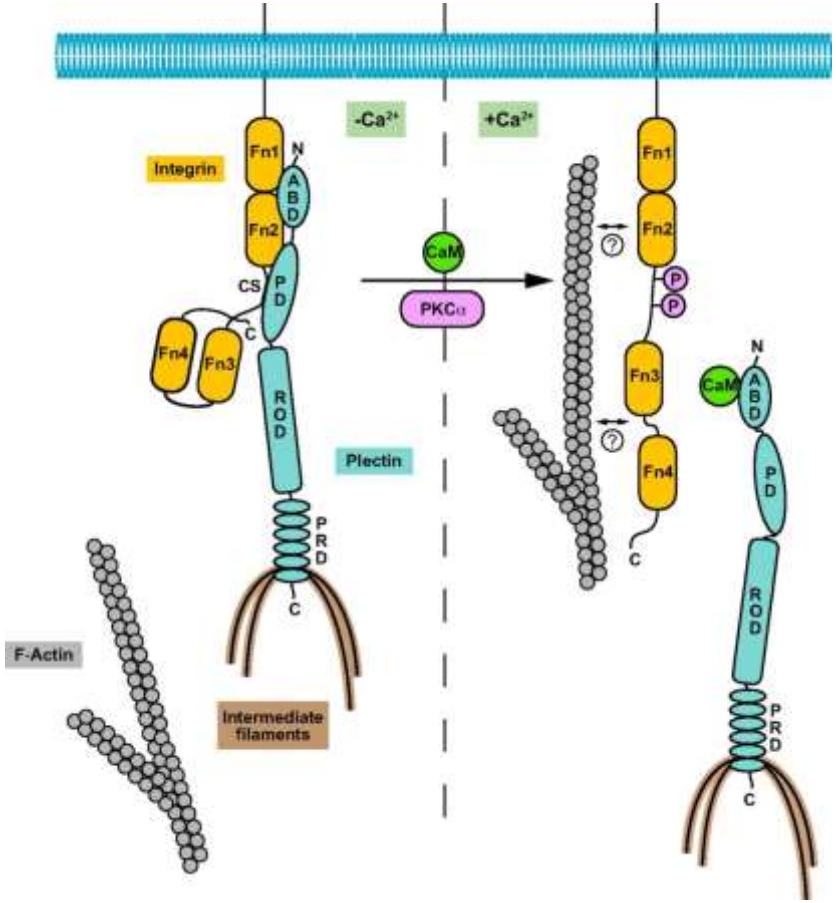
hypothetical models

Protein Function

Therapeutical Strategies



Konieczny P et al. J Cell Biol 2008;181:667-681



Kostan J et al. J. Biol. Chem. 2009;284:18525-18536