EPTRI
European Paediatric Translational Research Infrastructure

THE CHILDREN'S MEMORIAL HEALTH INSTITUTE

EPTRI General Assembly and Scientific Meeting
Warsaw, 28-29 July, 2026

Creating Preclinical Models for Rare Diseases: RD-Factory as a Platform, Netherton Syndrome as a Case Study

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EPTRI Scientific Meeting | 28–29 July 2026 | Warsaw, Poland

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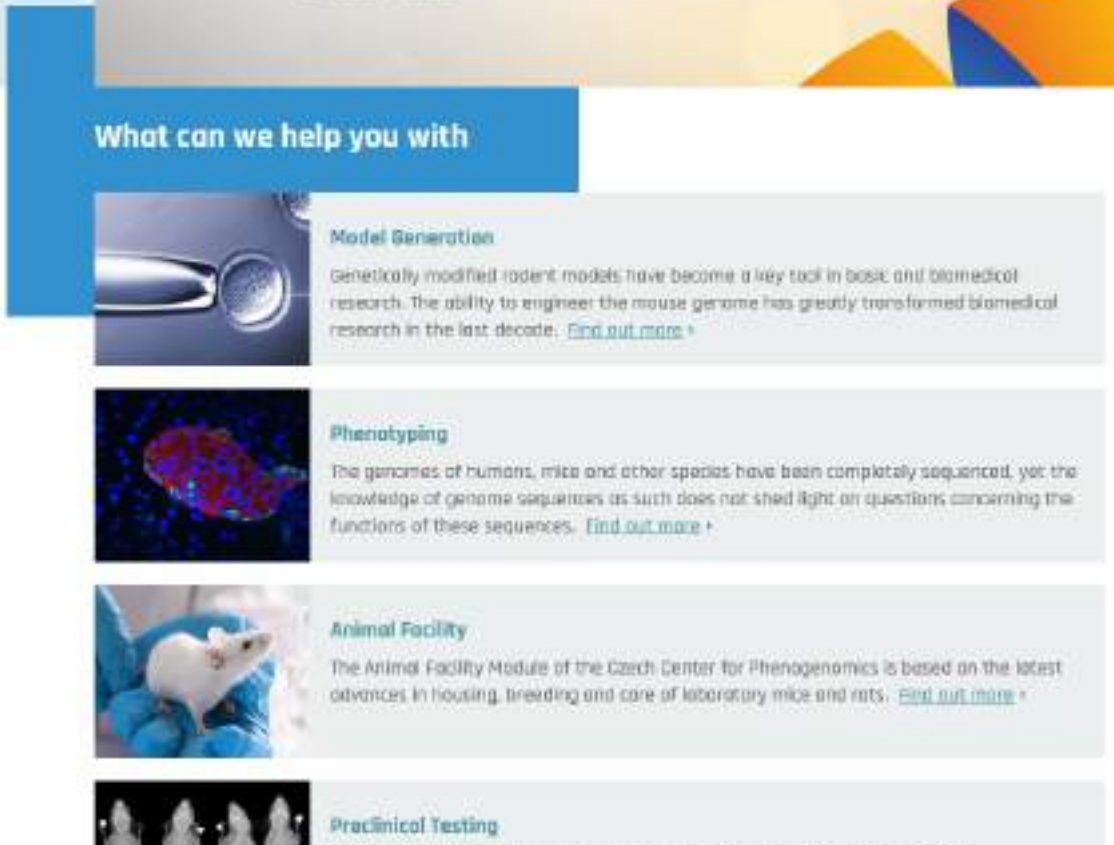
Content:

- The Czech Centre for Phenogenomics (CCP) – introduction
- INFRAFRONTIER – introduction
- IMPC (catalogue of mammalian gene functions)
- Towards rare and pediatric diseases
- RD-Factory programm
- Netherton syndrome – an example

Czech Centre for Phenogenomics



- 140 staff members
- 9,000 sqm
- Basic research
- Preclinical development
- 100-150 new mouse models per year
- CCP full operation since 2016

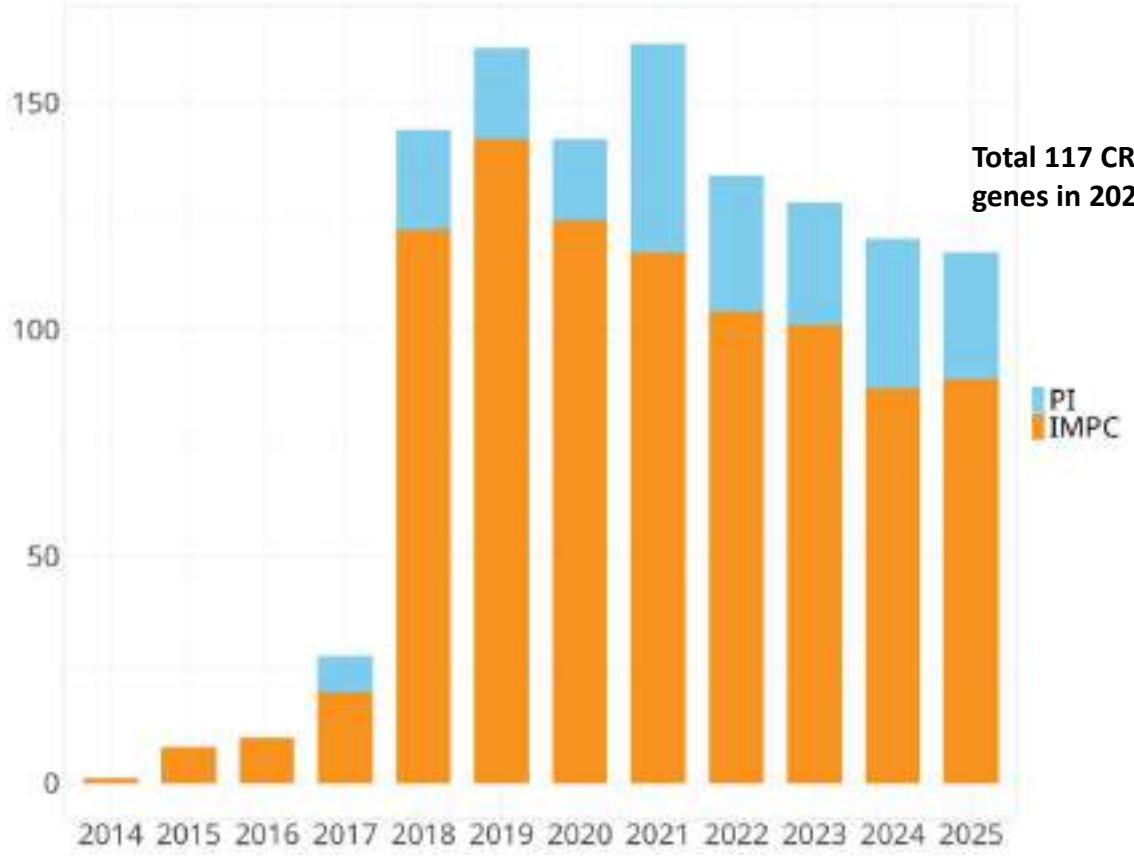
EPTRI

IMG

Czech Centre for Phenogenomics

CCP:
Service to the scientific community & building resources

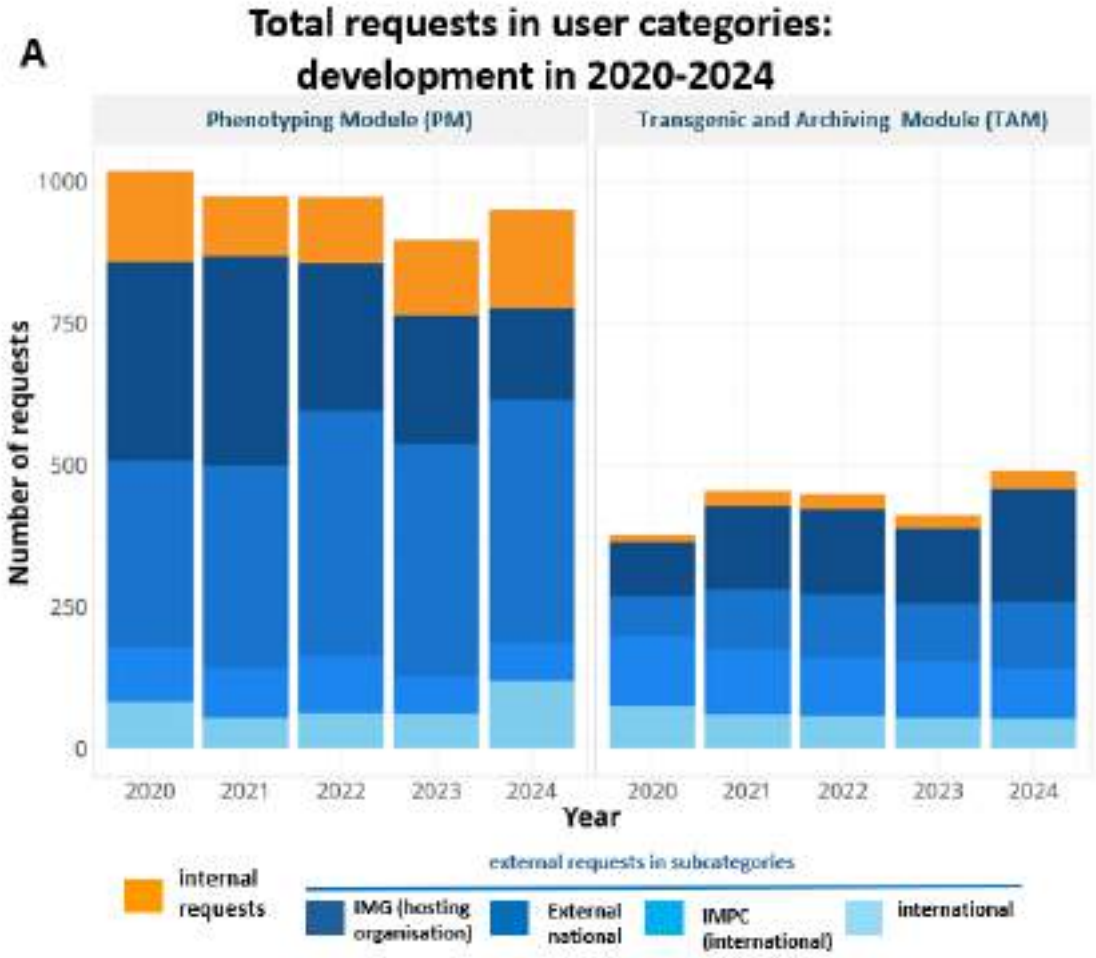
>1000 CRISPR genes !

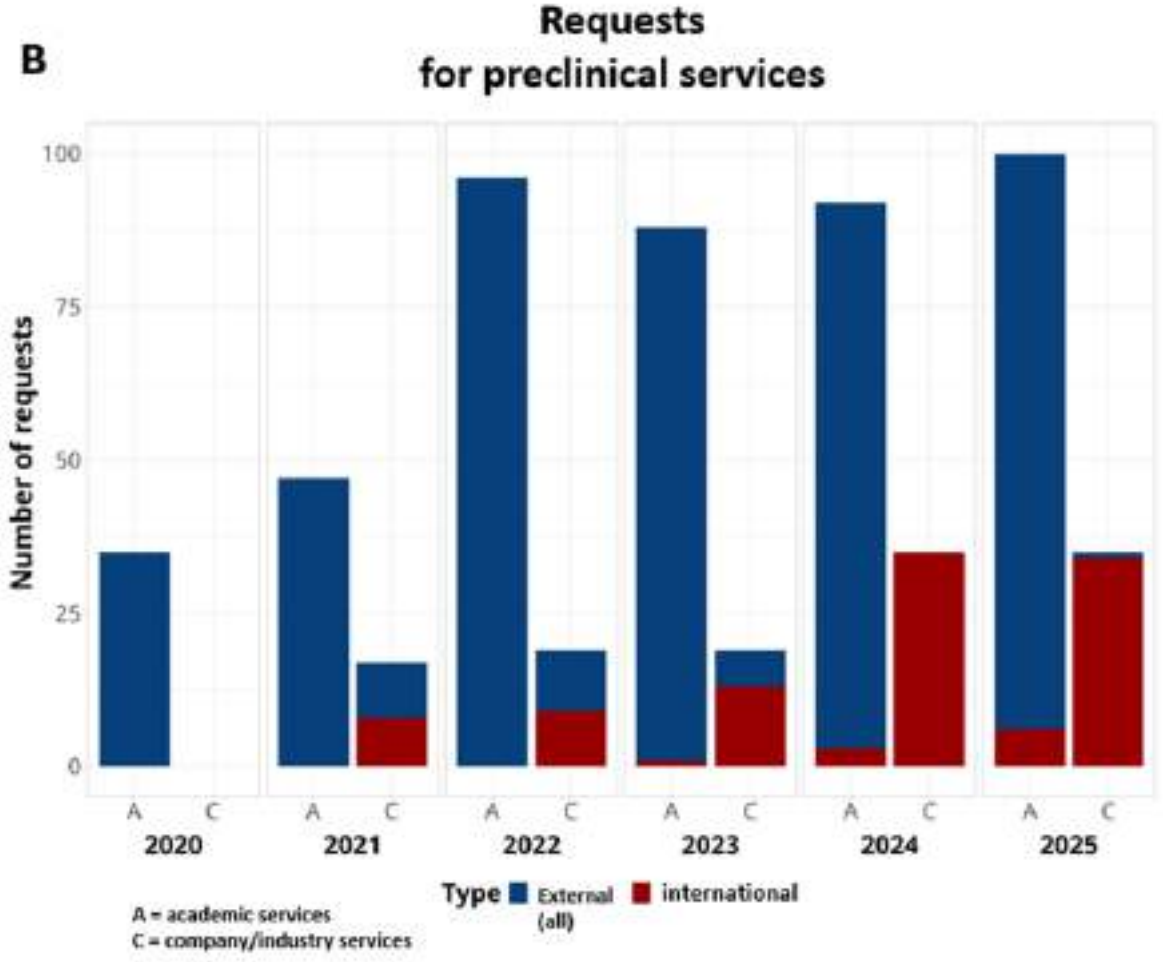


Total 117 CRISPR genes in 2025

CCP- requests for services :

high stable demand with increasing number for large preclinical services

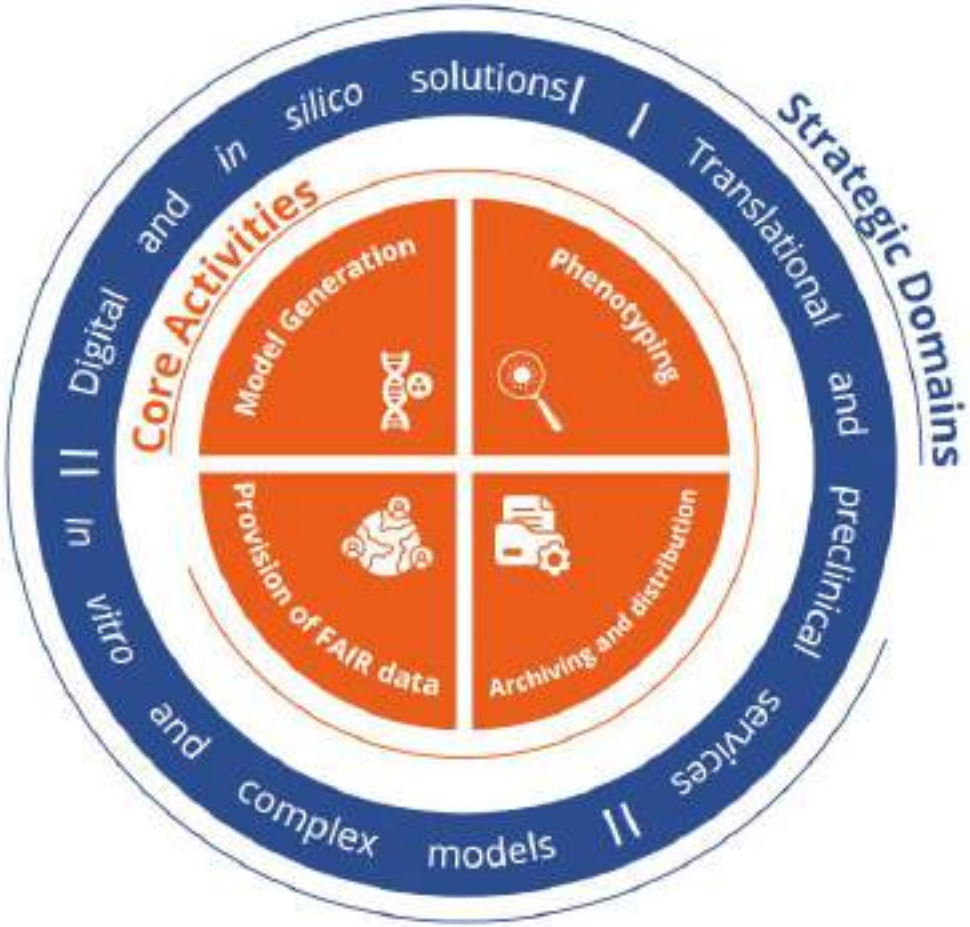





INFRAFRONTIER
...From models to causal mechanisms, from mechanisms to medicine ...

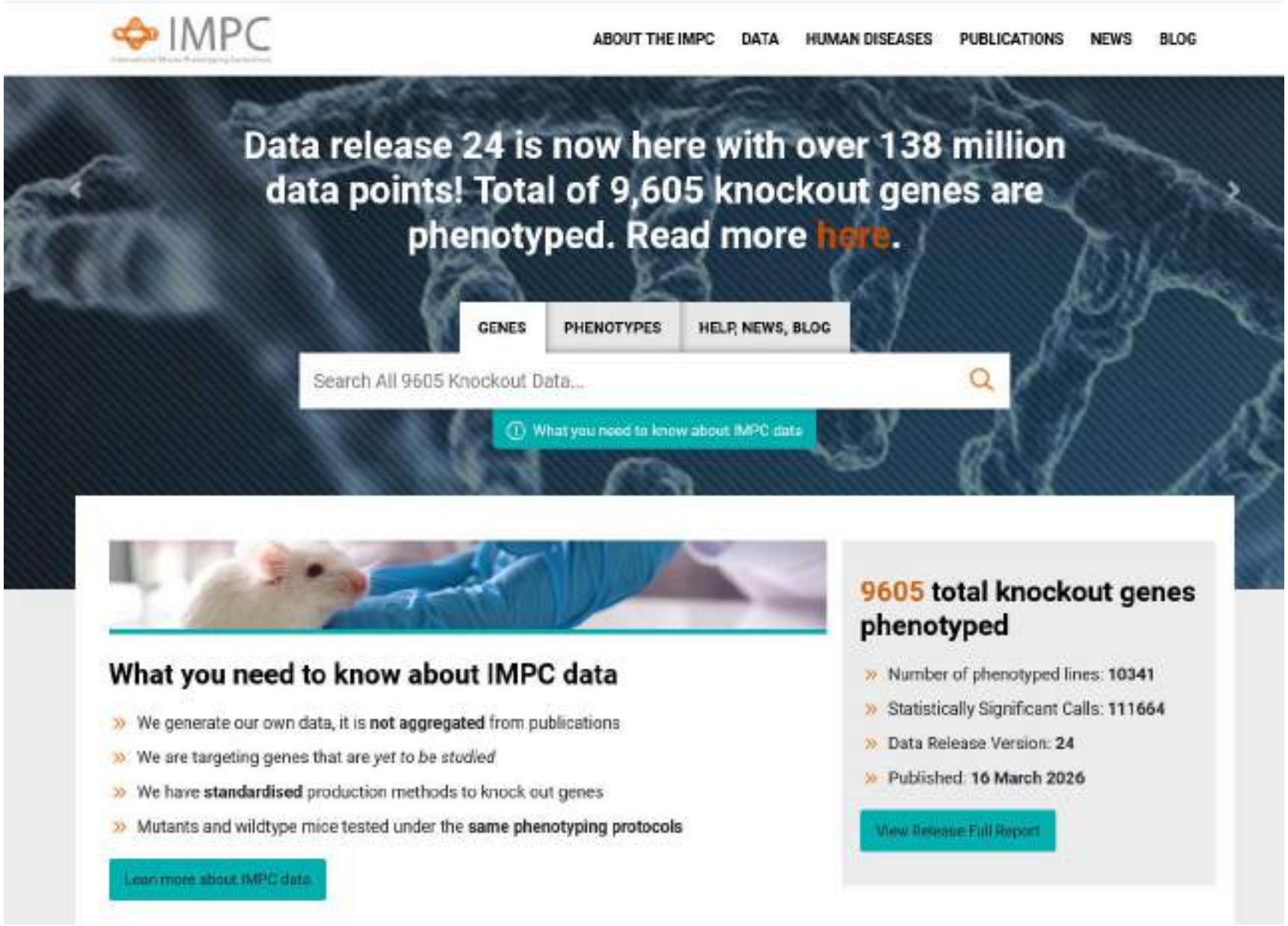
Czech Centre for Phenogenomics

*"... **advanced rodent model generation**, systemic as well as **specialized phenotyping** and **archiving** and **distribution of models** that mimic health and disease are the core services of INFRAFRONTIER ...*



Czech Centre for Phenogenomics

IMPC
International Mouse Phenotyping Consortium



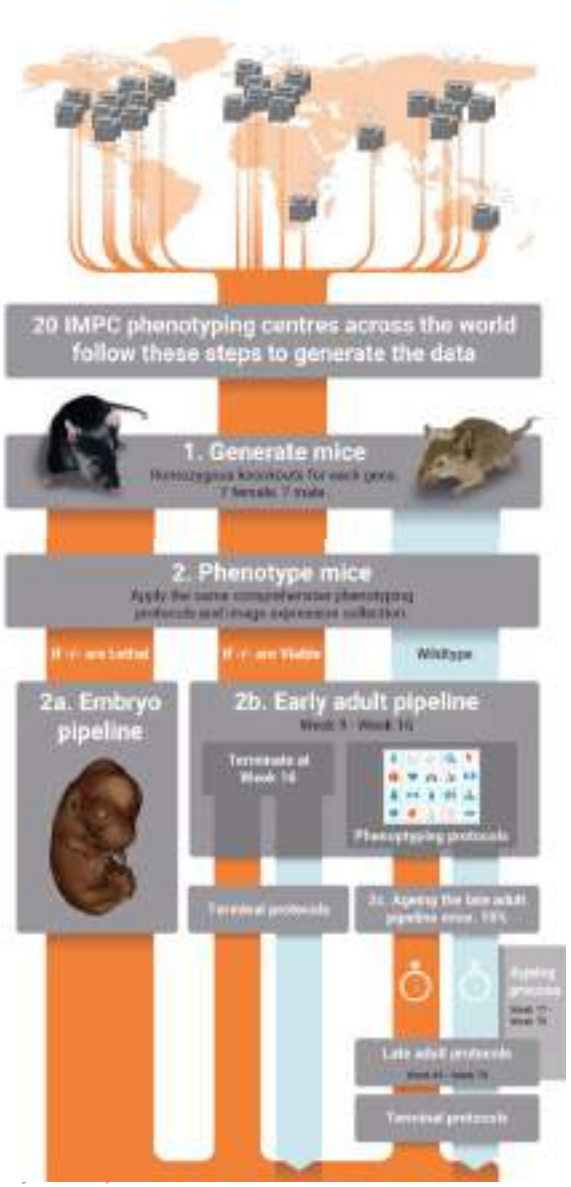
Czech Centre for Phenogenomics

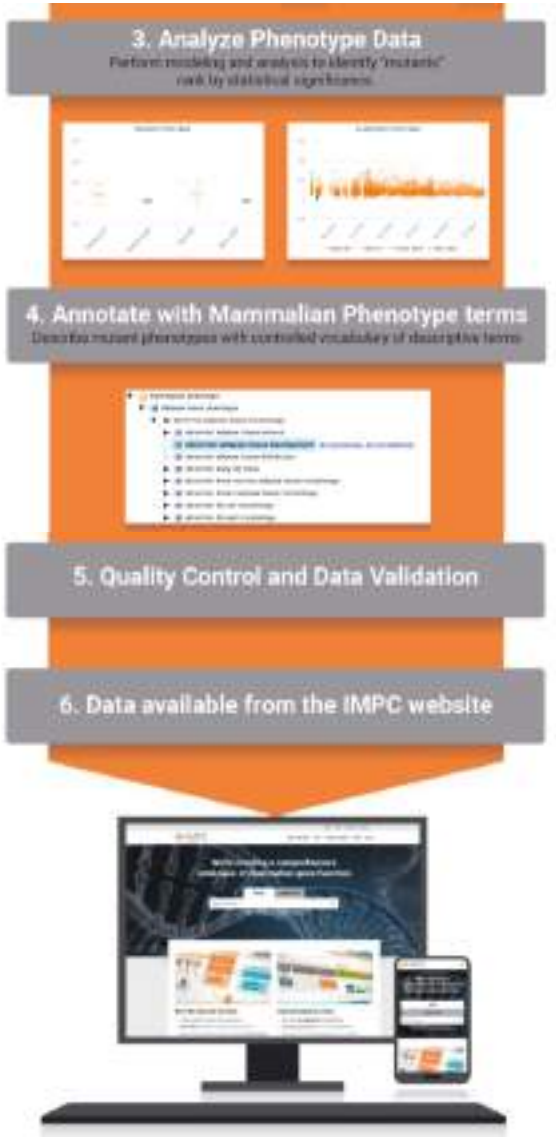
IMPC: ission and goals

…..to generate a comprehensive catalogue of mammalian gene function and provide the foundations for the functional analysis of human genetic variation

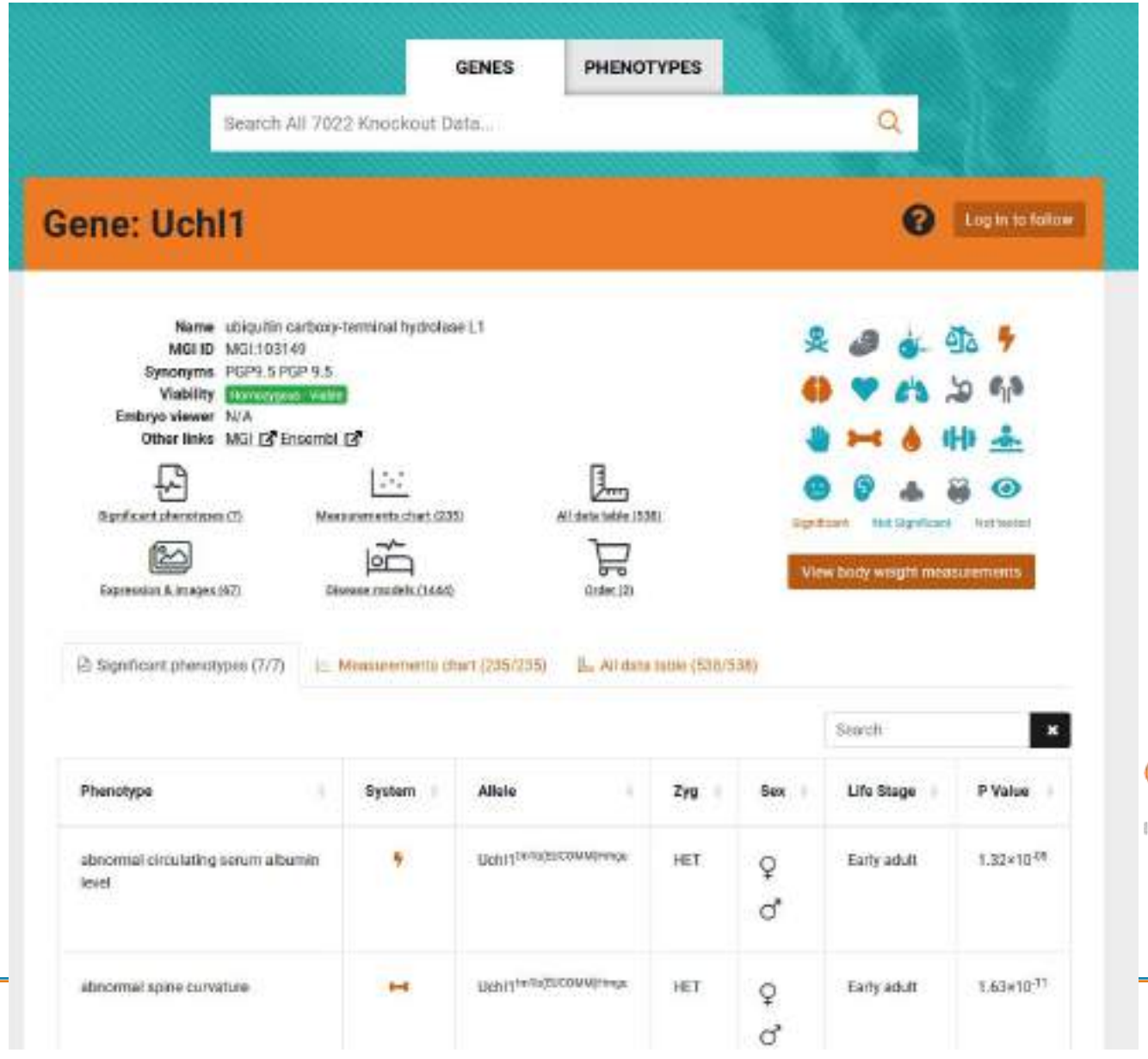
- insight into the function of **every gene** by the creation and analysis of null mutations
- relationship between genome and phenome by the generation of putative human pathogenic variants in both **coding and non-coding** sequences

IMPC
International Mouse Phenotyping Consortium





Phenotype traits: Open access



IMPC
International Mouse Phenotyping Consortium

Phenotyping platform

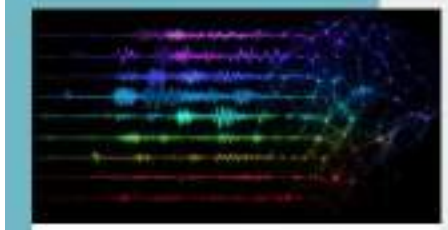
Biochemistry & Haematology

Bioimaging & Embryology

Cardiovascular

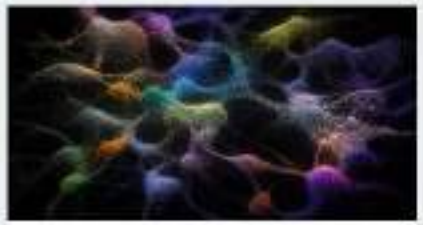
Vision

Biostatistics & Bioinformatics



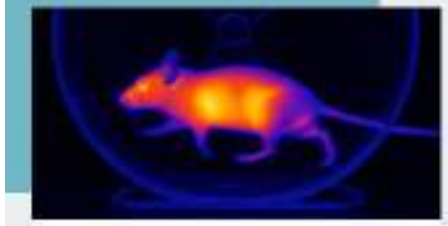
Electrophysiology

Histopathology



Immunology

Lung Function



Metabolism

Neurobiology & Behavior

Metabolomics

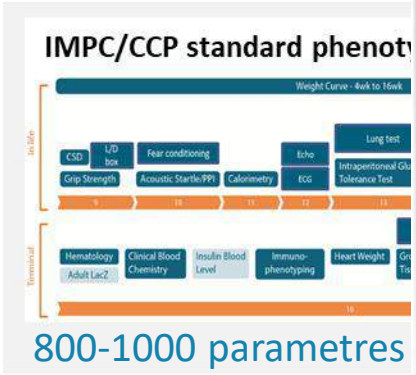
PDX & Cancer Models

Models of Infectious Diseases (BSL-3)

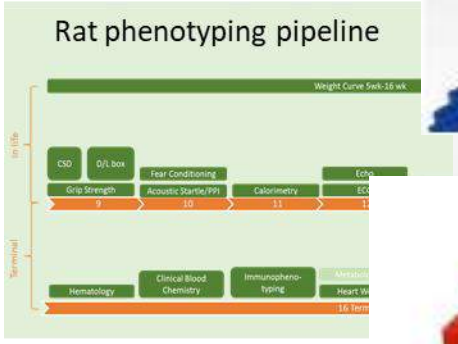
…… towards rare/pediatric diseases

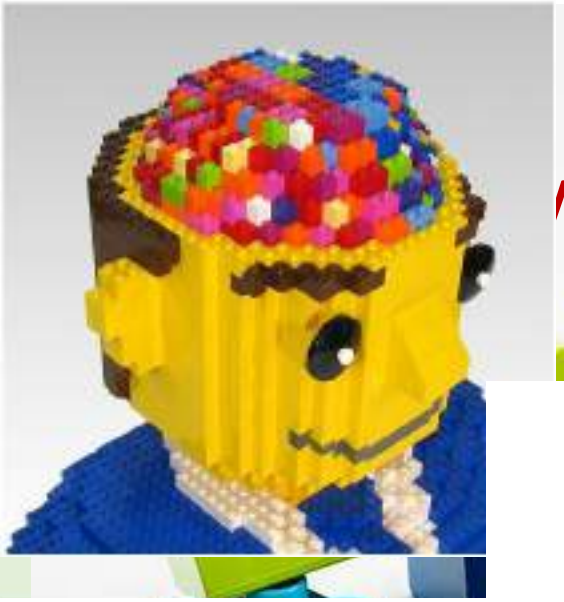
Systematic phenotyping pipeline

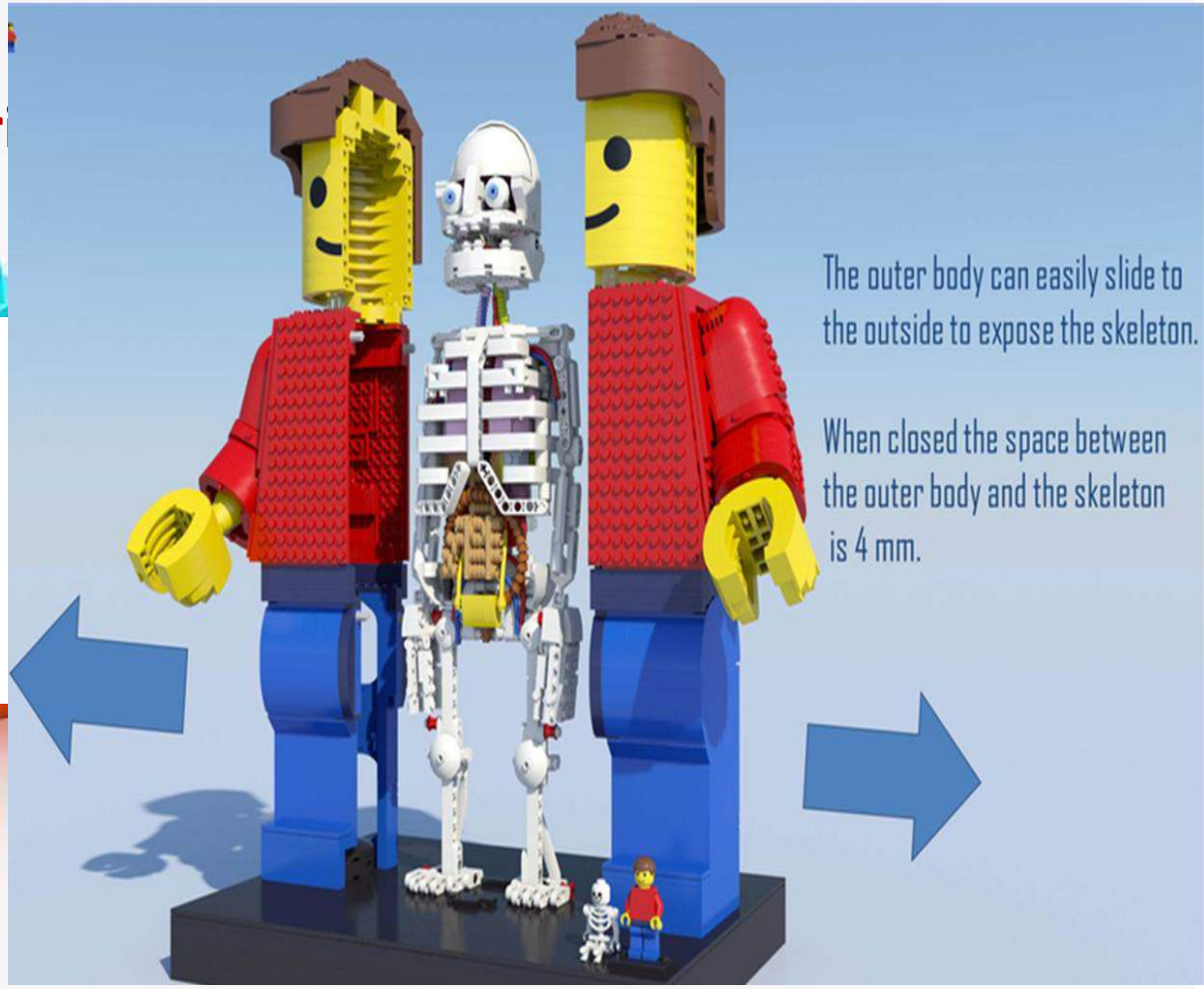
towards specialized phenotyping



800-1000 parametres

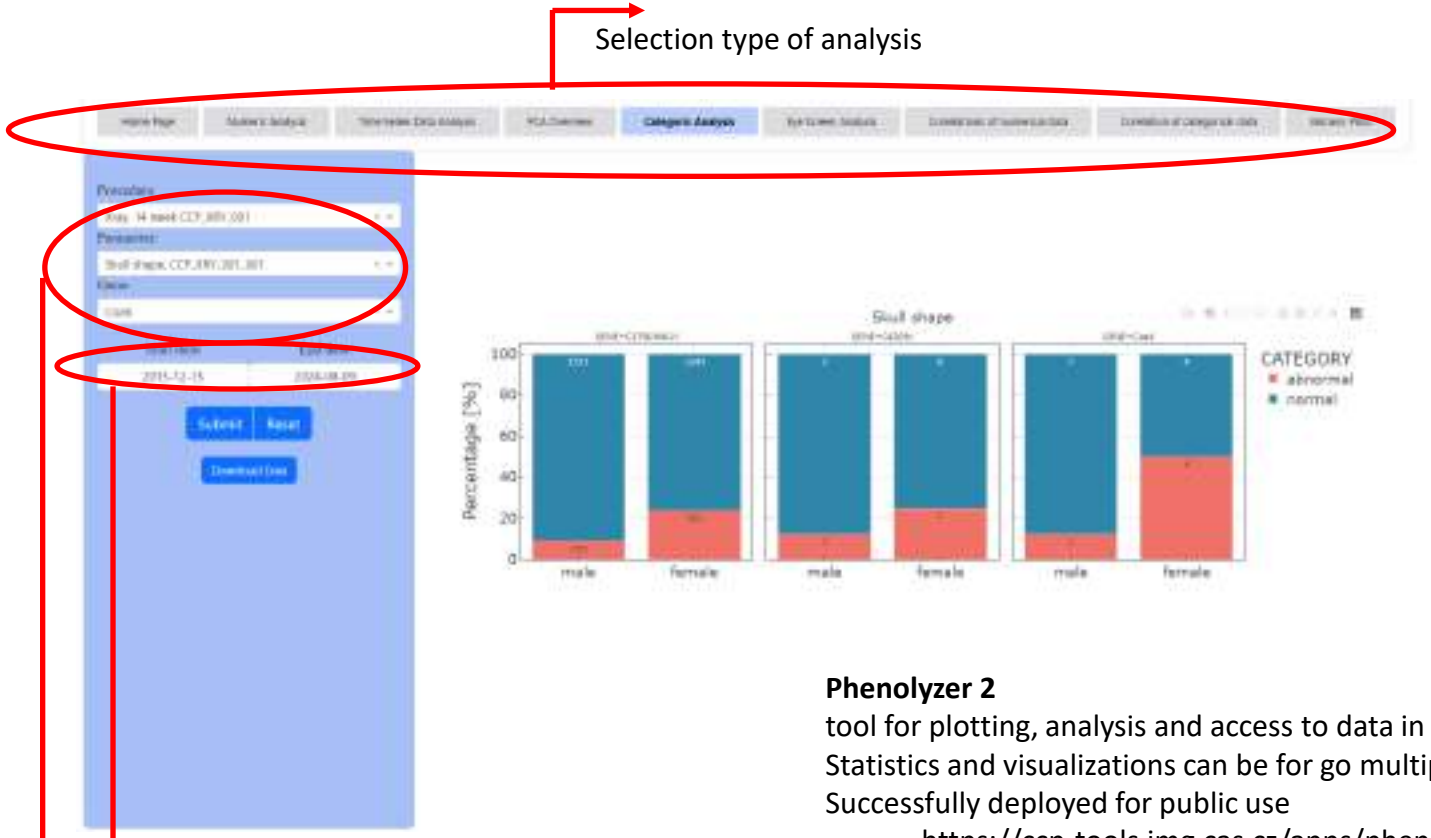


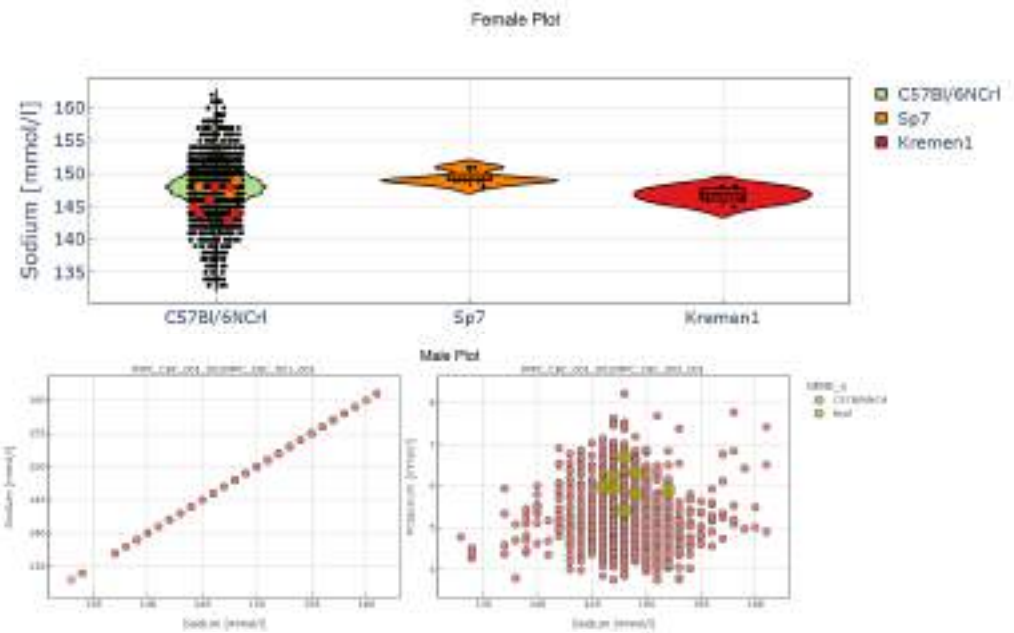




Pheno-pipeline: specific analysis ‚Phenolyzer 2‘

https://tesla.img.cas.cz/apps/ccp/phenolyze-2/





Phenolyzer 2

tool for plotting, analysis and access to data in our database

Statistics and visualizations can be for go multiple genes.

Successfully deployed for public use

https://ccp-tools.img.cas.cz/apps/phenolyze-2/

Added volcano plots. Phenolyzer integrates advanced methods such as principal component analysis (PCA), correlation, and regression analyses

Subgroup analysis based on allelic configuration

Vastly improved performance of the applications

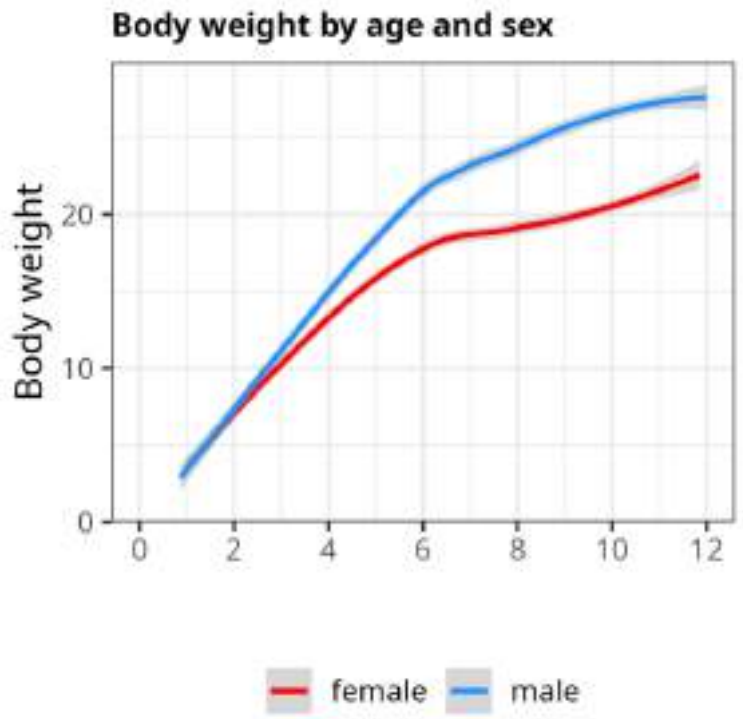
CCP's **Juvenalis study:**

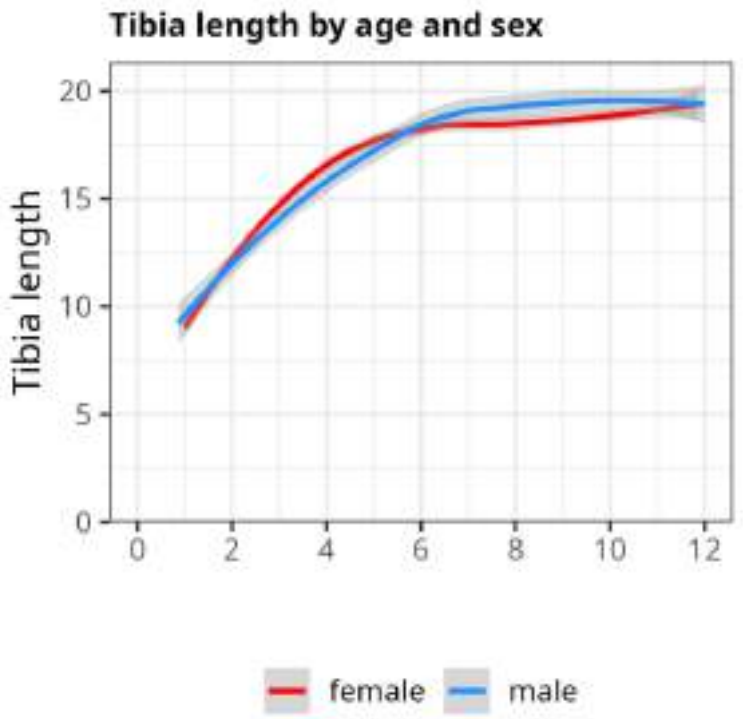
phenotyping juvenile mice to understand pediatric diseases

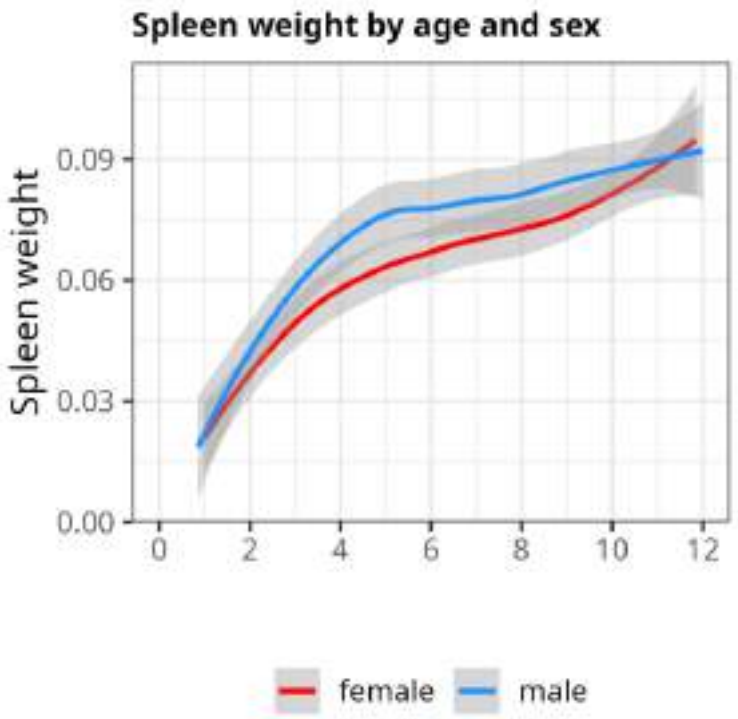
- **Many rare diseases manifest in childhood**, when organ systems are still developing; therefore, adult-only phenotyping can miss early, disease-relevant phenotypes.
- **Juvenile phenotyping in mice** (from early postnatal stages up to adulthood) allows us to capture dynamic changes in immune, skeletal, and cardiac development that mirror pediatric disease trajectories.
- The **Juvenalis study establishes age-matched baseline data in wild-type animals and applies tailored pipelines to subviable mutant strains** that cannot complete the full IMPC screen.
- Using these **baselines**, we can interpret early phenotypes in subviable strains and connect them more directly **to pediatric presentations of rare human diseases**.

CCP's **Juvenalis study:**

Example control data baselines (10 females, 10 males)



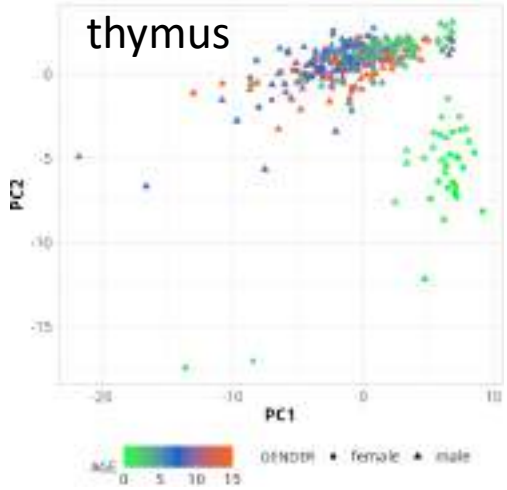


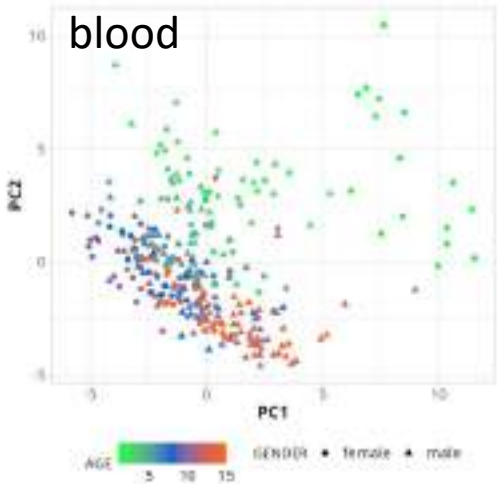


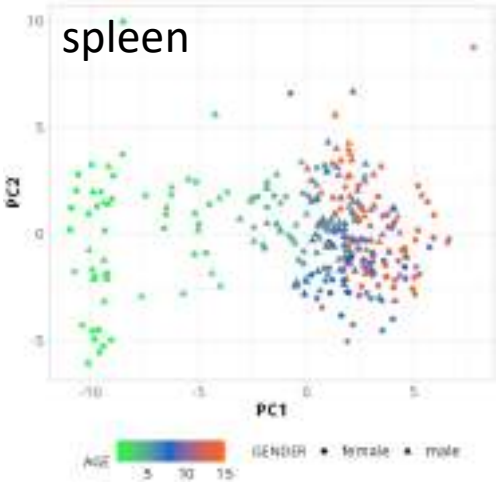
Czech Centre for Phenogenomics

CCP's **Juvenalis study:**

Immunology pipeline: the dynamics of immune system development







Thymus- one panel

thymus Panel	
viability	Hoechst33258
CD19	PB
CD8	BV605
GITR	BV711
Annexin V	FITC
CD5	PerCPCy5.5
TCRbeta	PE
CD25	PE-Cy7
CD4	APC
CD44	APC-eF780
Fc Block	

populations
DN1-DN4 thymocytes
DP thymocytes
CD4+ thymocytes
CD8+ thymocytes
T regulatory cells
pre-postselection T cells

Blood- one panel

blood Panel	
viability	Hoechst33258
CD5	BV421
CD44	BV510
CD8a	BV605
GITR	BV711
Ly6G	BV785
CD45	FITC
CD11b	PerCPCy5.5
CD161	PE
CD19	PE-CF594
CD25	PC7
CD4	APC
Ly6C	AF700
CD62L	APC-Cy7
Fc Block	

populations
T helper cells (eff/ resting)
T regulatory cells (eff/ resting)
T cytotoxic cells (eff/ resting/ naive)
NK cells
NKT cells
B cells
monocytes
neutrophils
eosinophils

Spleen- two panels

spleen Panel A	
viability	ghost dye UV450
CD5	BV421
CD49d	BV510
γδTCR	BV605
GITR	BV711
CD4	FITC
Klrg1	PerCPCy5.5
CD44	PE
CD25	PC7
CD8a	PE-CF594
CD161	APC
CD62L	APC-Cy7
Fc Block	

populations
γδT cells
T helper cells (eff/ resting)
T regulatory cells (eff/ resting)
T cytotoxic cells (eff/ resting/ naive)
NK cells
NKT cells

spleen Panel B	
viability	ghost dye UV450
CD5	BV421
Ly6G	BV421
CD19	BV510
Bst2	BV605
CD23	BV711
Ly6C	FITC
CD11b	PerCPCy5.5
CD21/35	PE
F4/80	PE-Dazzle594
CD11c	PC7
CD161	APC
MHCII	APC-Cy7
Fc Block	

populations
B cells
macrophages
monocytes
neutrophils
eosinophils
cDC
pDC
T cells
NK cells
NKT cells

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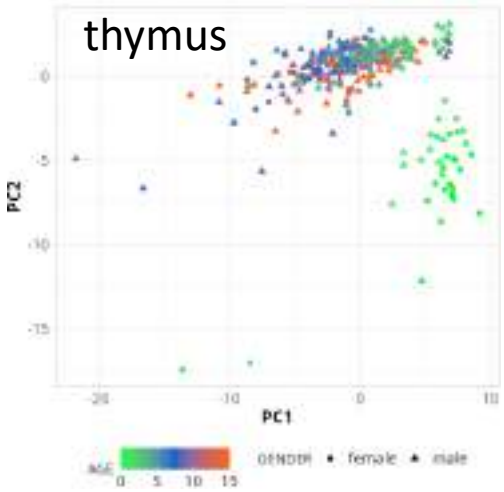
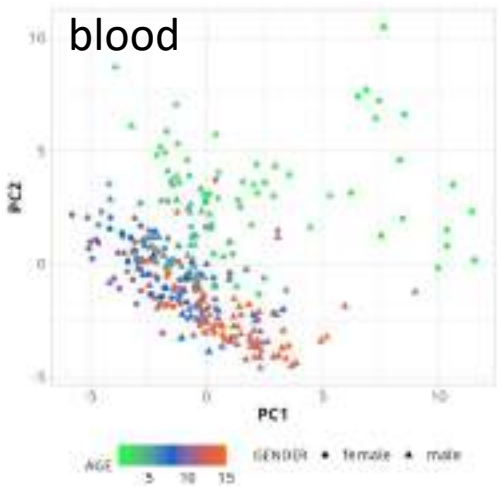
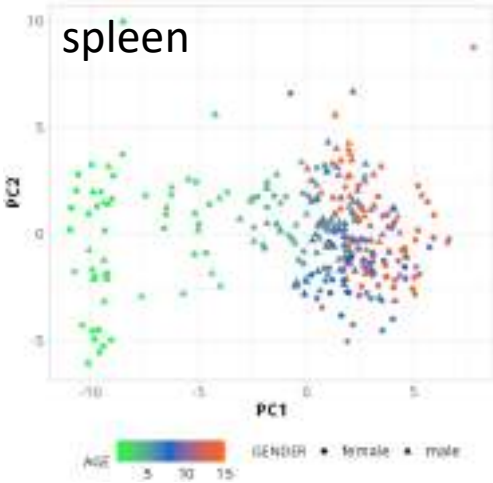
CCP's **Juvenalis study:**

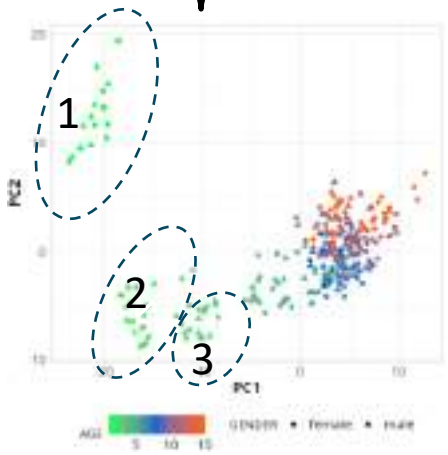
Immunology pipeline: the dynamics of immune system development







combined data from thymus/ blood/ spleen



During the first weeks (1-4), immune populations show a distinct phenotype

CCP's **Juvenalis study:**

All tested strains show increased blood neutrophils, suggesting an imbalance in the immune system

mouse-model examples:

- **Fgf23 mutant:**

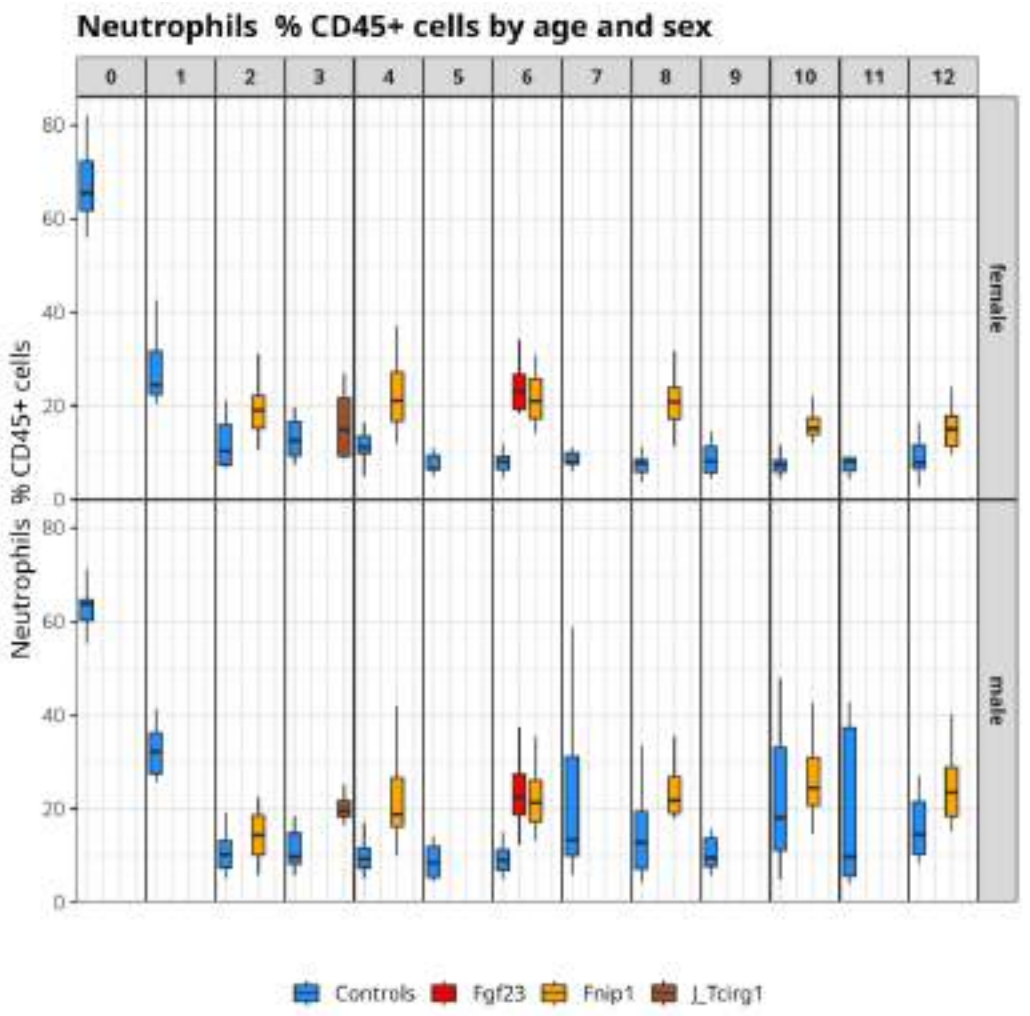
Early skeletal phenotypes measured up to 6 weeks, modelling disturbed bone and mineral metabolism relevant to pediatric skeletal disorders.

- **Tcirg1 mutant:**

Strong juvenile immune and cardio phenotypes measured up to 3 weeks, reflecting early-life immune imbalance and altered cardiac maturation.

- **Fnip1 mutant:**

Immunology and cardiac phenotyping up to 12 weeks, capturing prolonged developmental effects on immune system and heart relevant to childhood-onset rare disease.



New Strategic Goal

Rare Diseases - Pathogenic Gene Variants

IMPC
International Mouse Phenotyping Consortium

The Function of Human Genetic Variation

IMPC Strategy 2021-2030

+

Current patient needs & technological development

Czech Centre for Phenogenomics

Towards Rare Diseases - pathogenic gene variants

for the period: 2027-2035

A statement and details of the IMPC's goals for the next ten years:

Goal 1

Complete the generation of a null mouse mutant resource for the coding genome that delivers a comprehensive catalogue of mutant strains available to study mammalian gene function.

Goal 2

Design and produce a genome-wide mouse strain resource of human disease-associated coding variants associated with rare disease that can be used for validation of putative functional variants and insight into disease mechanism(s).

Goal 3

Design and generate mouse strains that model genetic variation in the non-coding genome for the IMPC and the global research community to use in a collective effort to assess functionality and mechanism(s) in health and disease.

Goal 4

Phenotype mouse strains with null mutations, human-disease coding variants, and variants in the non-coding genome to provide a comprehensive catalogue of baseline information on mammalian gene function, validate putative functional variants, examine the effects of mutations in the non-coding genome, and provide data-driven insight into disease mechanism(s) and other phenotypic outcomes.

Goal 5

Explore genetic context to realise the wider potential for mouse functional studies to provide models and mechanistic insights for therapeutic development, both conventional therapeutics and for precision medicine.

Goal 6

Develop data integration, analysis, and visualisation approaches to translate mouse functional genomics studies to the human gene and disease knowledge base and vice versa, underpinning synergies in the fundamental understanding of genetic and disease systems – enabled and strengthened by dynamic interactions and networks with human genome centres, clinical genetics consortia, and data-curated biobanks that we serve.

IMG

the Czech Centre for Phenogenomics

together with

the Institute of Molecular and Translational Medicine,

and other partners announces

RD (rare disease)-Factory programm:

the research programm to tackle rare diseases and their therapies

RD - factory program:

OPEN CALL FOR RD/GENE NOMINATIONS

We are pleased to announce the ***RD-factory PROGRAM*** call for proposals for preclinical studies on pathogenic gene variants causing rare human genetic diseases. The objective is to:

- create a suitable mouse model (disease-associated coding variants associated with rare disease) for the description of disease development and for therapy testing.
- design and test new therapeutic and curative gene and small molecule and biological and/or cellular therapies.
- test new appearing drugs and therapeutic approaches.
- provide services for development of novel diagnostic approaches for rare diseases, including the diagnostic, prognostic, predictive and monitoring biomarkers.

Online Application started ***October 1, 2024***

There is no deadline for submissions, and nominations can be made any time.

RD - factory program – continuous call :

Nomination and Evaluation Process

- The nomination call is open now till **December 2026**, with potential for extension.
- Proposals are be submitted through the **CCP online form** and evaluated in average within four weeks of registration.
- **Nominations not selected initially** will be reconsidered at **re-evaluation workshops** scheduled for July and December **2026.**

Selection

The selection from nominated rare diseases had **several aspects:**

- selected **diseases** are currently **not sufficiently researched** and are **not being intensively worked on elsewhere in the world**.
- We also evaluated whether our expertise could advance knowledge about these diseases and whether the proposal is feasible regarding **capacity and funding**.

Selection process

Possibilities to interact with research communities, maximal usage of the models

n-lorem FOUNDATION

- MANBA
- MAPK8IP3
- MAST4
- MECP2
- MED13L
- MEF2C
- MFN2
- MFSD8
- MN1
- MORC2
- MTAP
- MTOR
- MT-ND1
- MYH7
- MYT1L

The Jackson Laboratory

RD - Factory program:

1st round	2nd round	3rd round
CTNNB1 Syndrome	LCHAD deficiency	GRIN2B-related Neurodevelopmental Disorder
MADD Deficiency	DEAF1 Syndrome – DEAF1	Refsum disease (PHYH mutation)
Pitt Hopkins Syndrome	Ataxia Telangiectasia – ATM	Drug resistant epilepsy (RRAGB mutation)
Harlequin Ichthyosis	Familiar Mediterranean Fever (FMF) – MEFV	Neurodevelopmental Disorder with severe Motor Impairment and Absent Language syndrome (DHX30 mutation)
Canavan Disease	DEE PACS2 syndrome – PACS2	Tetrallogy of Fallot
Bloom Syndrome	AGO1-related syndrome	Myofibrillar Myopathy Type 13 with Rimmed Vacuoles syndrome
ADSL Deficiency	CFC Syndrome Type 4 – MAP2K2	SPATA5
KCNH1-Related Developmental and Epileptic Encephalopathy	SATB2-associated syndrome (SAS)	TBA
Liang-Wang Syndrome (LIWAS)	ARSACS (Autosomal Recessive Spastic Ataxia) – SACS	TBA
YWHAG Developmental and Epileptic Encephalopathy	NBIA – C19orf12 (c.204_214del) MPAN	TBA
Lessel-Kreienkamp Syndrome (Ago2)	CORD (Cone-Rod Dystrophy) – ABCA4	TBA
Developmental Epileptic Encephalopathy (DEE65)	KAT6A Syndrome (Arboleda-Tham)	TBA

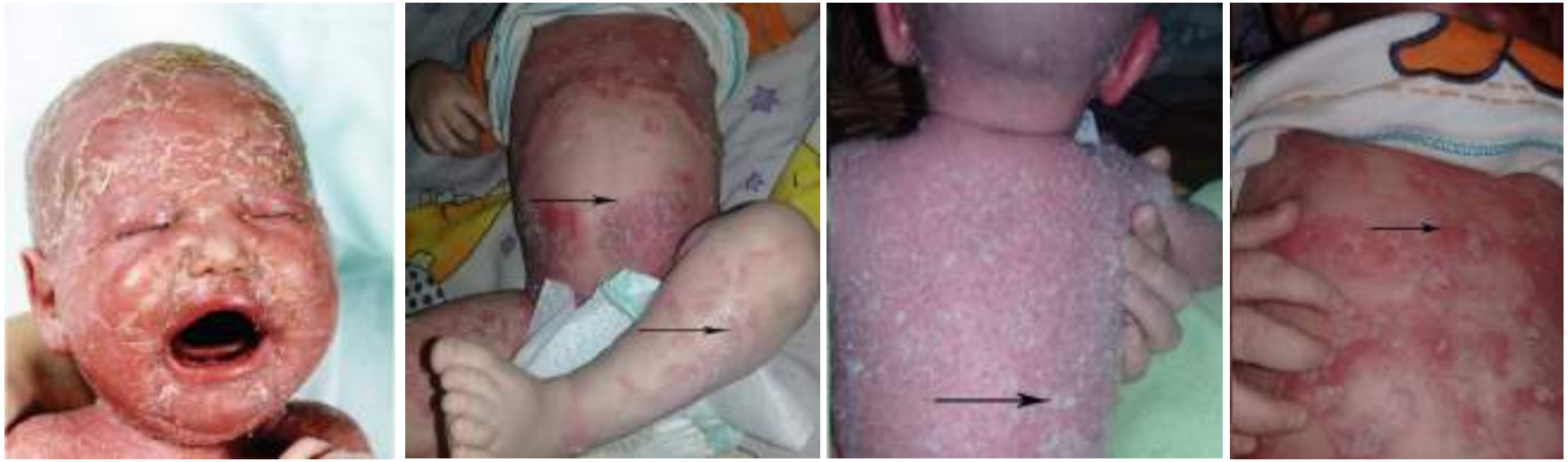
31 selected RDs from 130+ nominated

RD-Factory programm - example:

Netherton syndrom

Netherton Syndrome (NS)

- Autosomal recessive
- Prevalence 1 : 200 000
- Caused bay mutations in thein the gene **SPINK5**
- Gene **SPINK5** encodes for **LEKTI**
- **LEKTI -** inhibitor of serine proteases - important for the proteolytic homeostasis of the skin/epidermis



Saleem et al. 2018

Symptoms

- skin barrier failure, Ichthyosis Linearis Circumflexa
- generalized red, scaly skin (erythroderma)
- fragile "bamboo hair" that breaks easily,
- severe immune system problems like allergies and high IgE; frequent infections

Netherton Syndrome (NS)

Current treatment

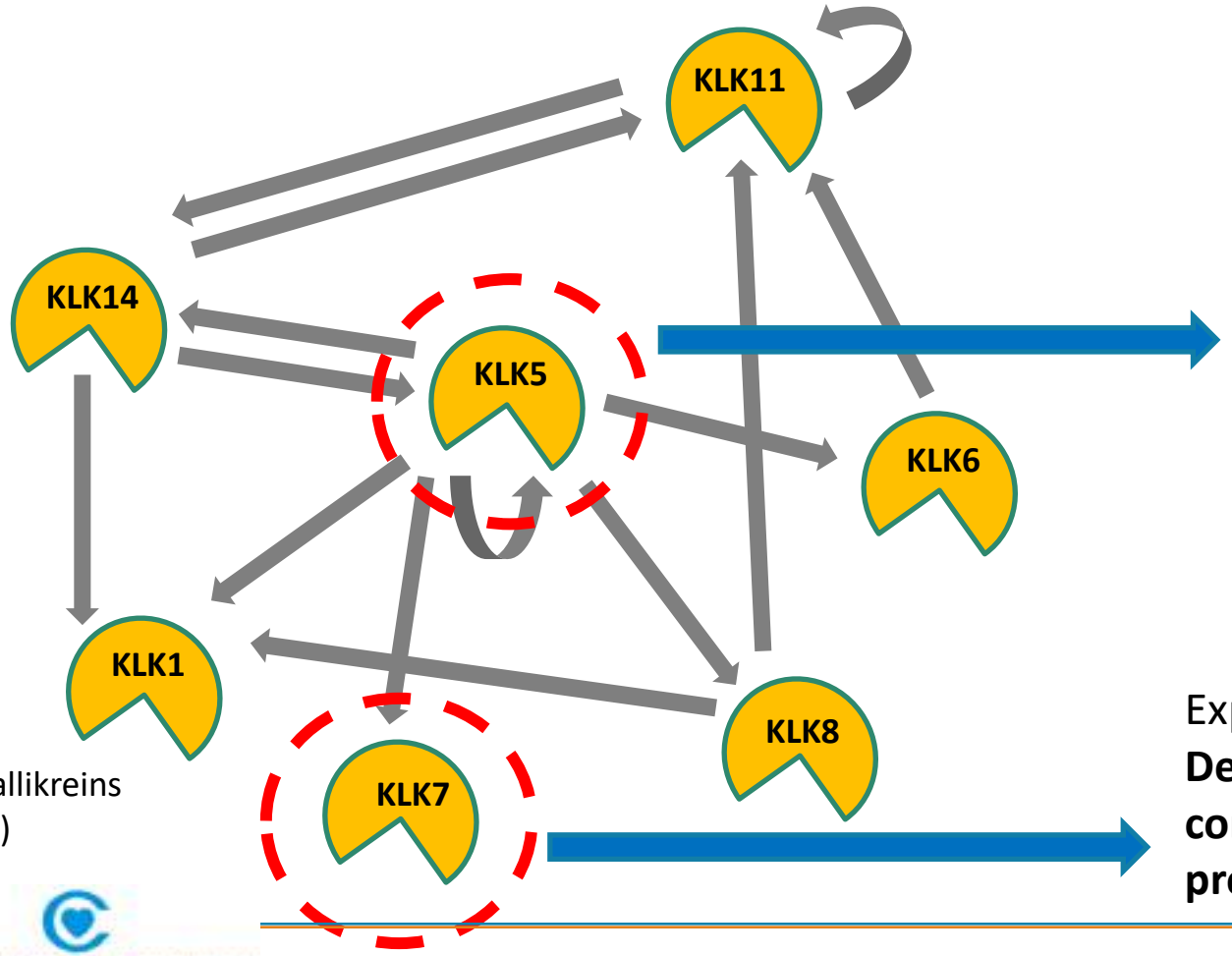
emollients for treatment of the skin disorder
topical steroids and topical immunomodulators
IL-17 antagonist secukinumab.

Experimental

Small molecule protease inhibitors
ShRNA ihibition of proteolytic pathway
Gene substitution/repair

Netherton Syndrome (NS)

in epidermis



Expressed in SC
Degradation of corneodesmosomal proteins

PAR-2 activation

↓ LEKTI

↑ Proteolytic activity of kallikreins (KLK5, KLK14, KLK7)

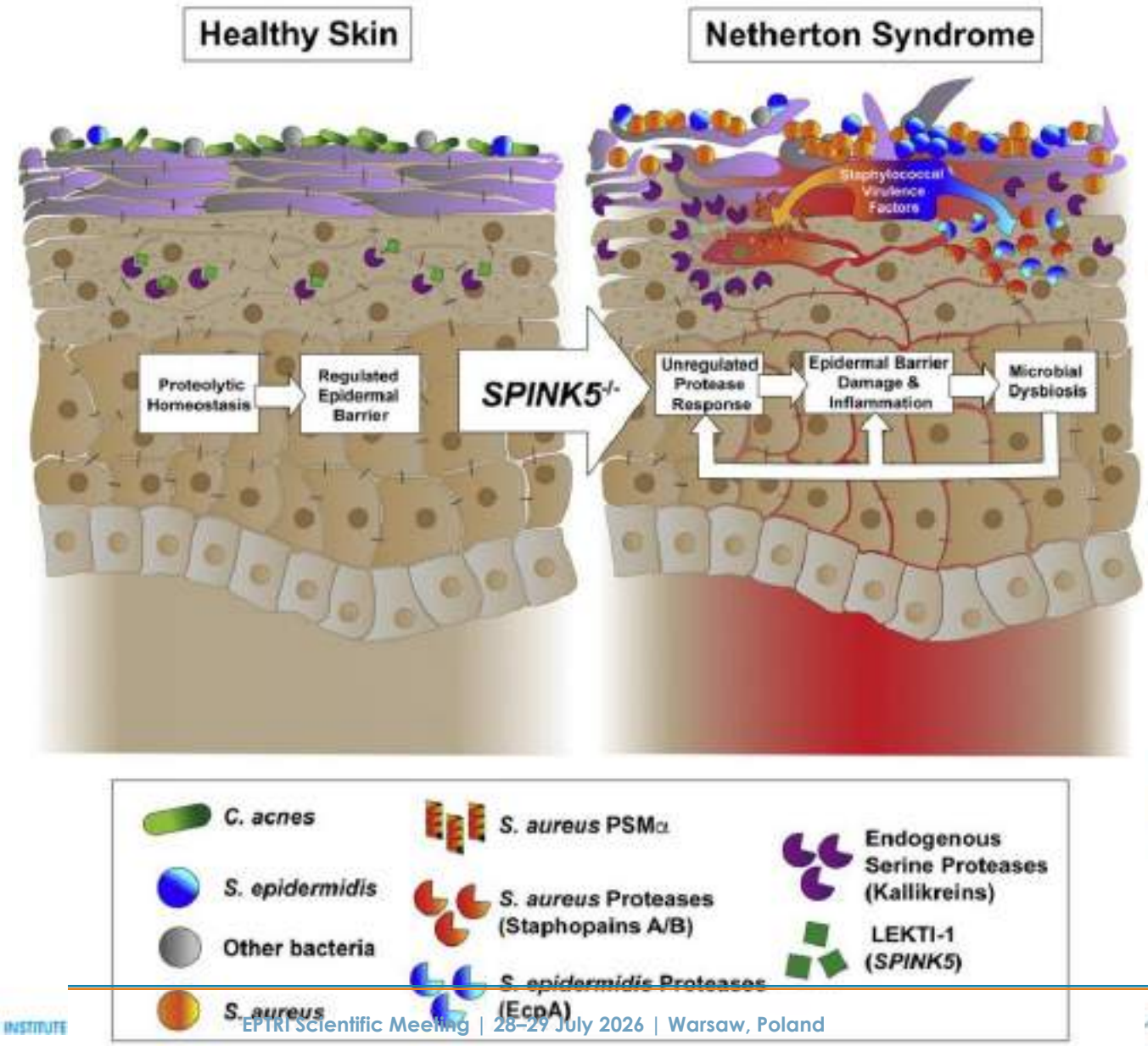
Expressed in SC
Degradation of corneodesmosomal proteins

Netherton Syndrome

↓ LEKTI

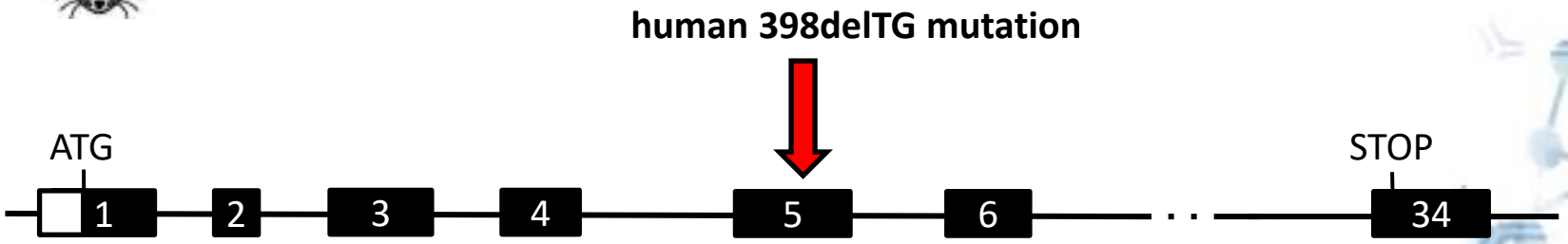
↑ Proteolytic activity of kallikreins (KLK5, KLK14, KLK7)

Epidermal barrier damage



Generation of a first mouse model for Netherton syndrome

Spink5 -/-



human wt: 5´CTG TG**T** **G**CT GAG AAT GCG 3´

human 398delTG: 5´CTG TGC TGA . . .3´

murine wt: 5´CTG TG**T** **G**CT GAG AAT GCG 3´

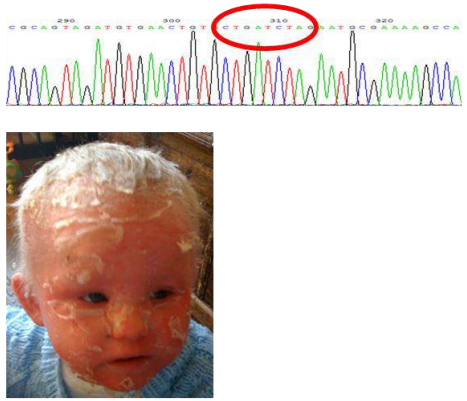
murine 402delTG: 5´CTG TGC TGA . . . 3´

Netherton syndrome:

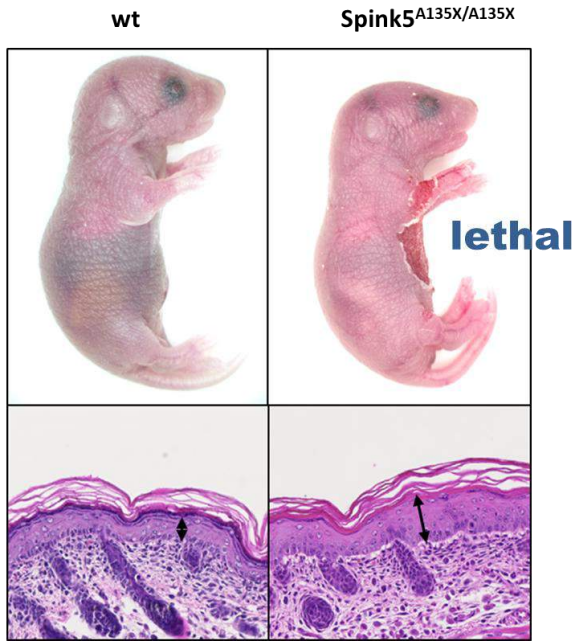
KLK5 and KLK7 Ablation Fully Rescues Lethality of Netherton Syndrome-Like Phenotype

Generation of a mouse models for Netherton syndrome

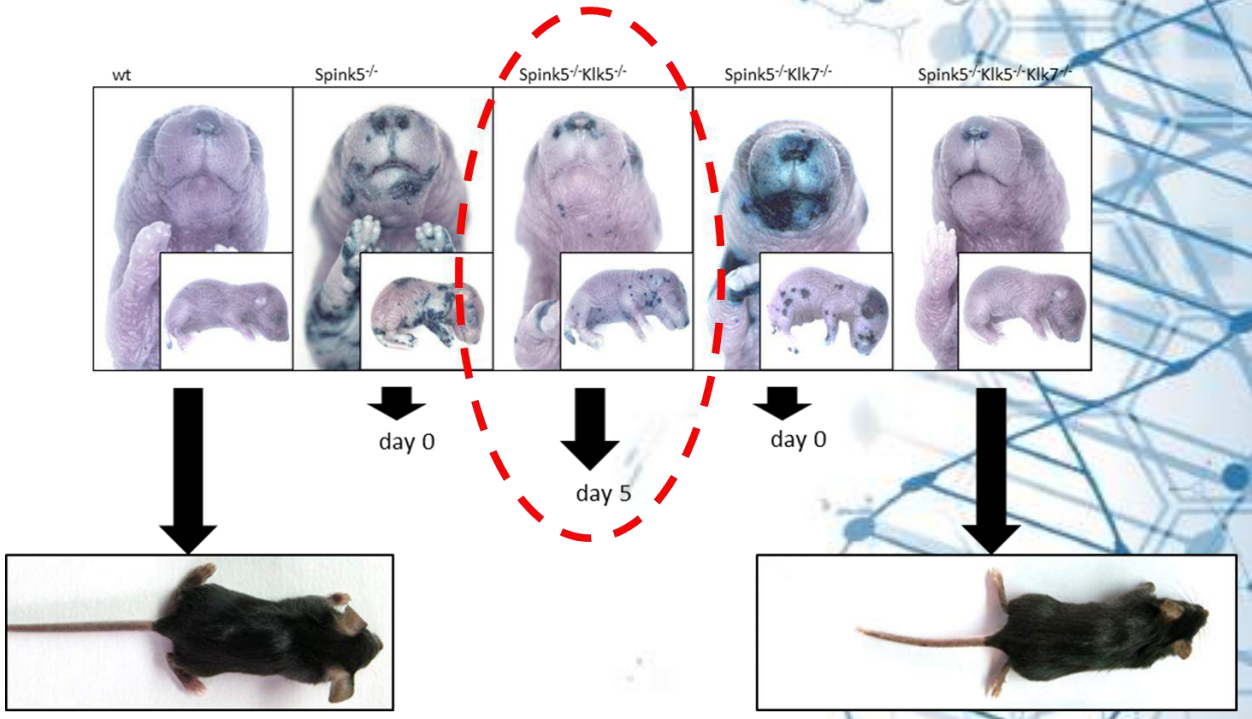
Spink5$^{-/-}$ cDNA sequencing:



Abnormal diferentiation of epidermis:
Acanthosis
Parakeratosis



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



Kasparek et al., PLOS Genetics, 2017

CCP vision:
validated humanized avatars for translational testing

- **Humanized ‘avatar’ models represent highly precise, human-relevant disease models designed to mimic key molecular and phenotypic features of patient disease.**
- **standardized platforms for rare disease research and preclinical development.**
- **enabling testing of gene therapy concepts, vector/delivery solutions, and other targeted therapeutic interventions.**

- **Our long-term aim is to validate these models to a level where they can be recognized by EMA as reliable tools for therapy development and preclinical testing.**

Czech Centre for Phenogenomics

Invitation: You are welcome!

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IMG


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European Paediatric Translational Research Infrastructure
THE CHILDREN'S MEMORIAL HEALTH INSTITUTE
EPTRI General Assembly and Scientific Meeting
Warsaw, 28-29 July, 2026
Thank you for your attention !
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