



# How micro-CT can provide insight into dynamic disease processes

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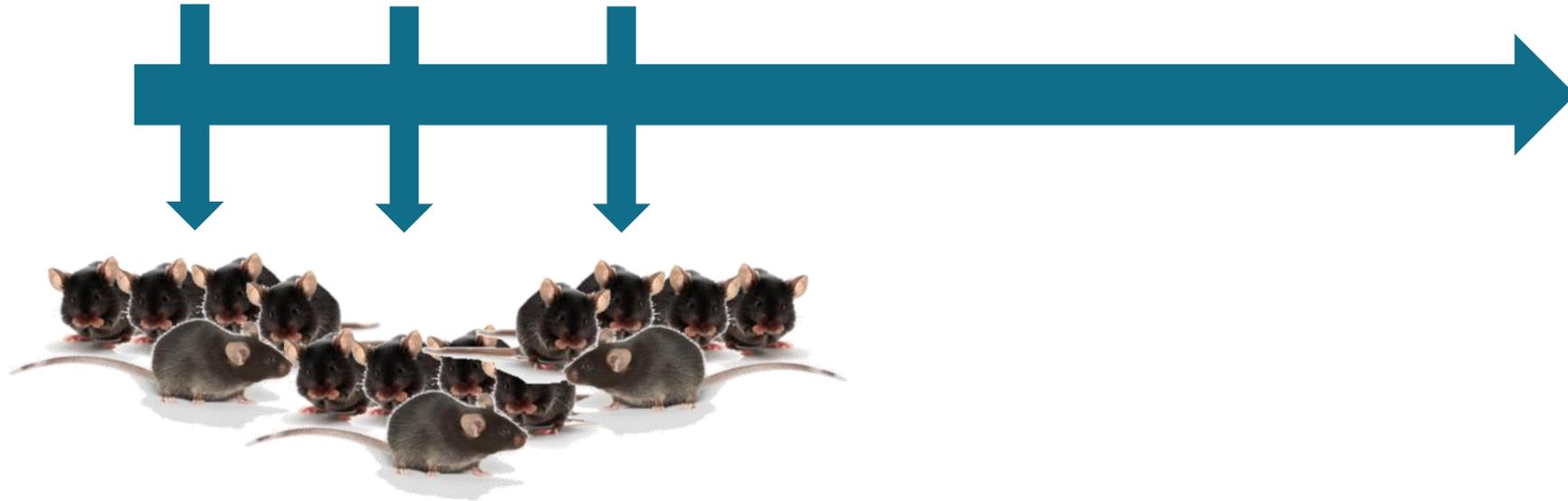
*KU Leuven, Belgium*

# Evaluating disease progression and therapy...



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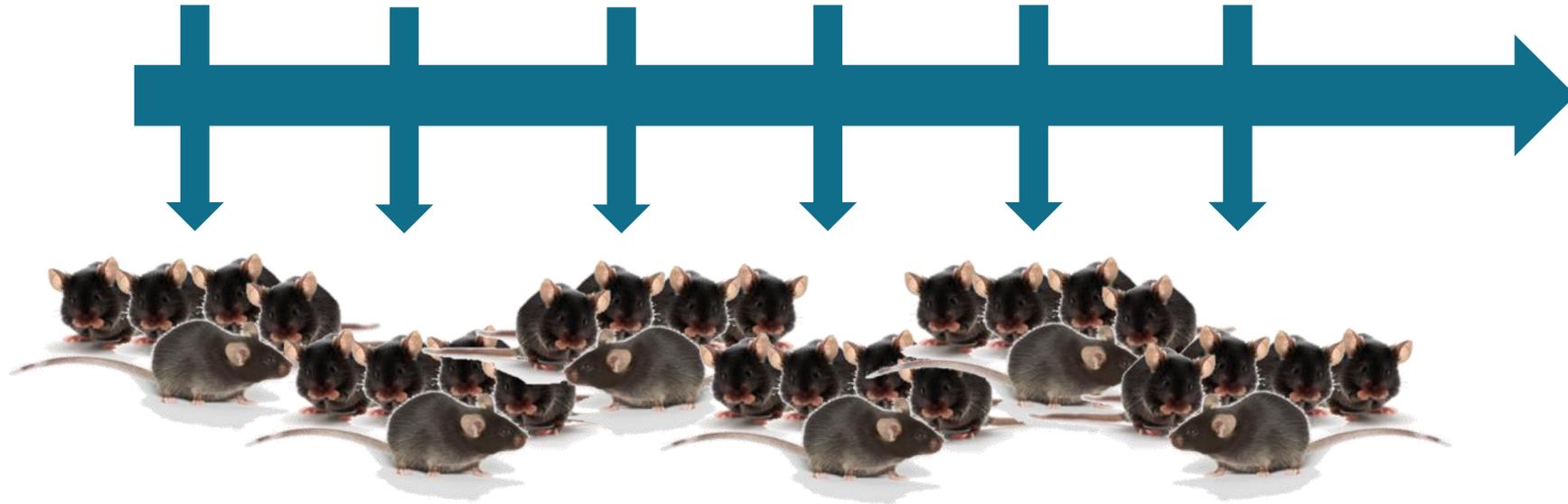
establish disease model...



# Evaluating disease progression and therapy...

establish disease model...

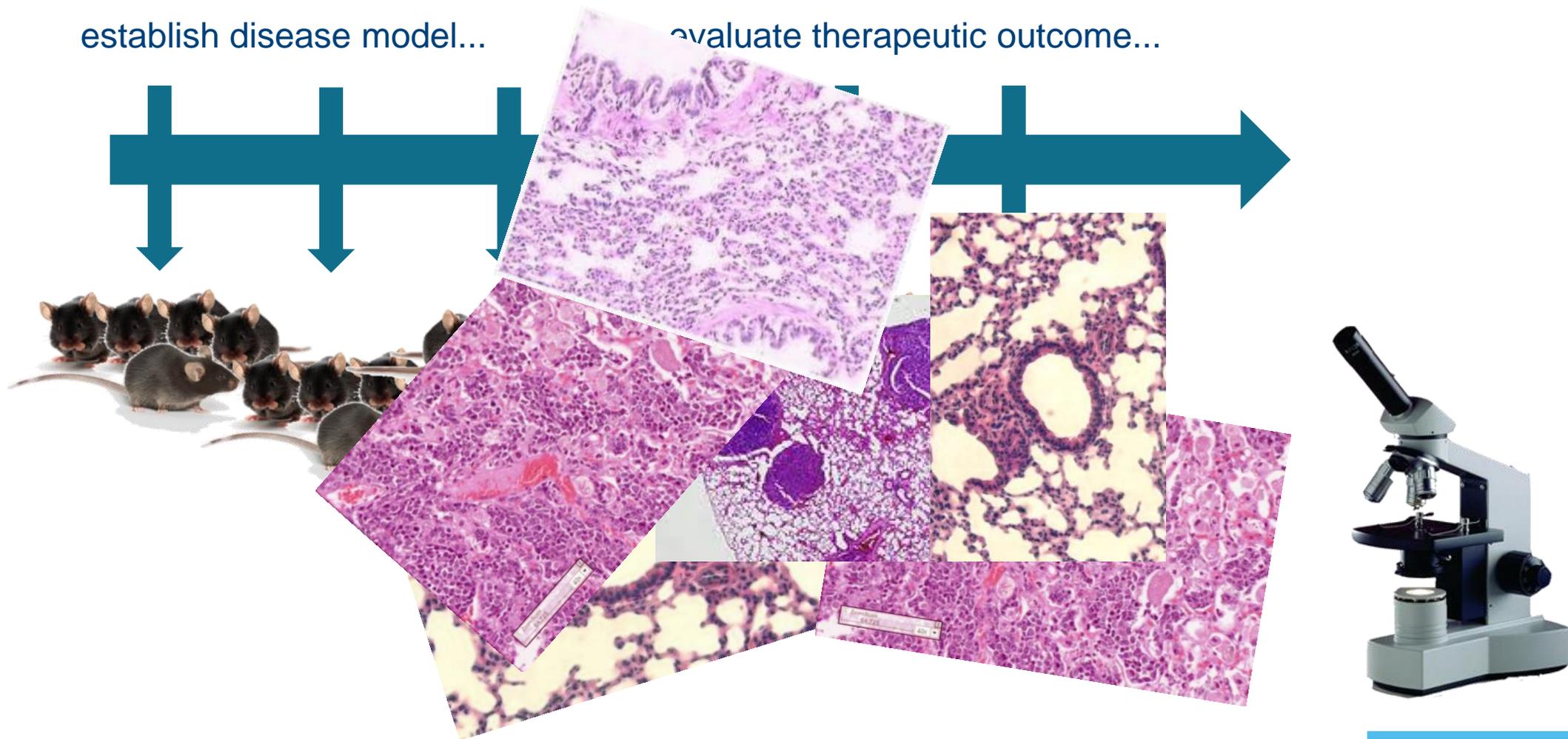
evaluate therapeutic outcome...



# Evaluating lung disease and therapy...

establish disease model...

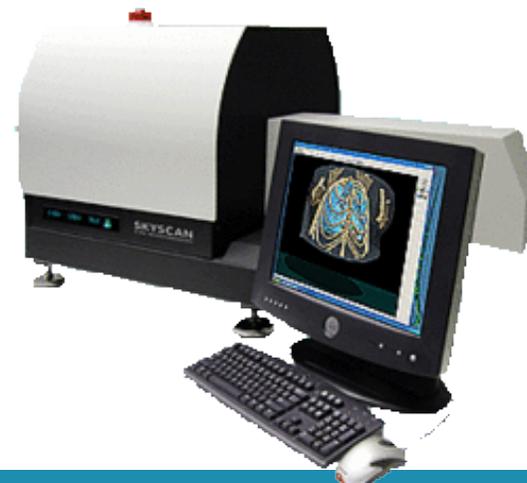
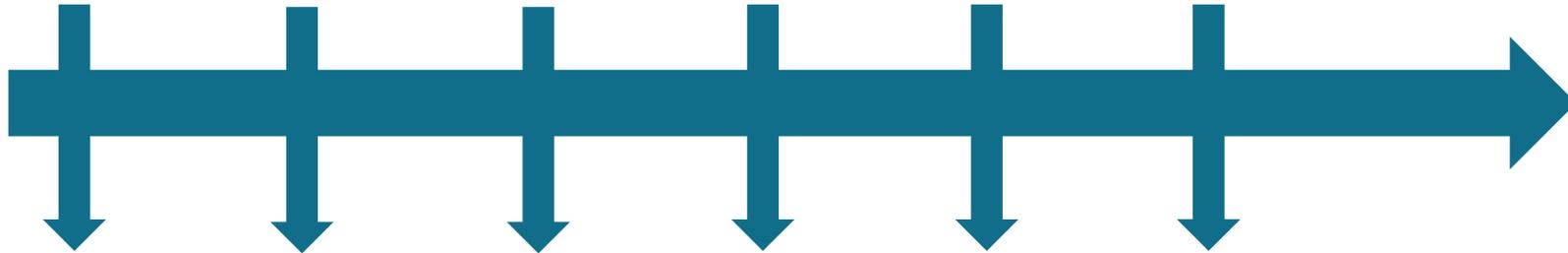
evaluate therapeutic outcome...

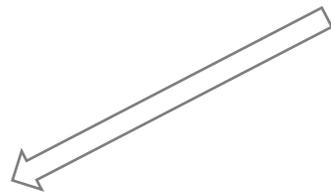
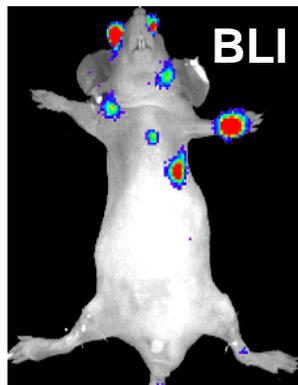
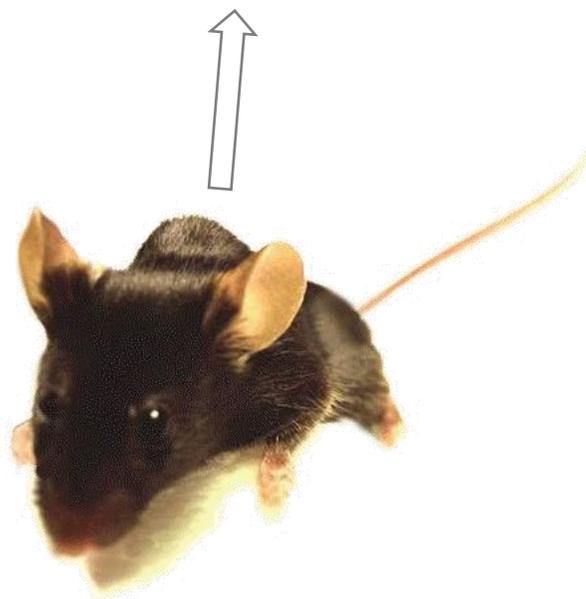


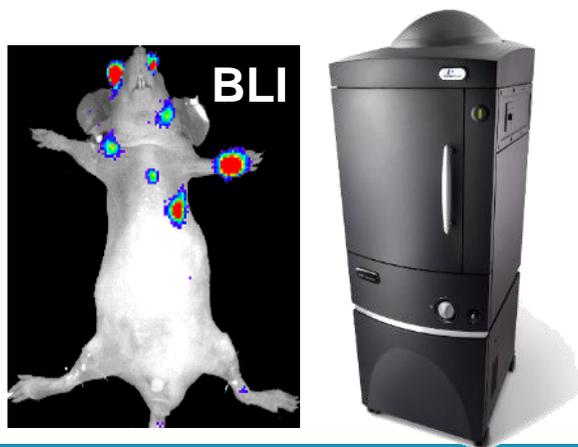
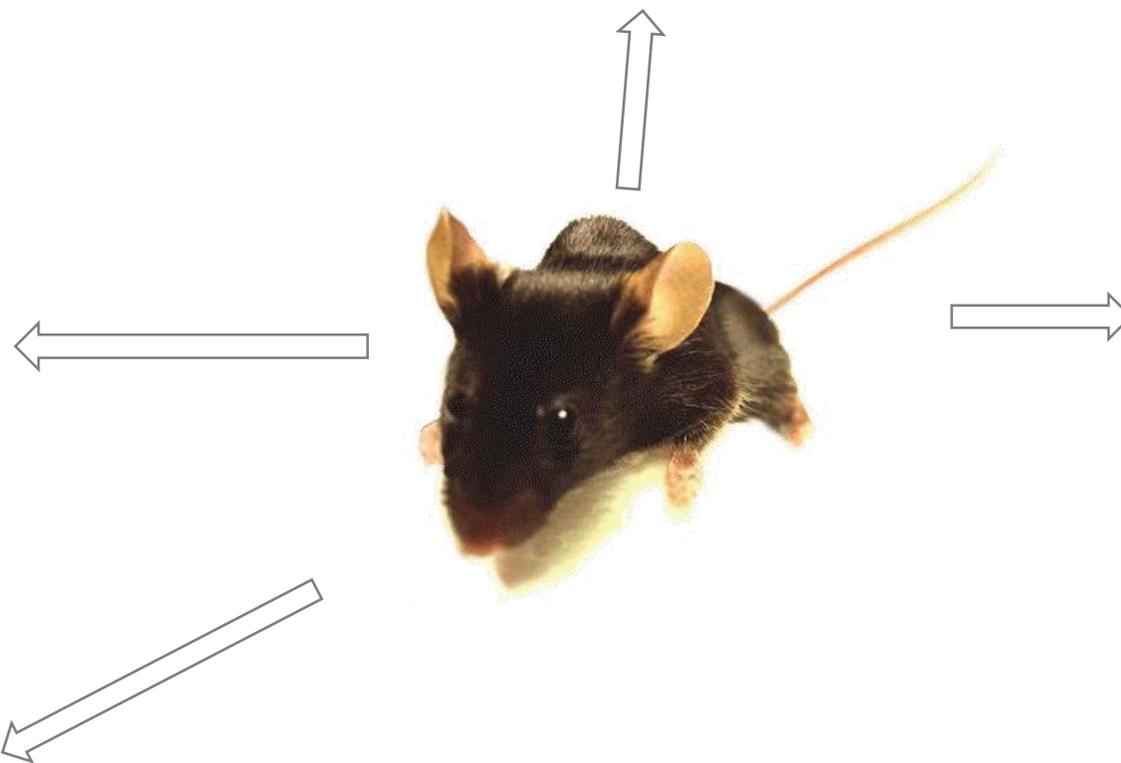
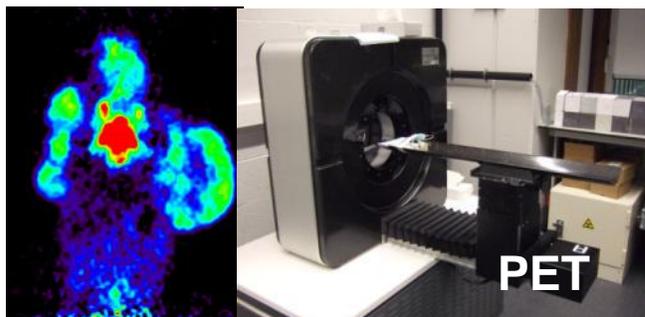
# Monitoring lung disease dynamically

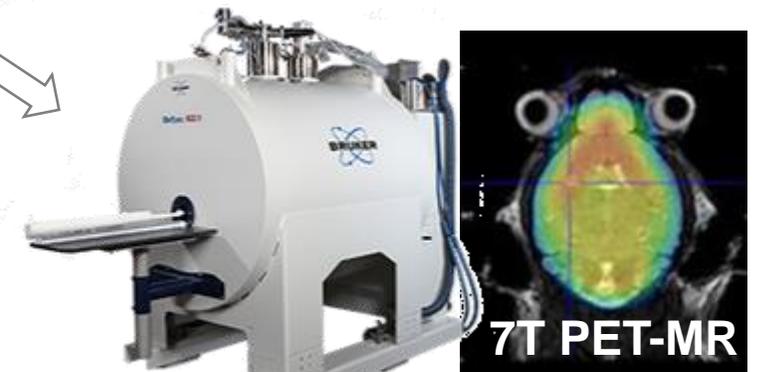
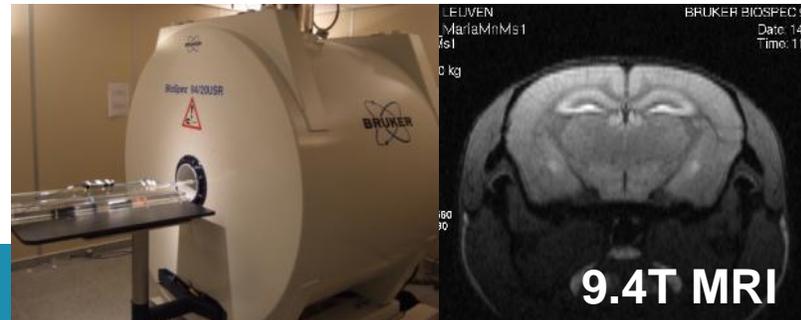
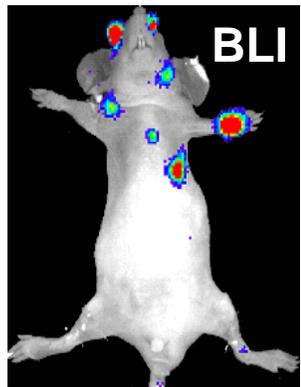
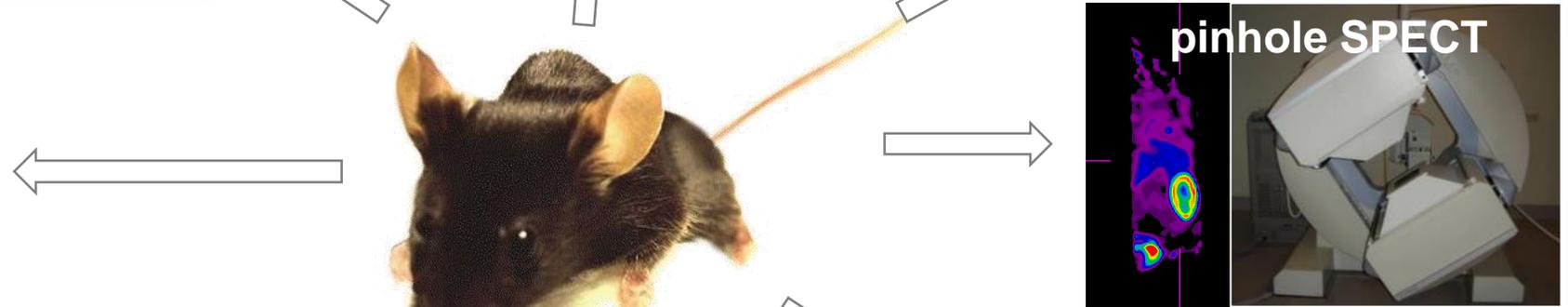
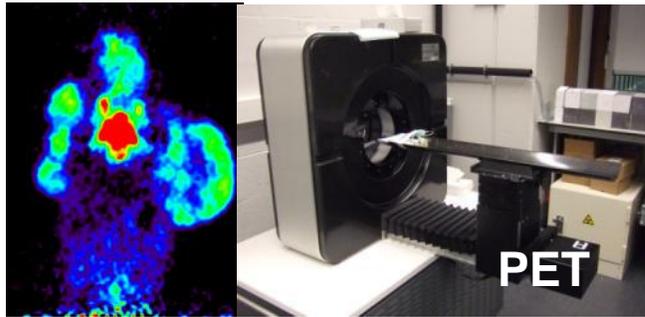
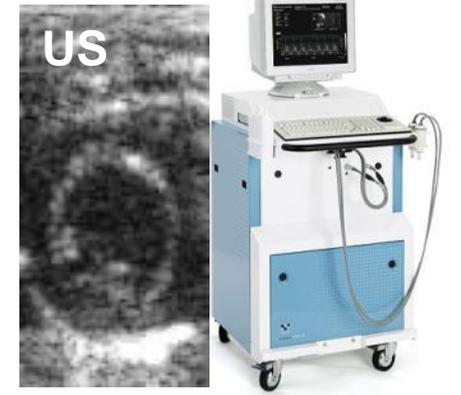
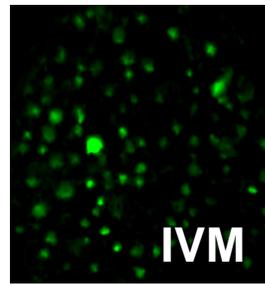
establish disease model...

evaluate therapeutic outcome...

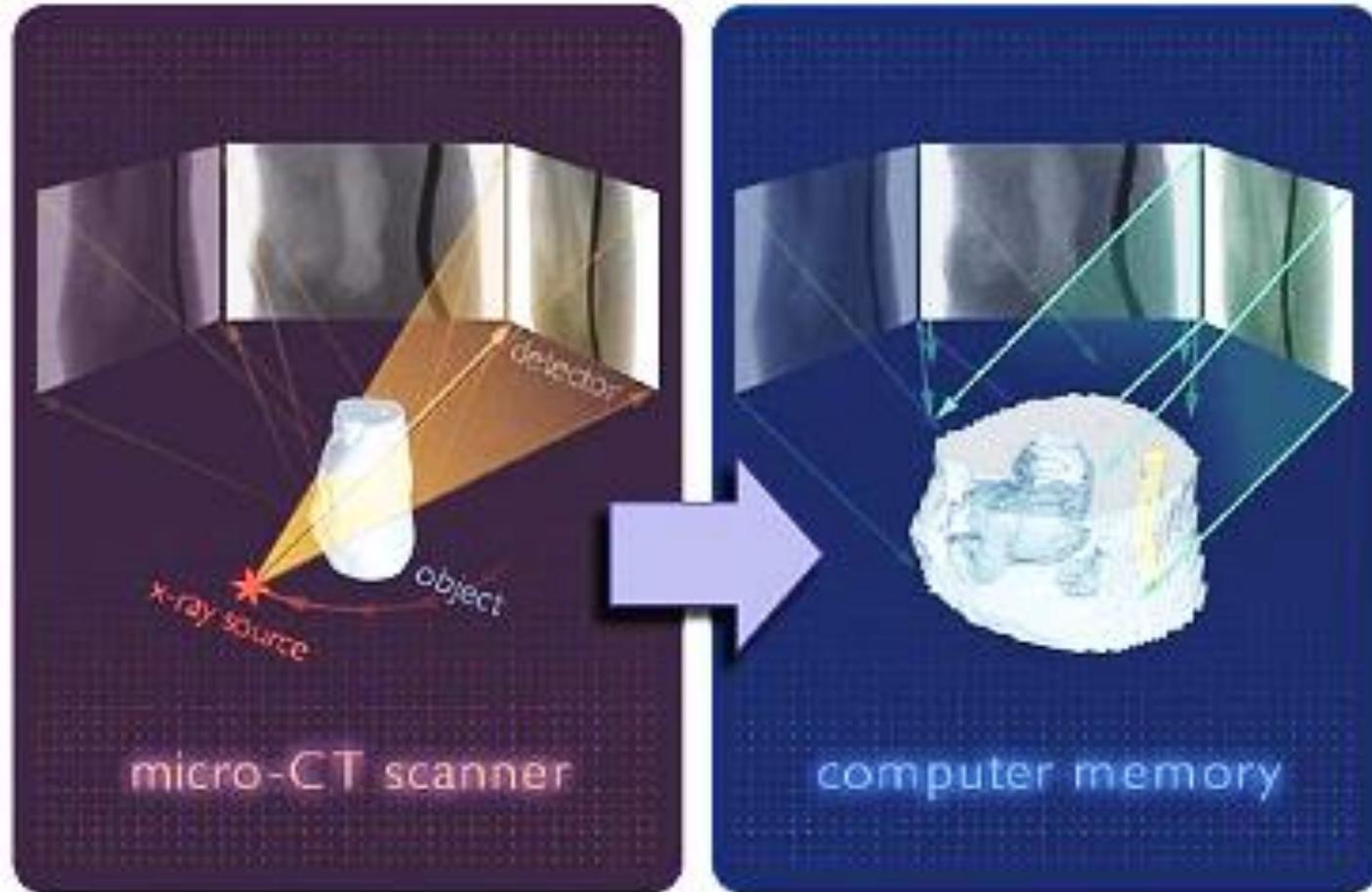






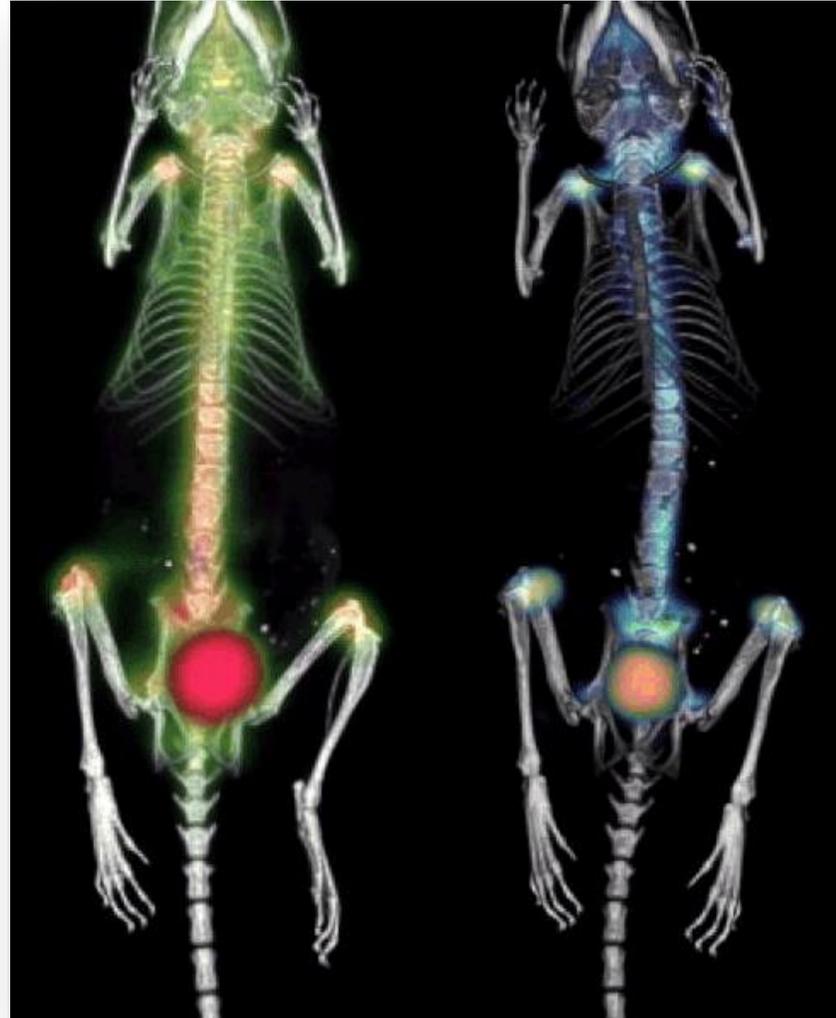


# micro-computed tomo... what??



# micro-computed tomo... what??

*It's the 'CT' in PET-CT and SPECT-CT...*

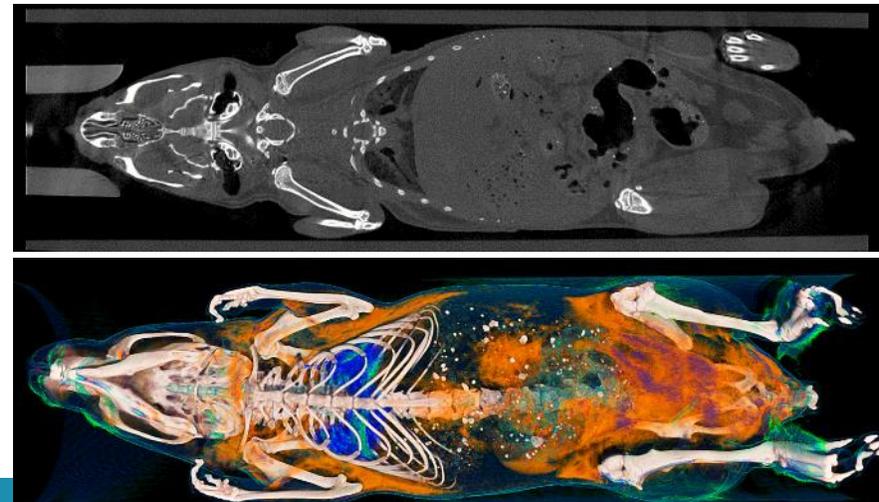
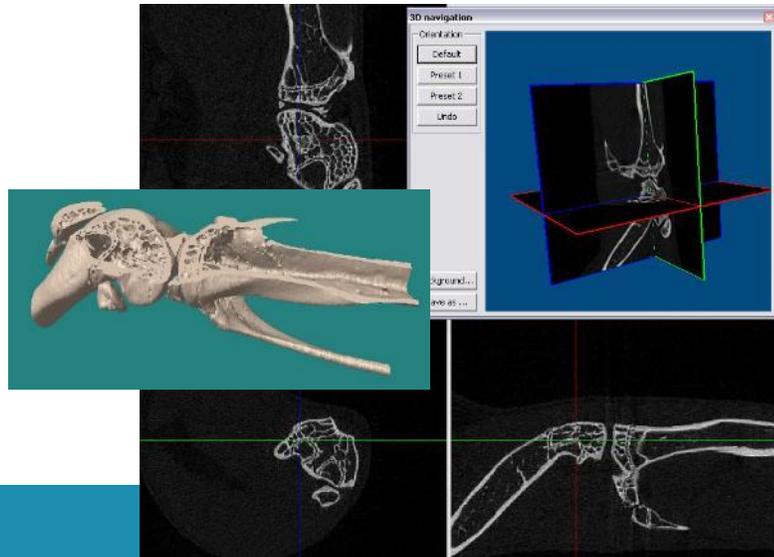


# *In vivo* micro-CT comes in two flavors

*small FOV, very high resolution*



*Large FOV, high resolution & low-dose*



# Lung disease imaging with $\mu$ CT

*$\mu$ CT has shown to be very useful for studying mouse lung fibrosis...*

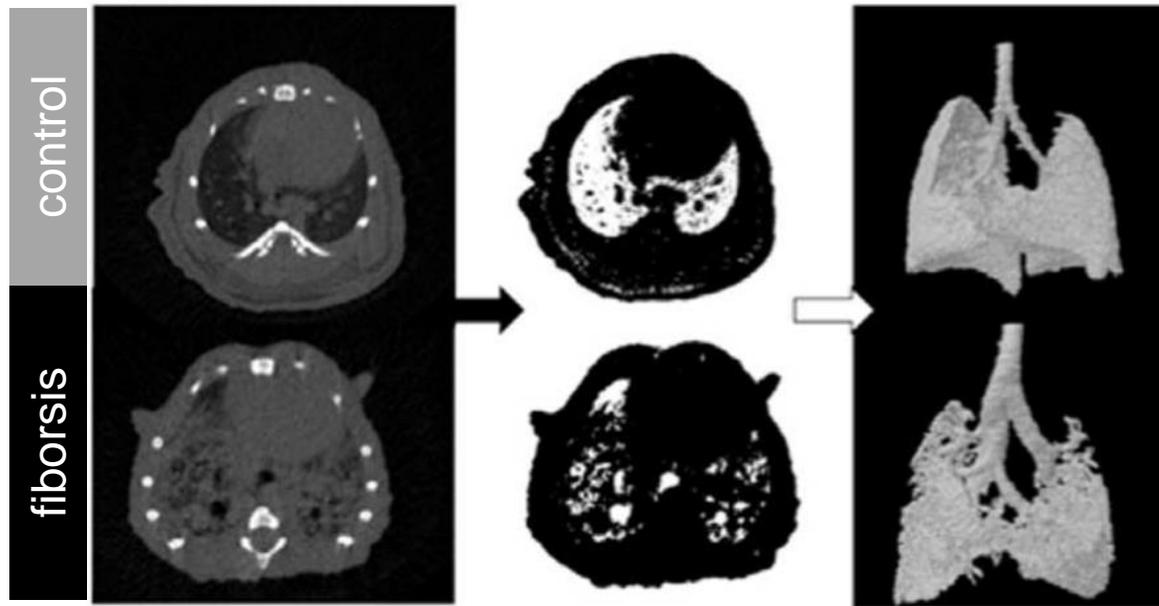
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PLOS ONE

## Quantification of Lung Fibrosis and Emphysema in Mice Using Automated Micro-Computed Tomography

Ellen De Langhe<sup>1,2\*</sup>, Greetje Vande Velde<sup>3</sup>, Jeroen Hostens<sup>4</sup>, Uwe Himmelreich<sup>3</sup>, Benoit Nemery<sup>5</sup>, Frank P. Luyten<sup>1,2</sup>, Jeroen Vanoirbeek<sup>5,9</sup>, Rik J. Lories<sup>1,2,9</sup>

<sup>1</sup> Laboratory for Skeletal Development and Joint Disorders, Department of Development and Regeneration, KU Leuven, Leuven, Belgium, <sup>2</sup> Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium, <sup>3</sup> Biomedical NMR Unit/MoSAIC, Department of Imaging and Pathology, KU Leuven, Leuven, Belgium, <sup>4</sup> SkyScan, Kontich, Belgium, <sup>5</sup> Research Unit of Lung Toxicology, Department of Public Health, KU Leuven, Leuven, Belgium



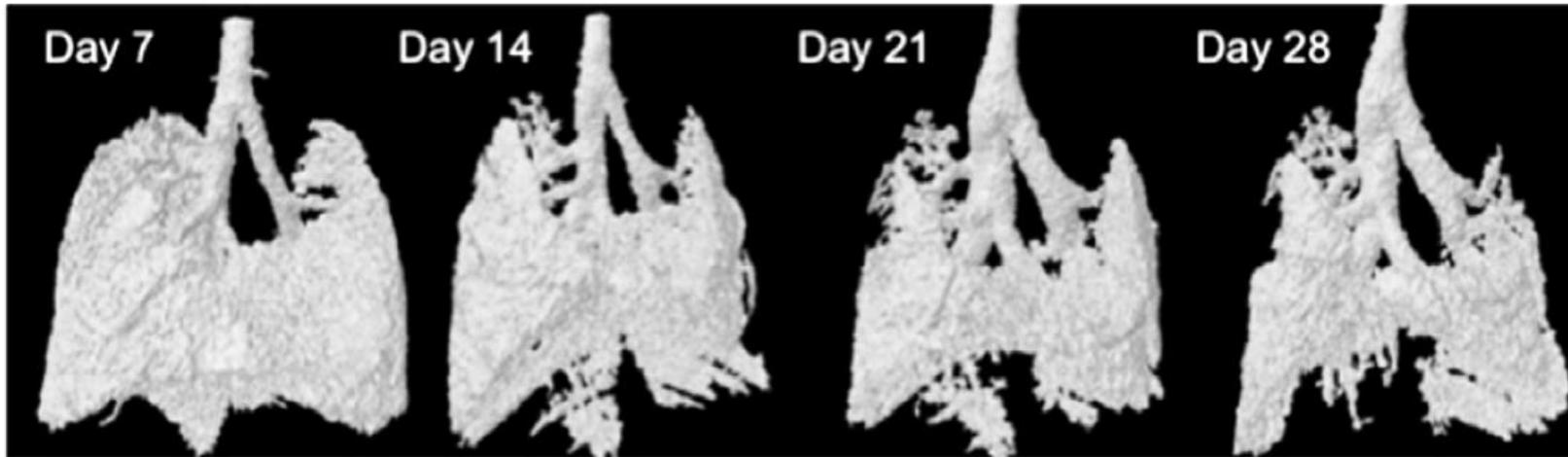
*Mouse is breathing...*

→ *Retrospective gating to deal with movement (4D)*

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# Lung disease imaging with $\mu$ CT

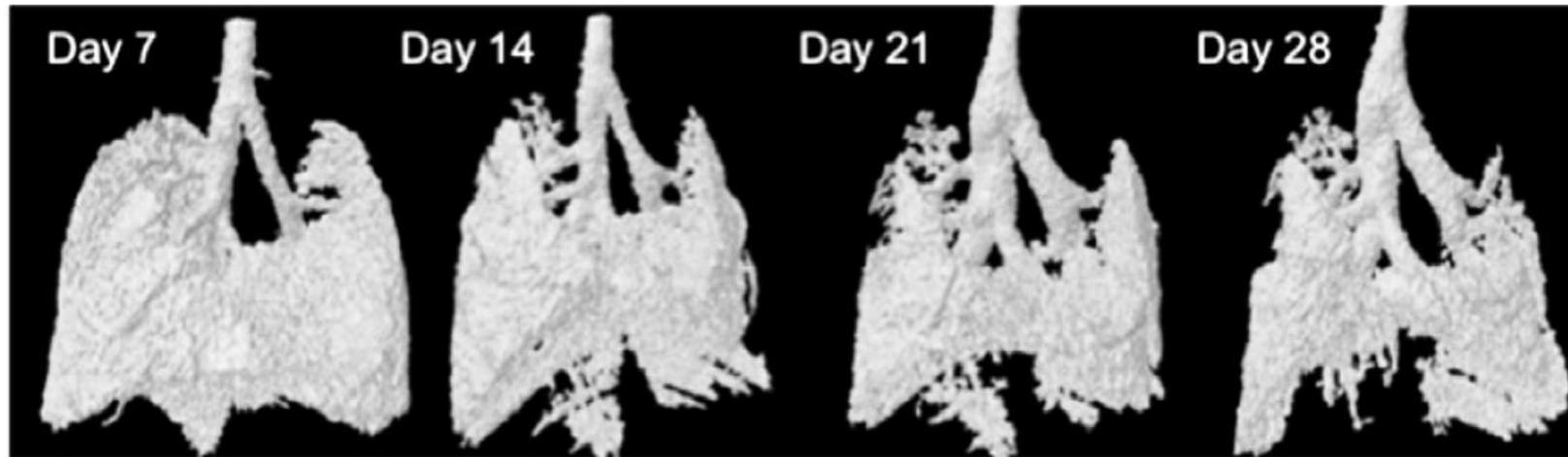
*$\mu$ CT has shown to be very useful for studying mouse lung fibrosis...*



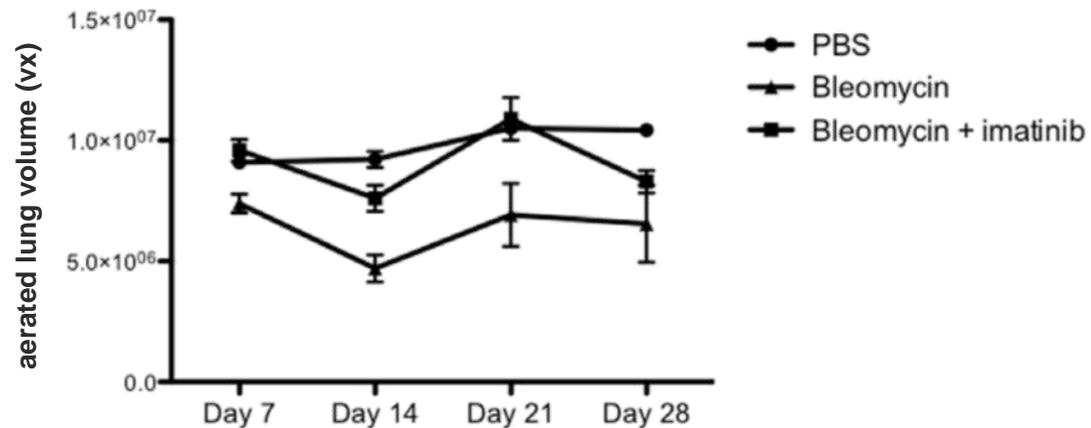
*We can do this longitudinally...*

# Lung disease imaging with $\mu$ CT

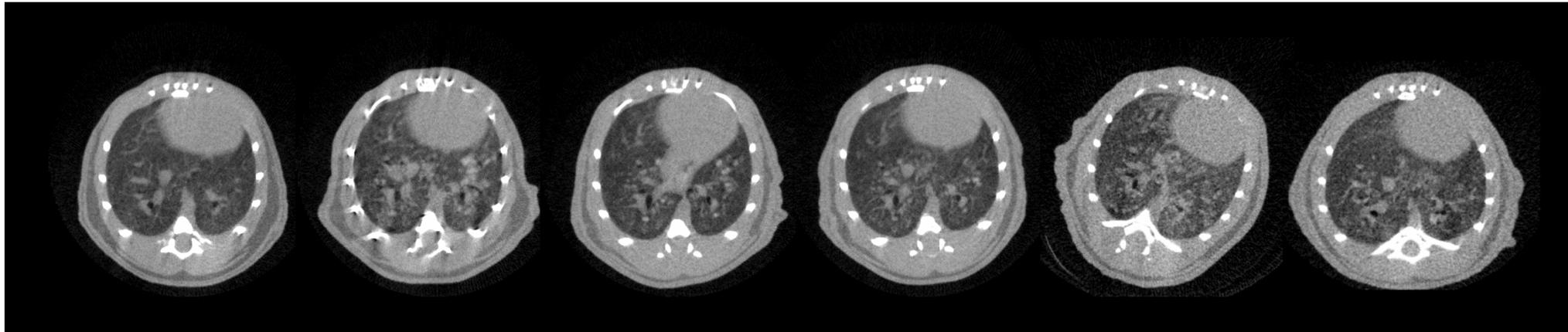
*$\mu$ CT has shown to be very useful for studying mouse lung fibrosis...*



*We can do this longitudinally... quantitatively... and evaluate therapy.*



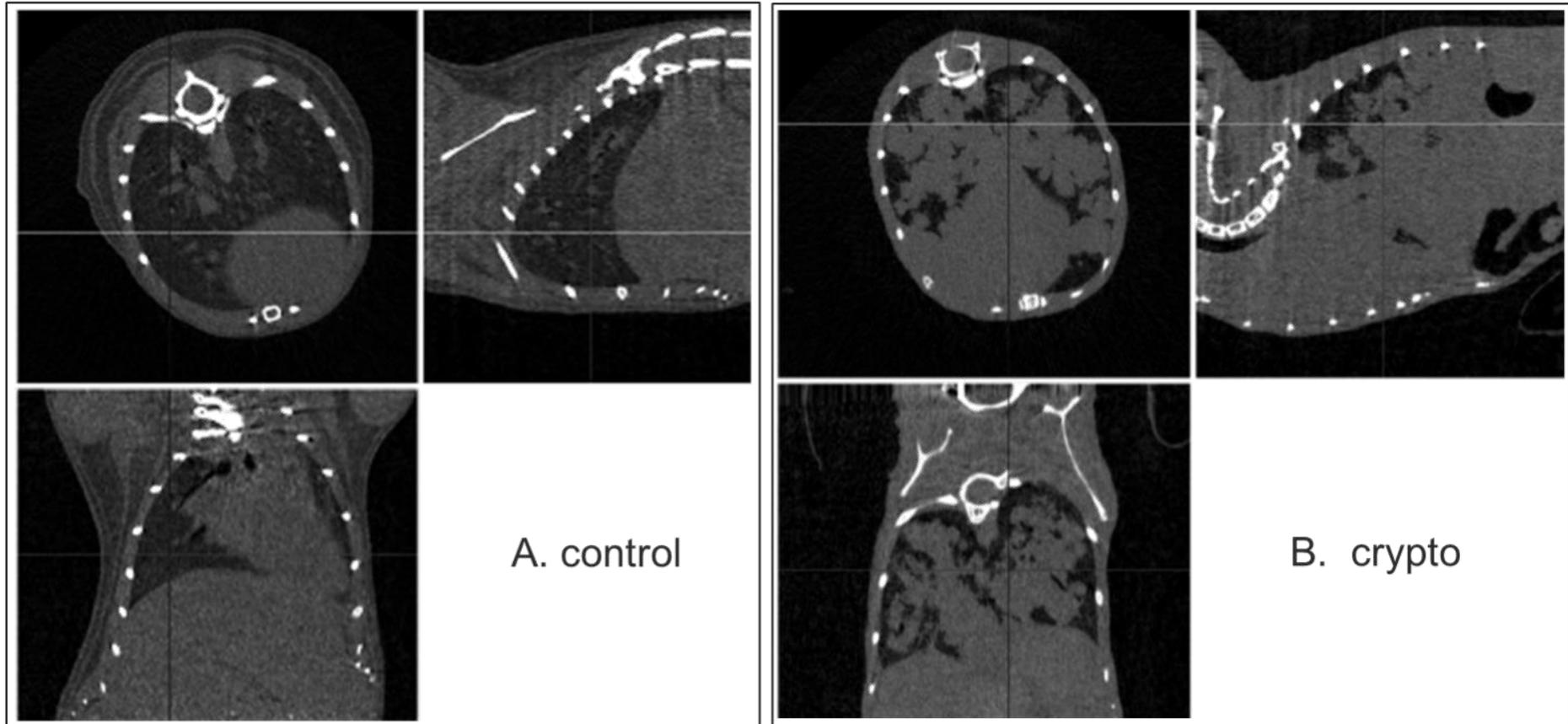
# Lung diseases: low-dose $\mu$ CT



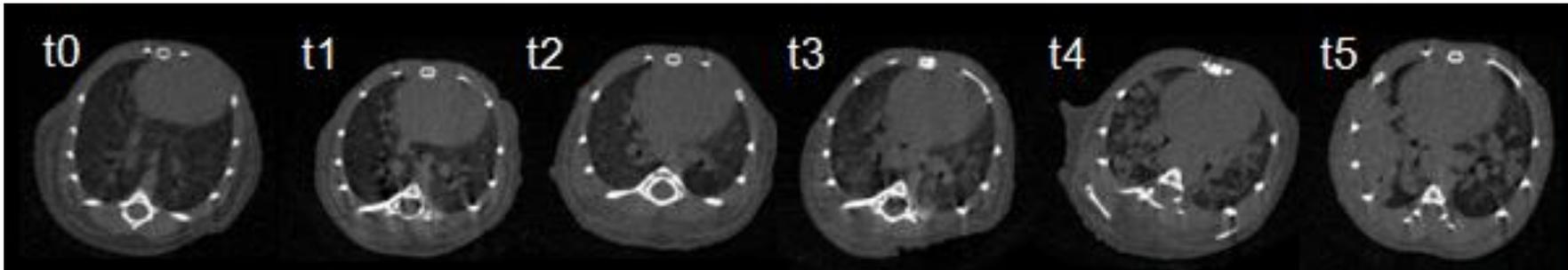
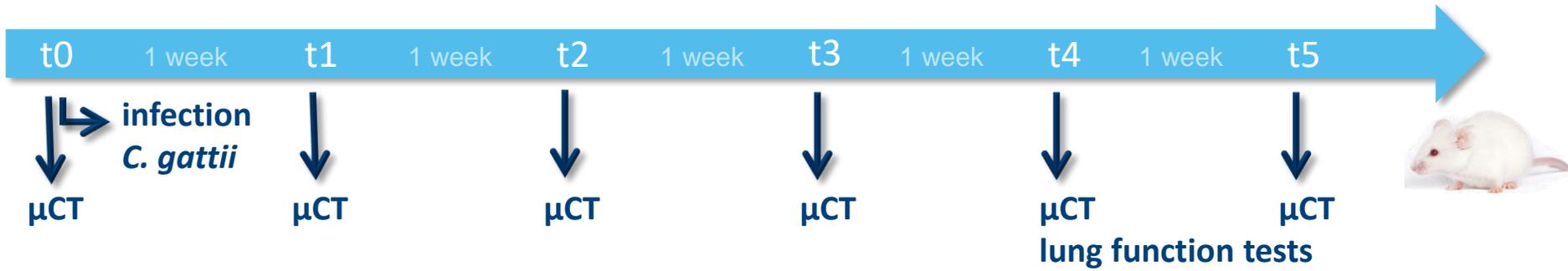
- Lung fibrosis: bleomycin-induced, silicosis
- Lung infections: aspergillosis, cryptococcosis, influenza,...
- Asthma, emphysema, COPD
- Lung metastasis
- ...

# Lung infection imaging with $\mu$ CT

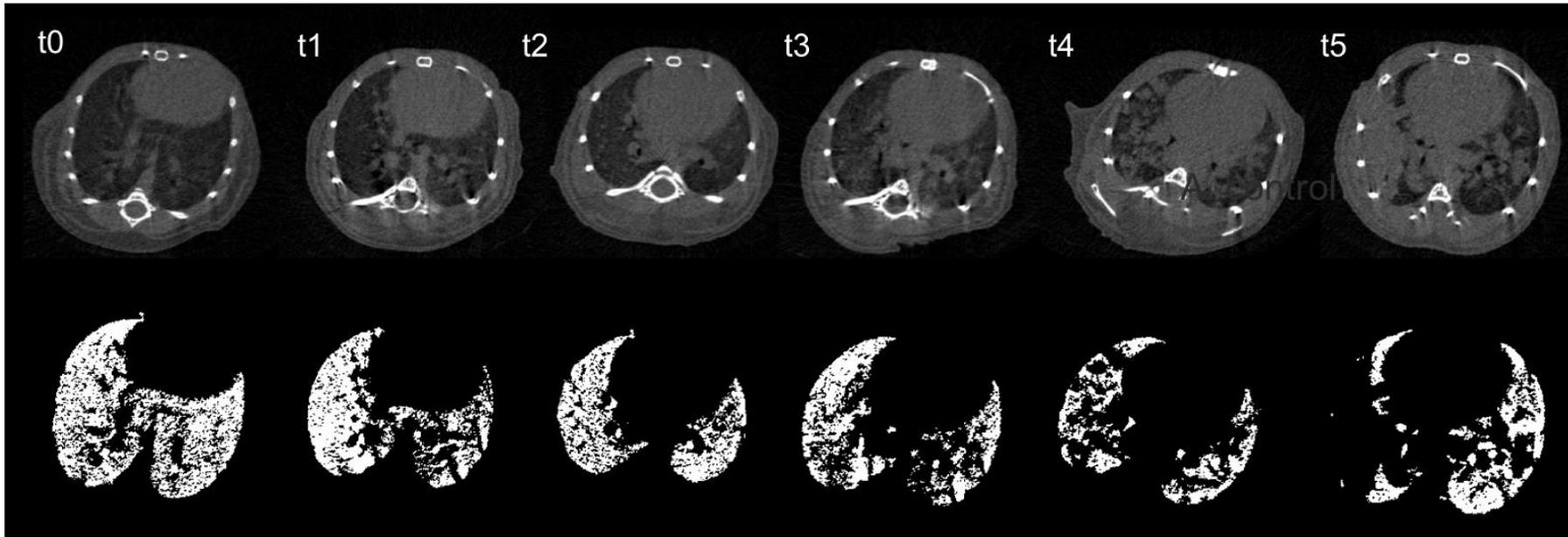
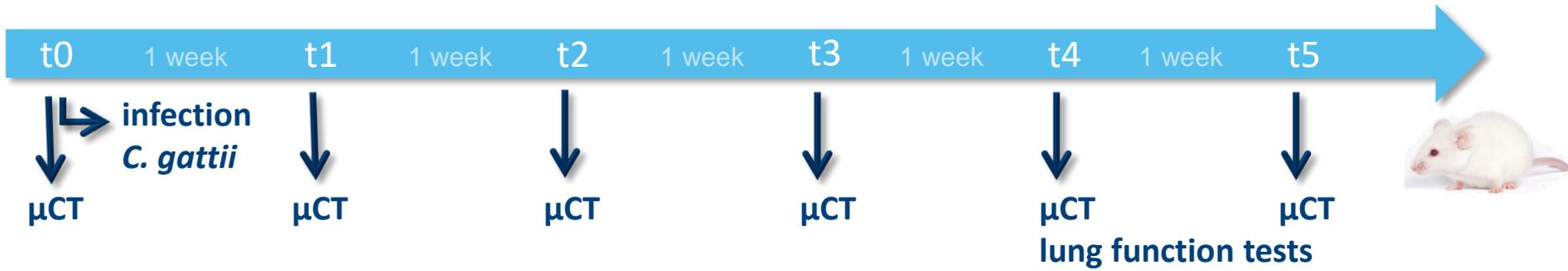
## Fungal lung infection: cryptococcosis



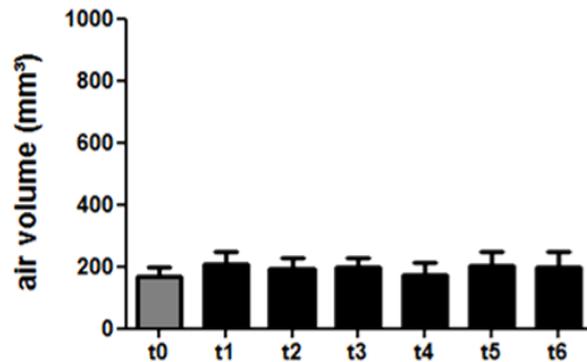
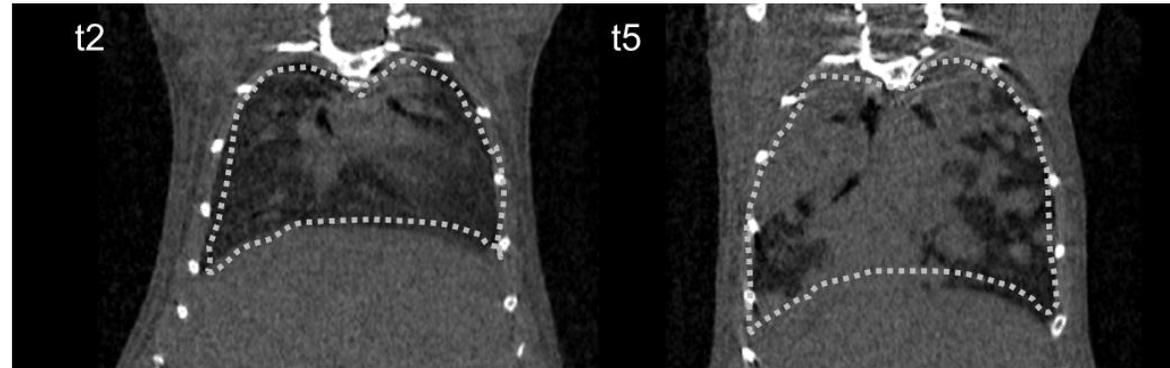
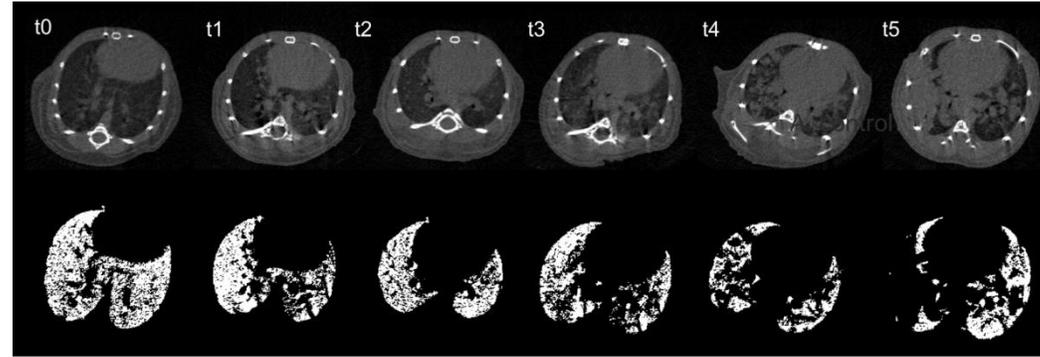
# Lung infection imaging with $\mu$ CT



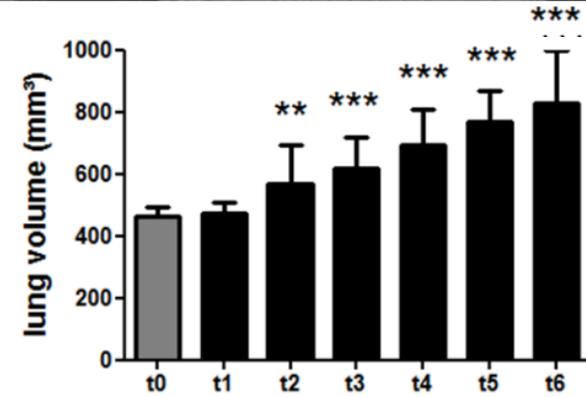
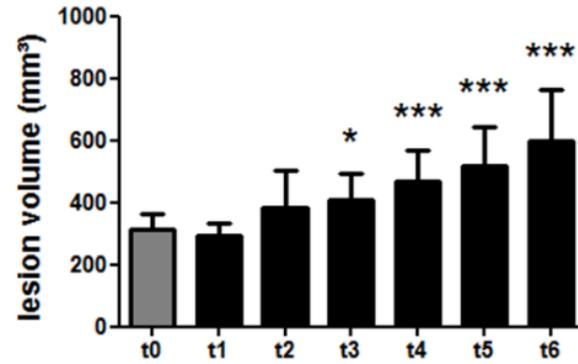
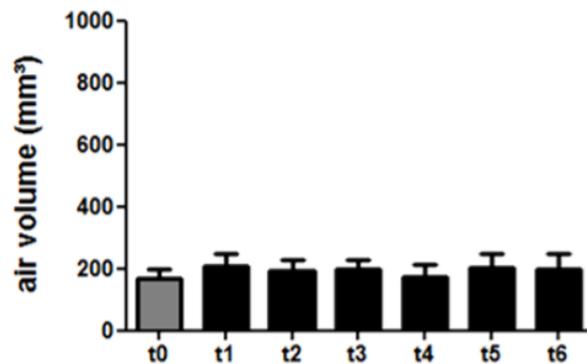
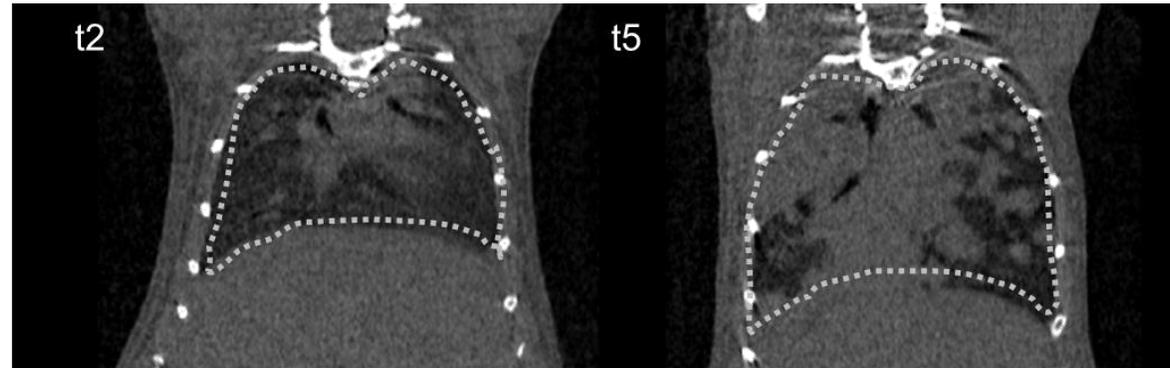
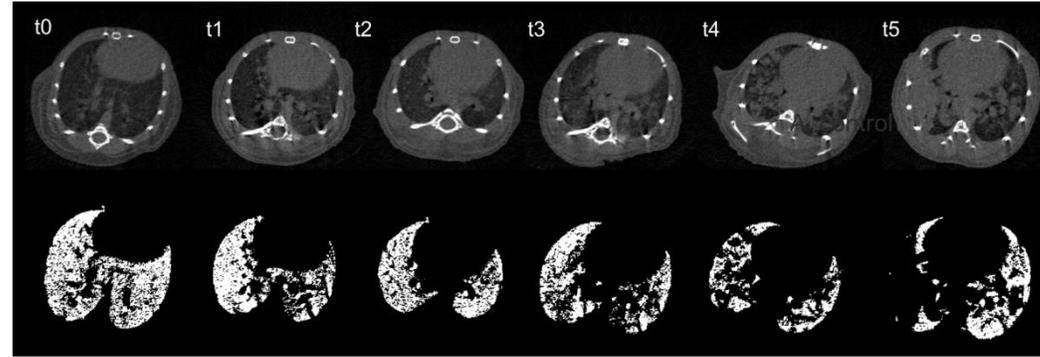
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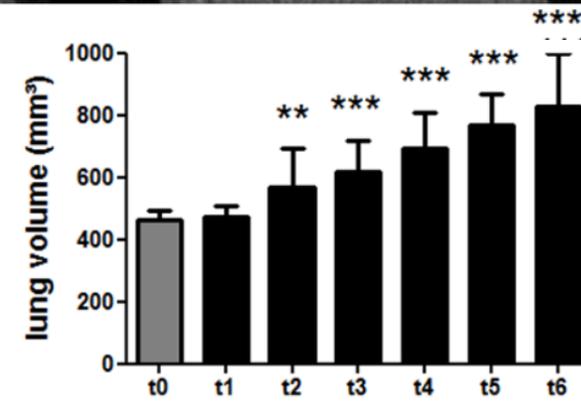
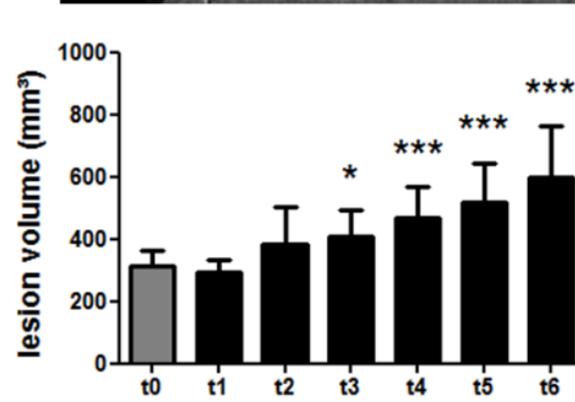
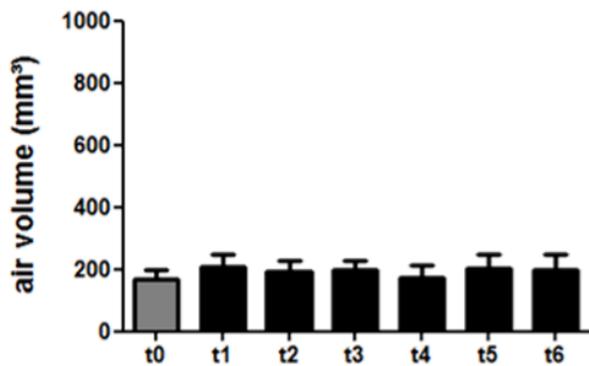
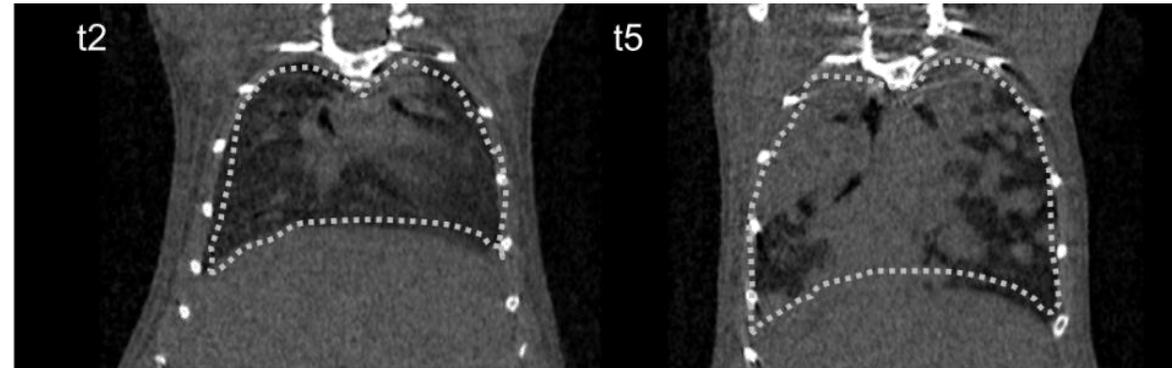
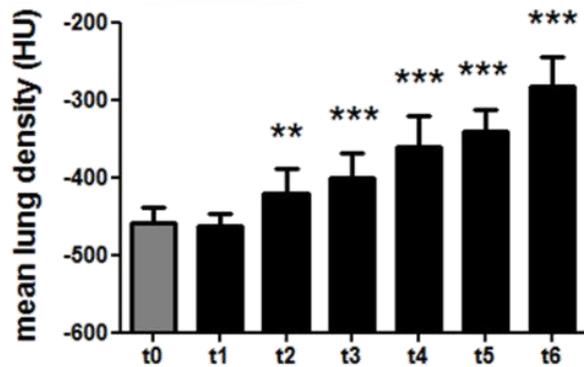
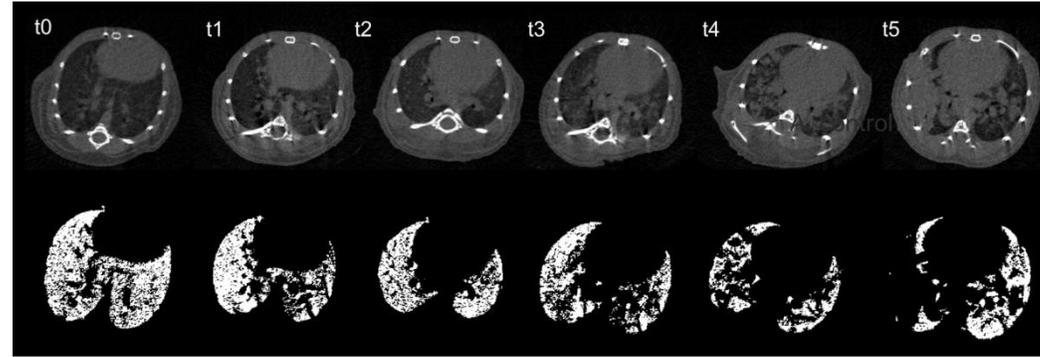
# Lung infection imaging with $\mu$ CT



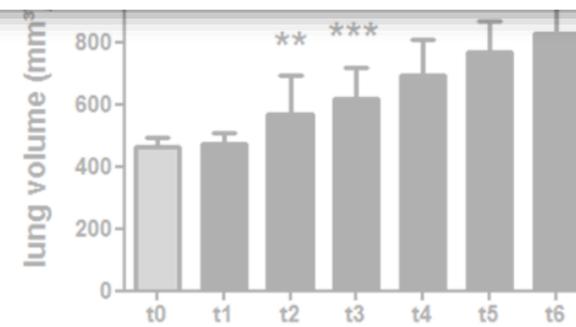
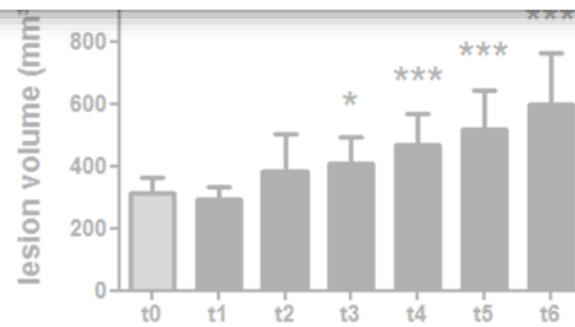
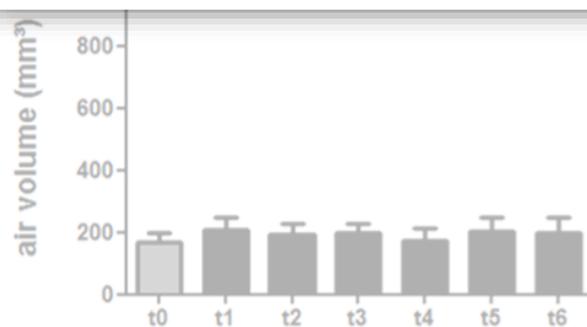
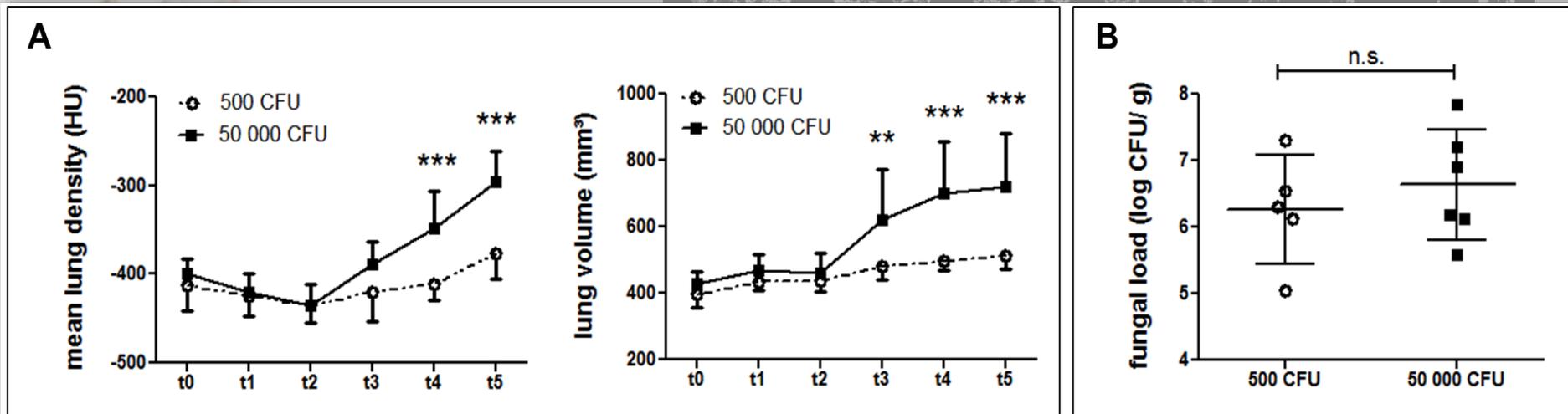
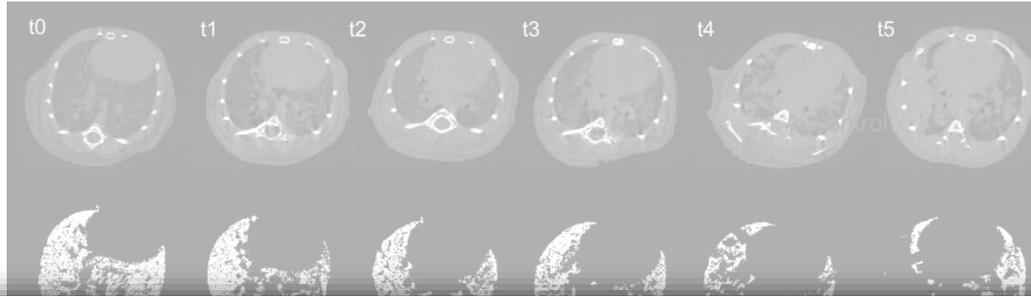
# Lung infection imaging with $\mu$ CT



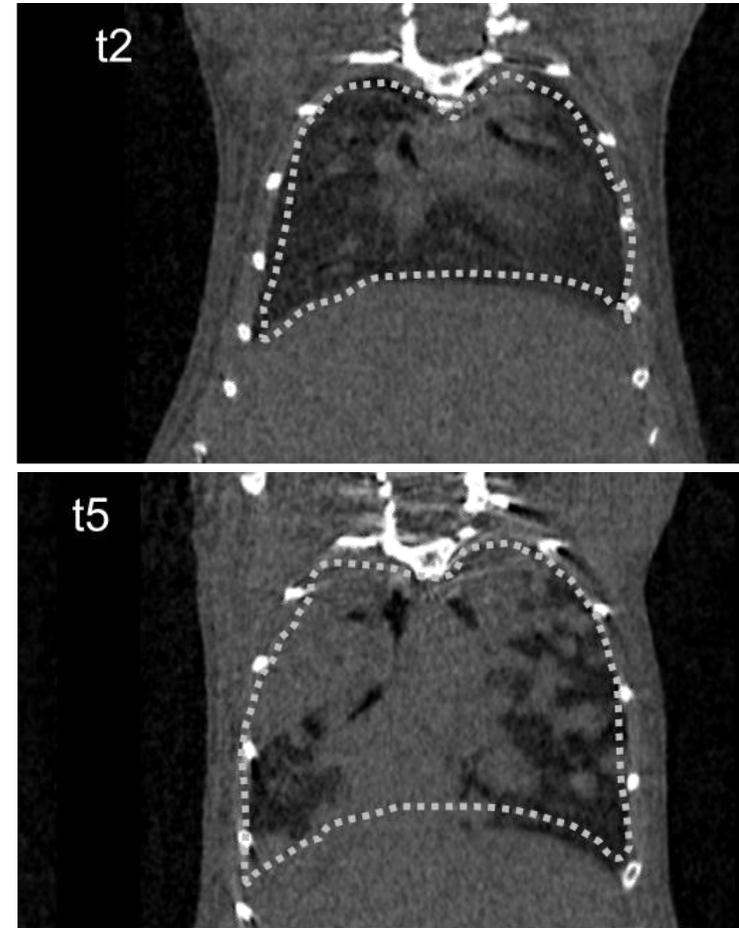
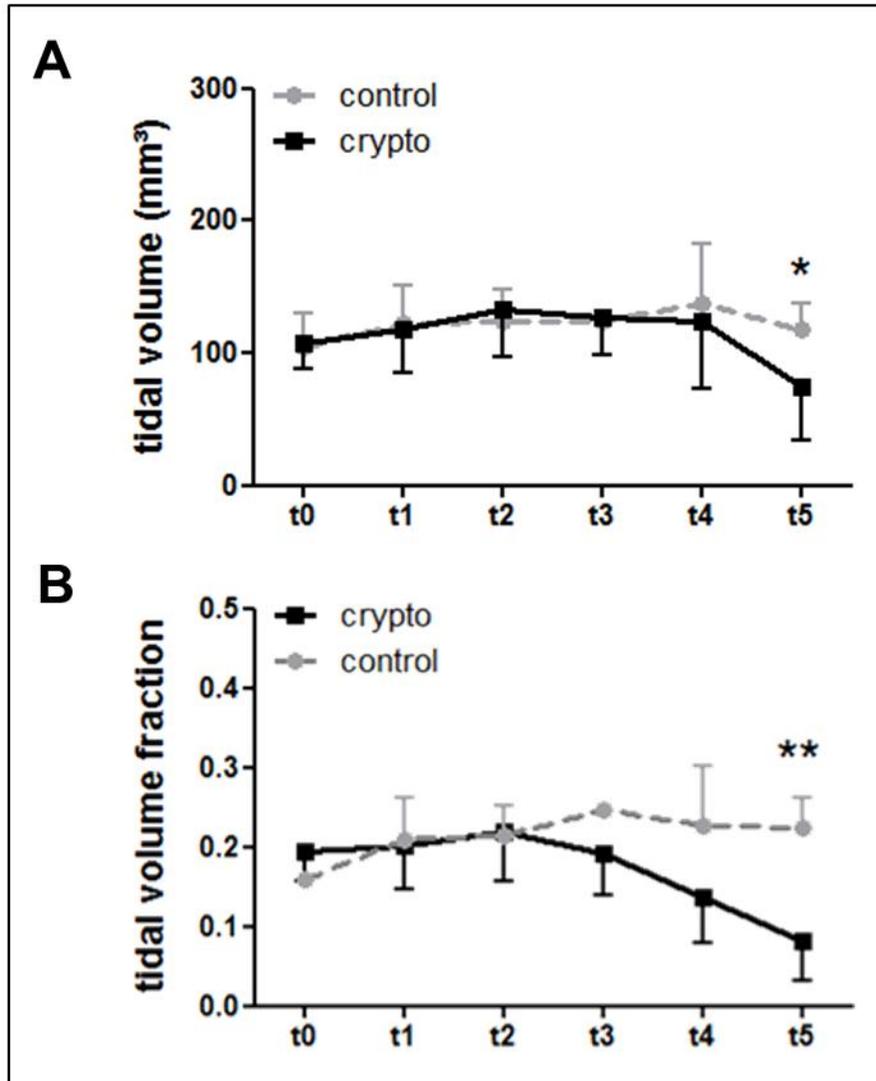
# Lung infection imaging with $\mu$ CT



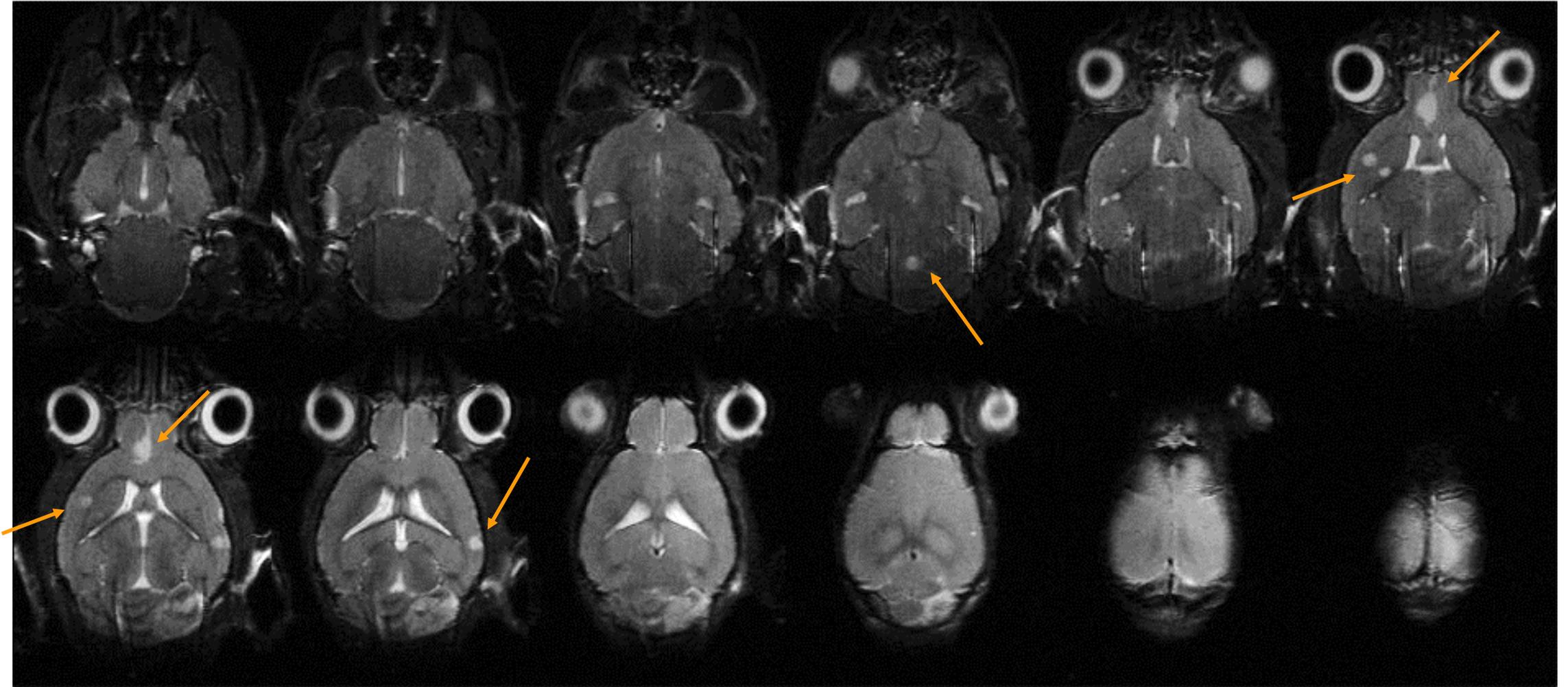
# Lung infection imaging with $\mu$ CT



# Lung infection imaging with $\mu$ CT



# Brain infection imaging with... MRI



# Imaging brain and bones?

## CT

- no soft tissue contrast (CAs)
- Limited anatomical information
- Good contrast for bone & air
- Foreign body detection = good
- Even better resolution
- Potential radiotoxicity
- 3D (4D, 5D)
- Easy to use
- cheap



## MRI

- Good soft tissue contrast
- anatomical information
- Bad contrast for bone & air
- Foreign body -> artefacts
- Good resolution
- No ionizing radiation
- 3D
- Versatile – complicated
- expensive

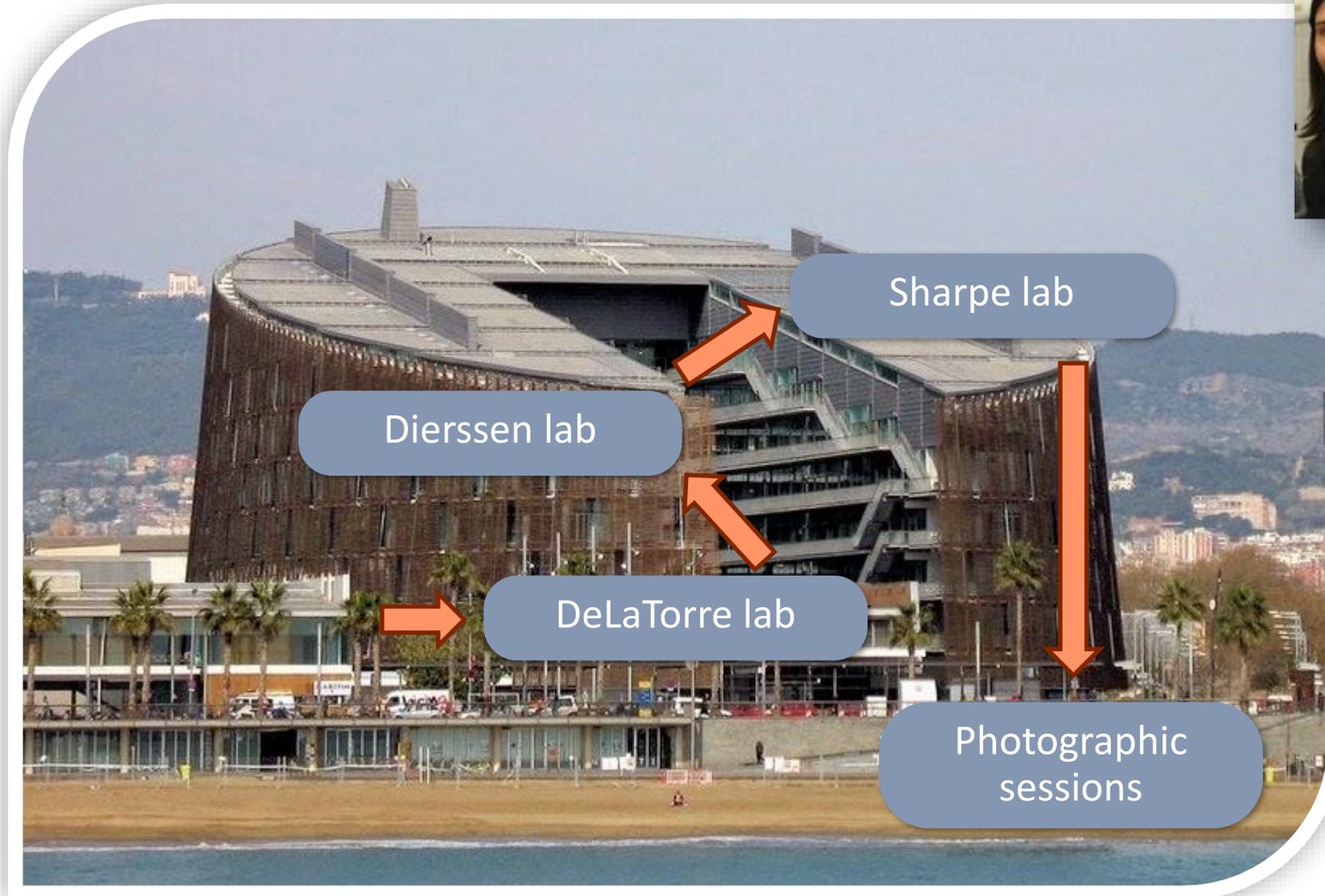


*A multimodal imaging approach combines the pro's of individual methods*

# Let's go to Barcelona !



Neus Martínez-  
Abadías



# Let's go to Barcelona !



Neus Martínez-  
Abadías

The collage illustrates the process of facial scanning. It features a 3D rig of four cameras, a software interface showing a grid of photos and a large image of a baby's face, a 3D orange model of a baby's head with blue tracking points, and a 3D grey model of a baby's face with multi-colored tracking points.

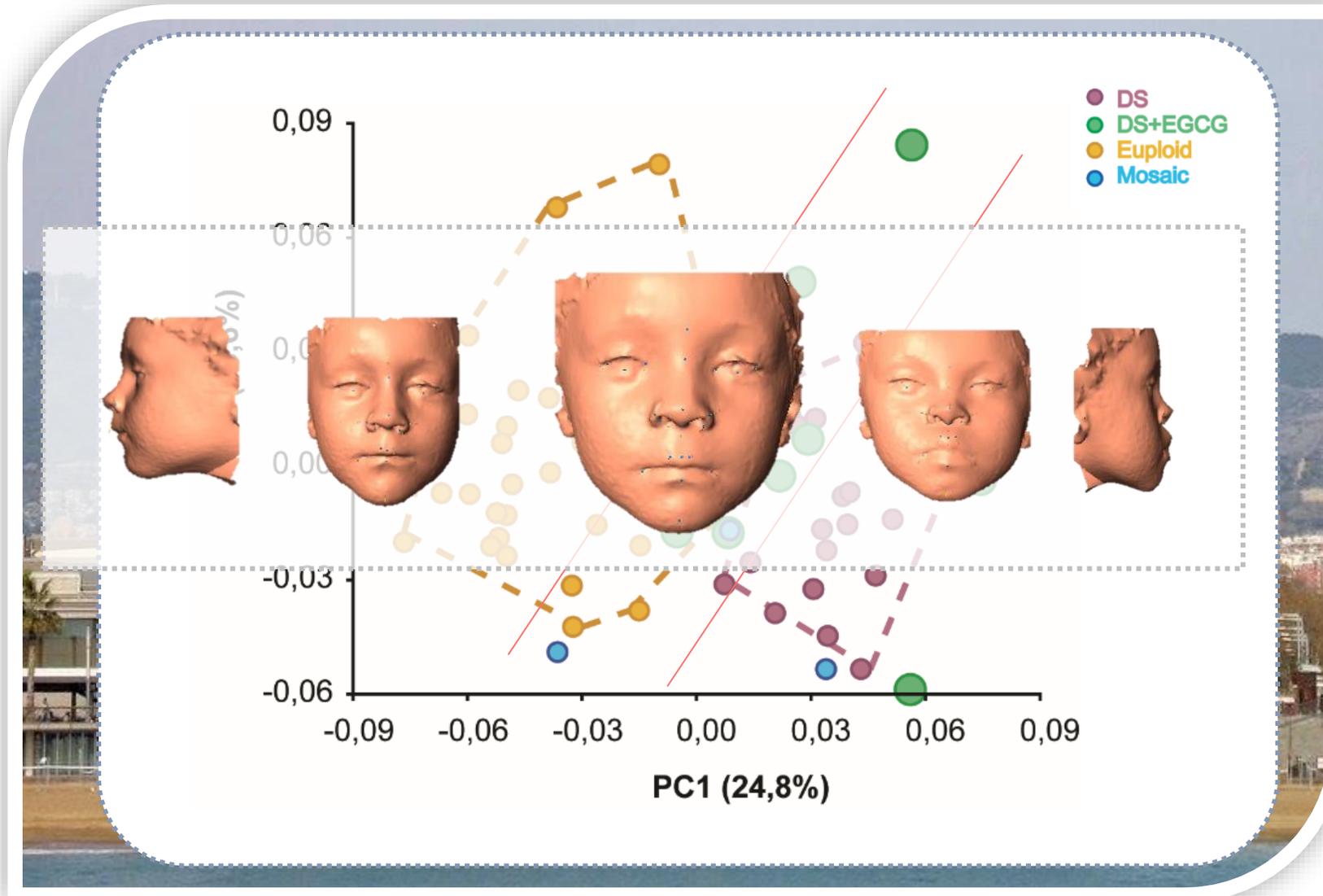
Sharpe lab



Photographic sessions



# Effect of green tea extract (EGCG) on facial shape?

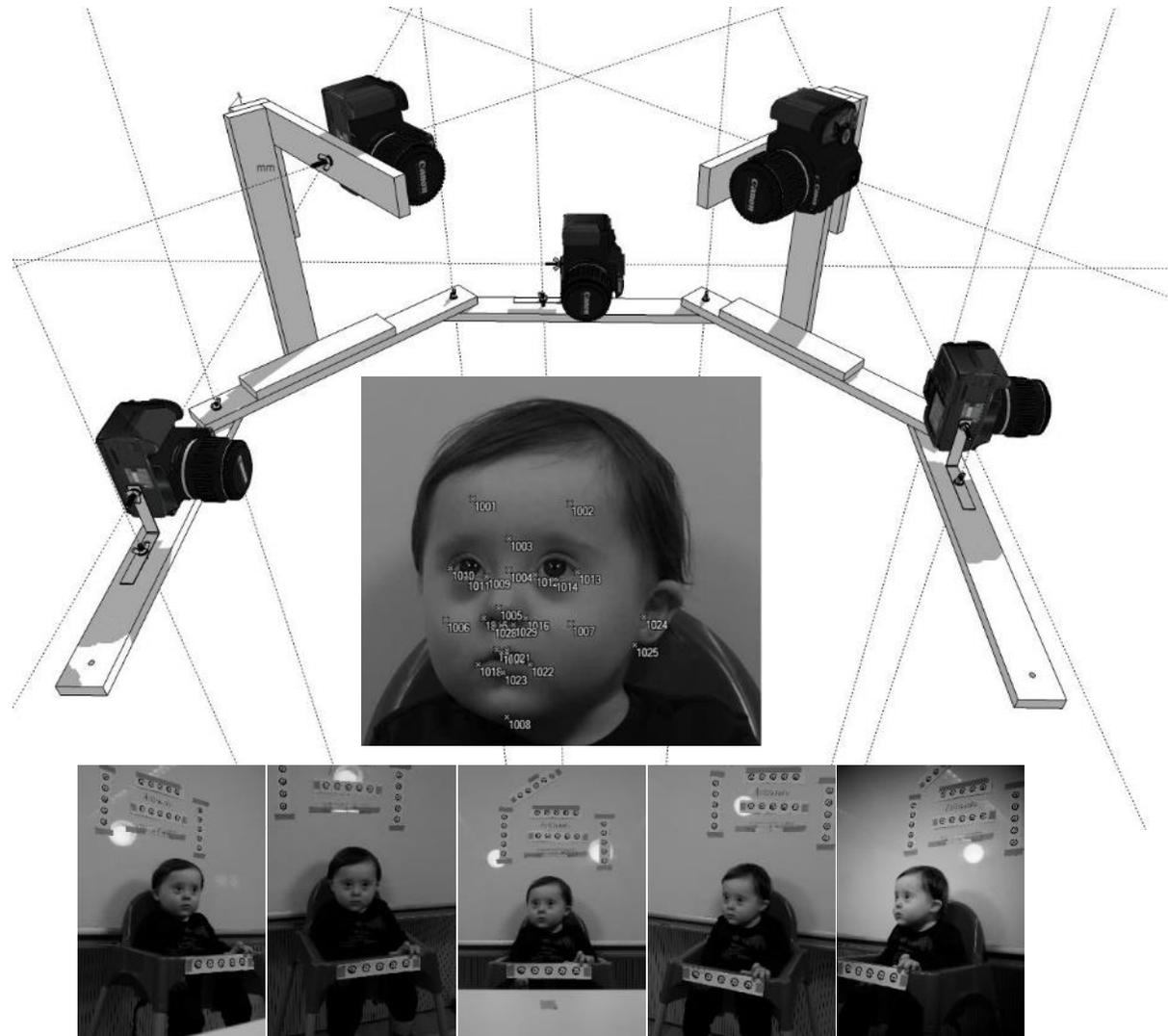


# Testing the hypothesis

Comparative facial shape analysis (0-2 years old)  
European population



# Photogrammetry

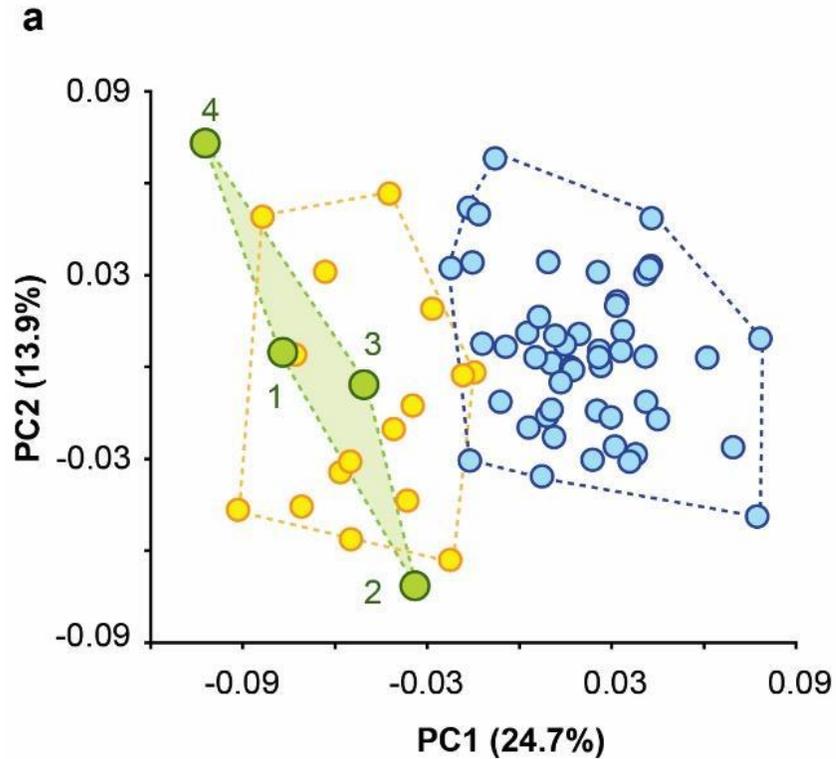


# Photogrammetry

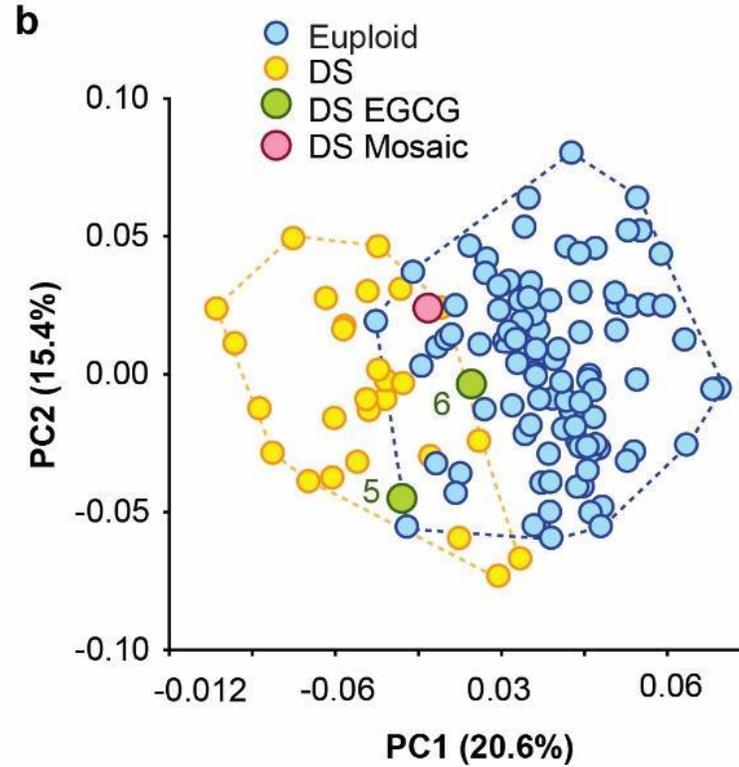


# DS+EGCG → intermediate phenotype

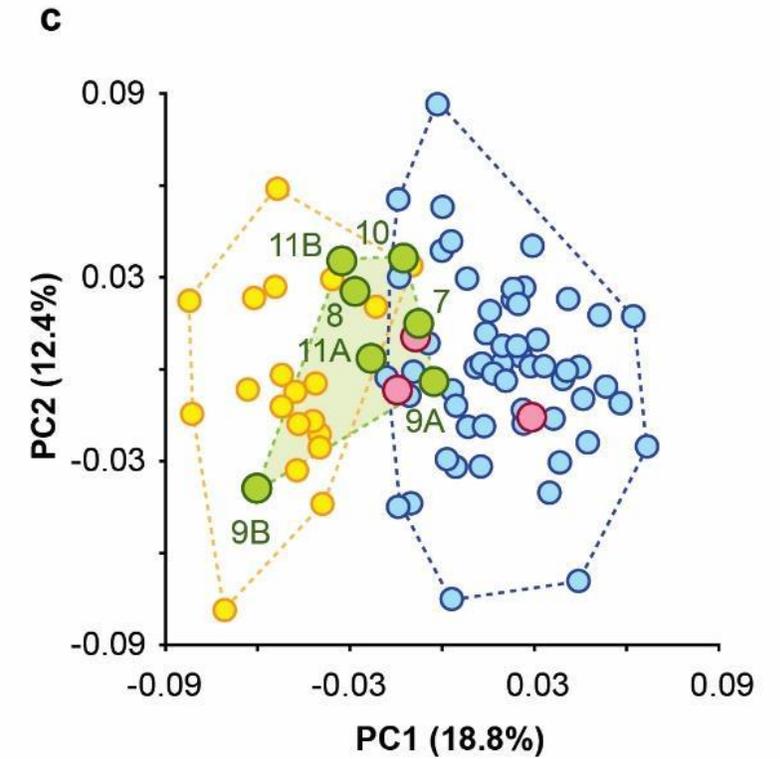
13 to 18 years old



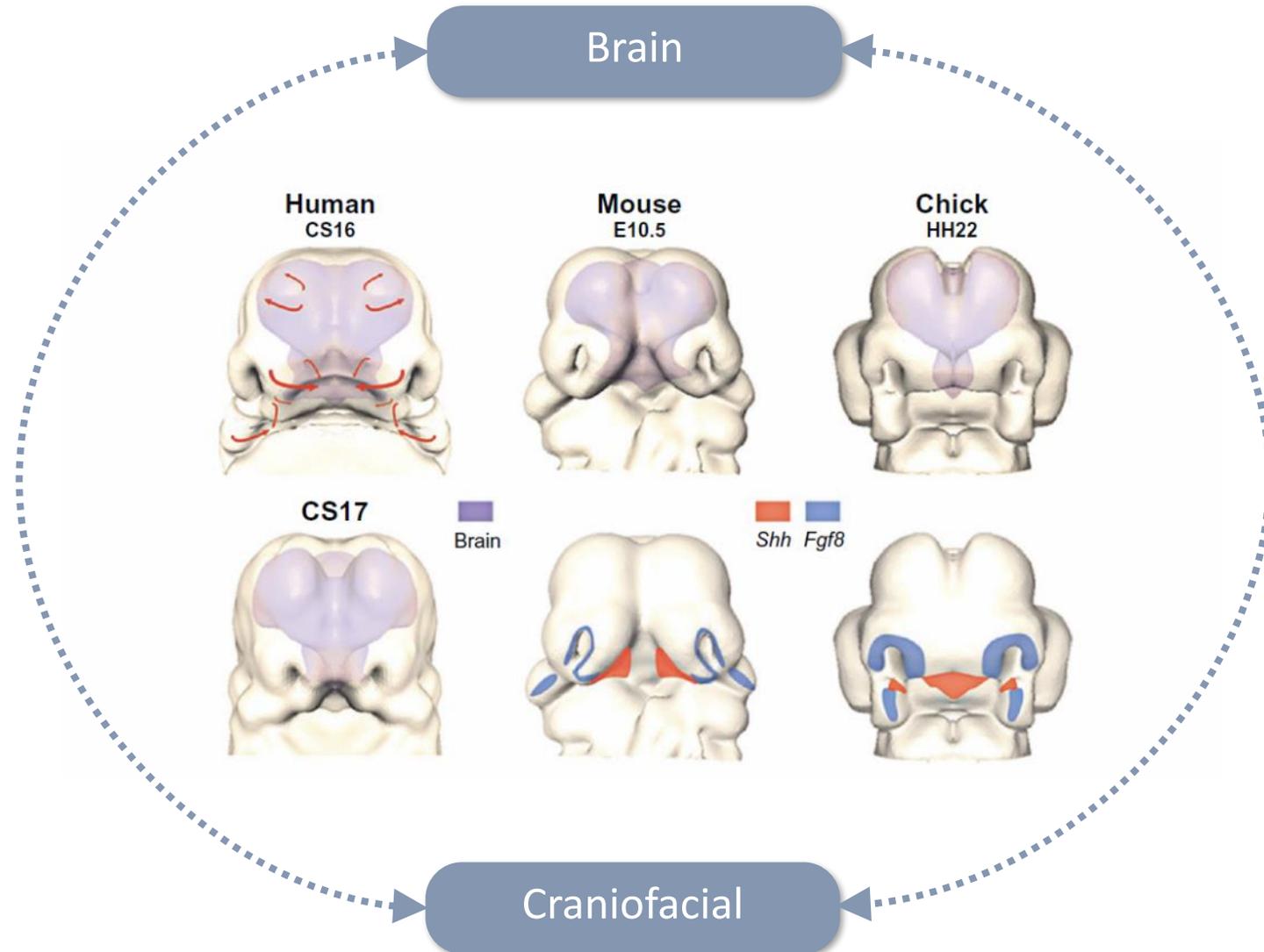
4 to 12 years old



0 to 3 years old

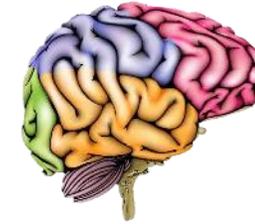


# Brain and face: integration of two developing systems

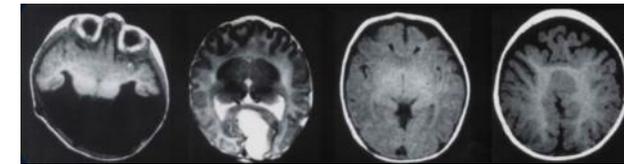


Marcucio et al, *Curr Top Dev Biol*, 2015

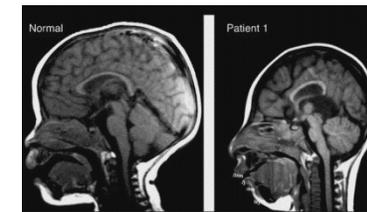
# Brain and face: integration of two developing systems



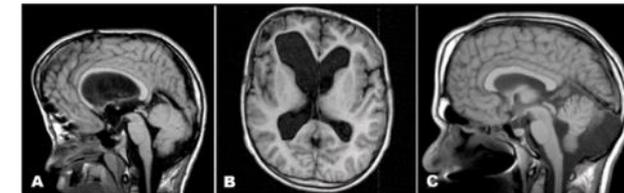
Holoprosencephaly



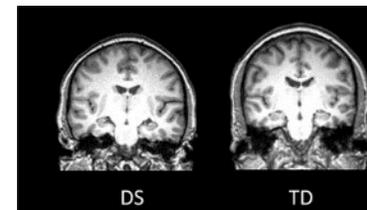
Microcephaly



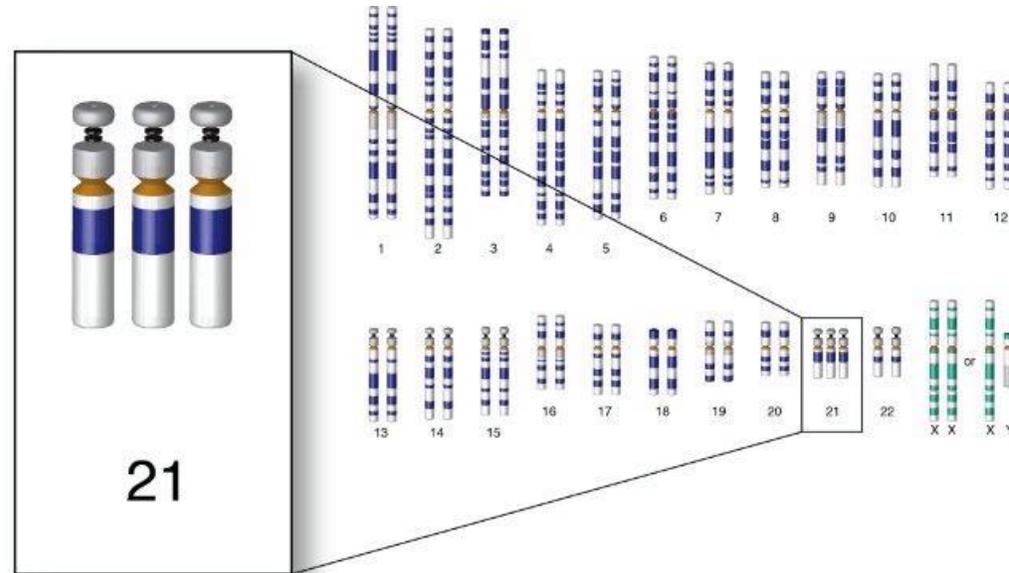
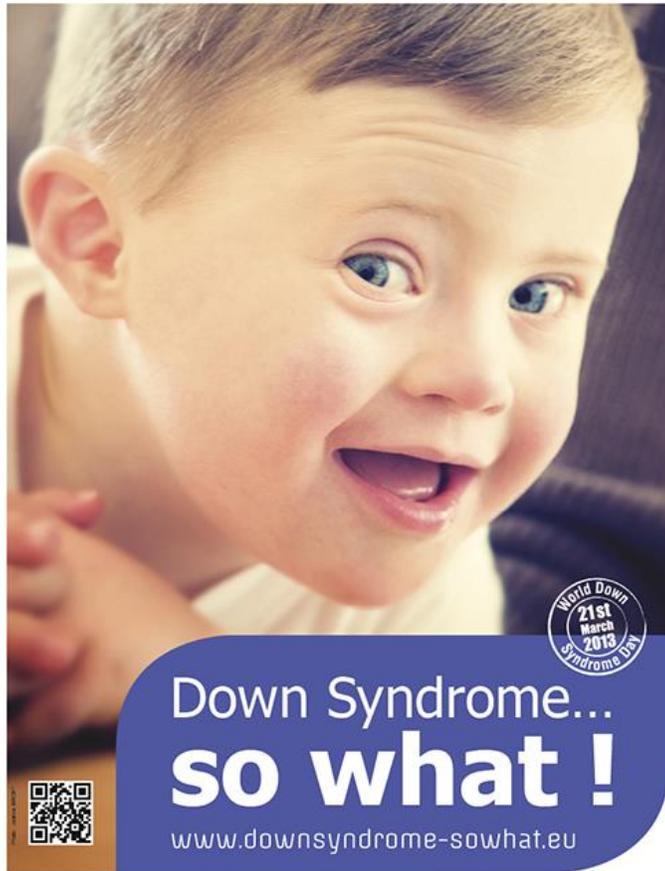
Apert syndrome



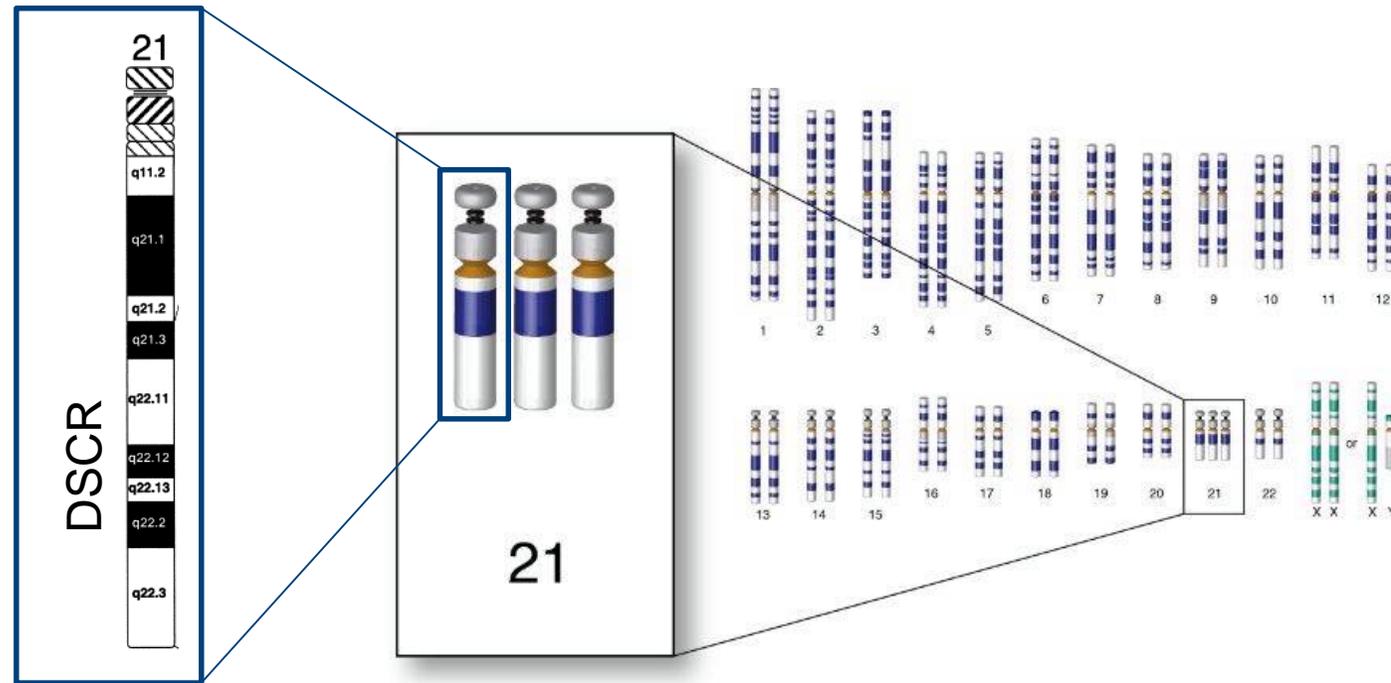
Down syndrome



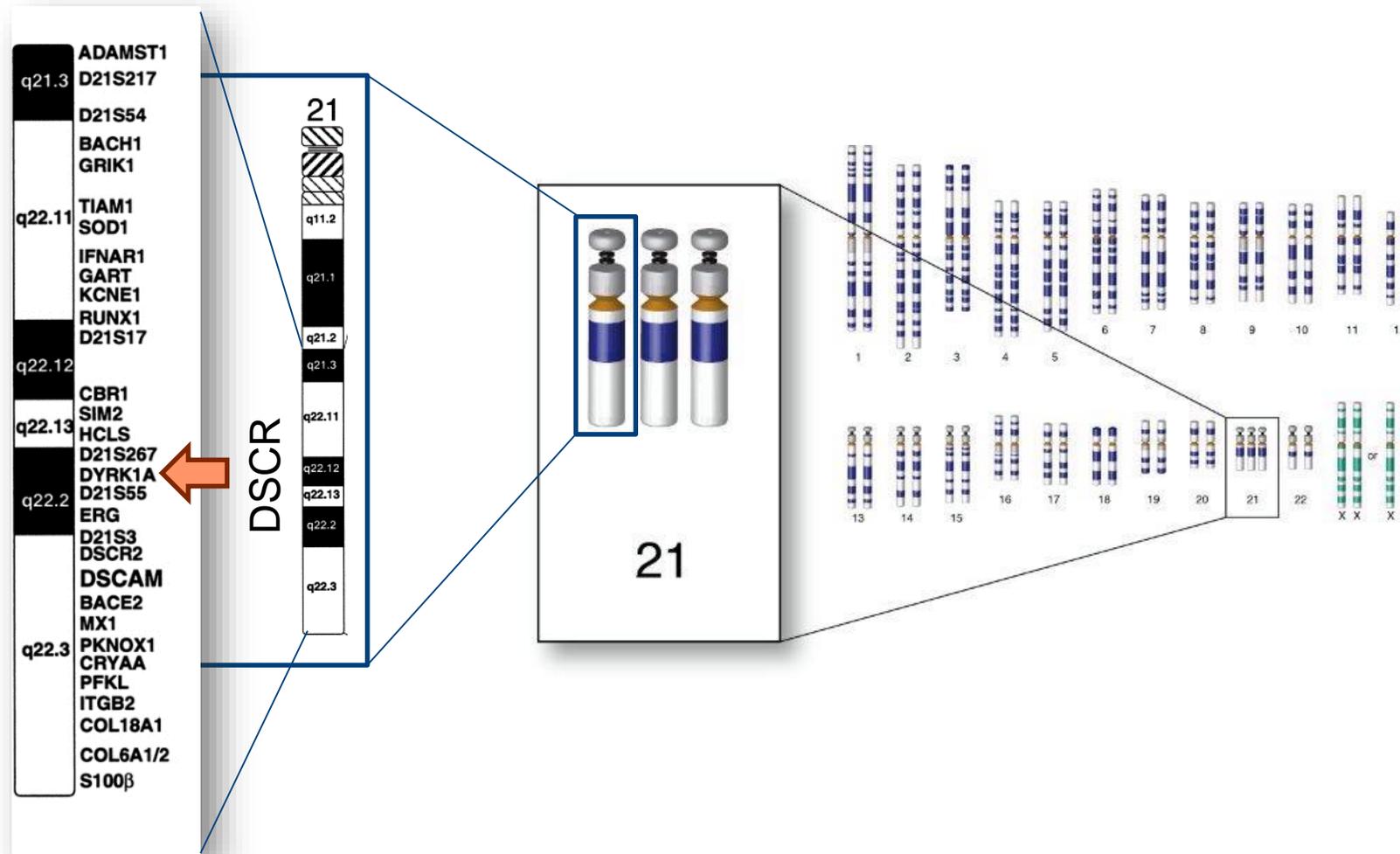
# Down syndrome: Trisomy 21



# Down syndrome: Trisomy 21



# Down syndrome: Trisomy 21



# DYRK1A overexpression in Down syndrome



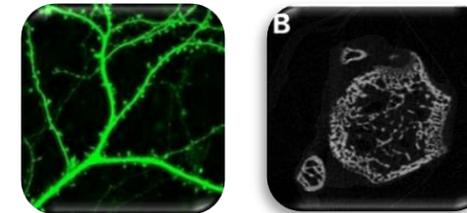
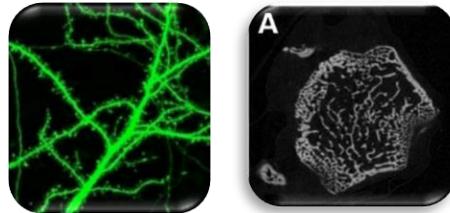
2 copies DYRK1A



3 copies DYRK1A

Euploid

Down syndrome



$H_0$

*Dierssen, Nat Rev Neurosci 2013*  
*Blazek et al, Hum Mol Gen, 2015*

Reduce Dyrk1A expression



Epigallocatechin gallate (EGCG)

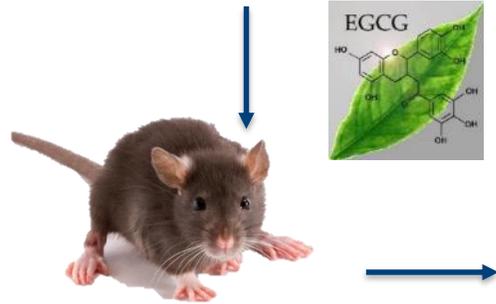
(Slide courtesy: Dr. Neus Martinez Abadias)

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# Experimental analysis on mouse models

Perform longitudinal morphometric study of a Down syndrome mouse model by *in vivo* non invasive imaging (SkyScan 1278  $\mu$ CT and Bruker 9.4T MRI).

Pregnant Ts65Dn mice treated or not treated (E9)



Pups: Ts65Dn and control mice treated and not-treated pre and perinatally with EGCG.

$\mu$ CT and MRI (Leuven, Belgium)

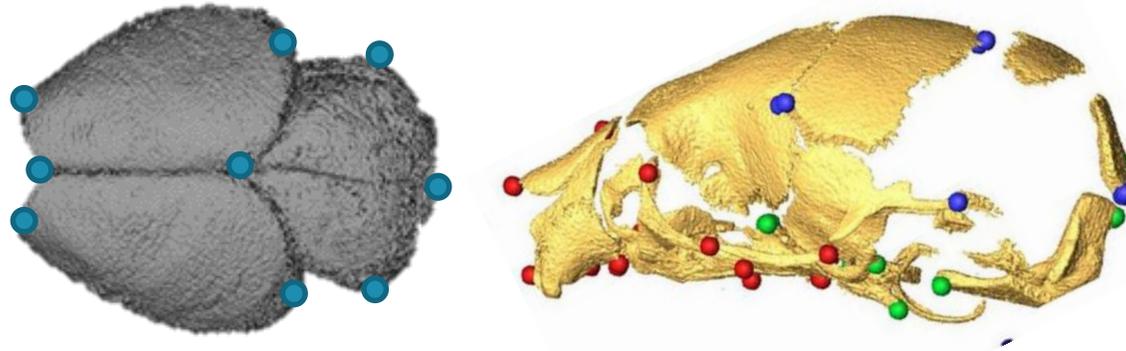


P3  $\longrightarrow$  P14  $\longrightarrow$  P28

Perform neurobehavioral and neurodevelopmental tests

# Experimental analysis on mouse models

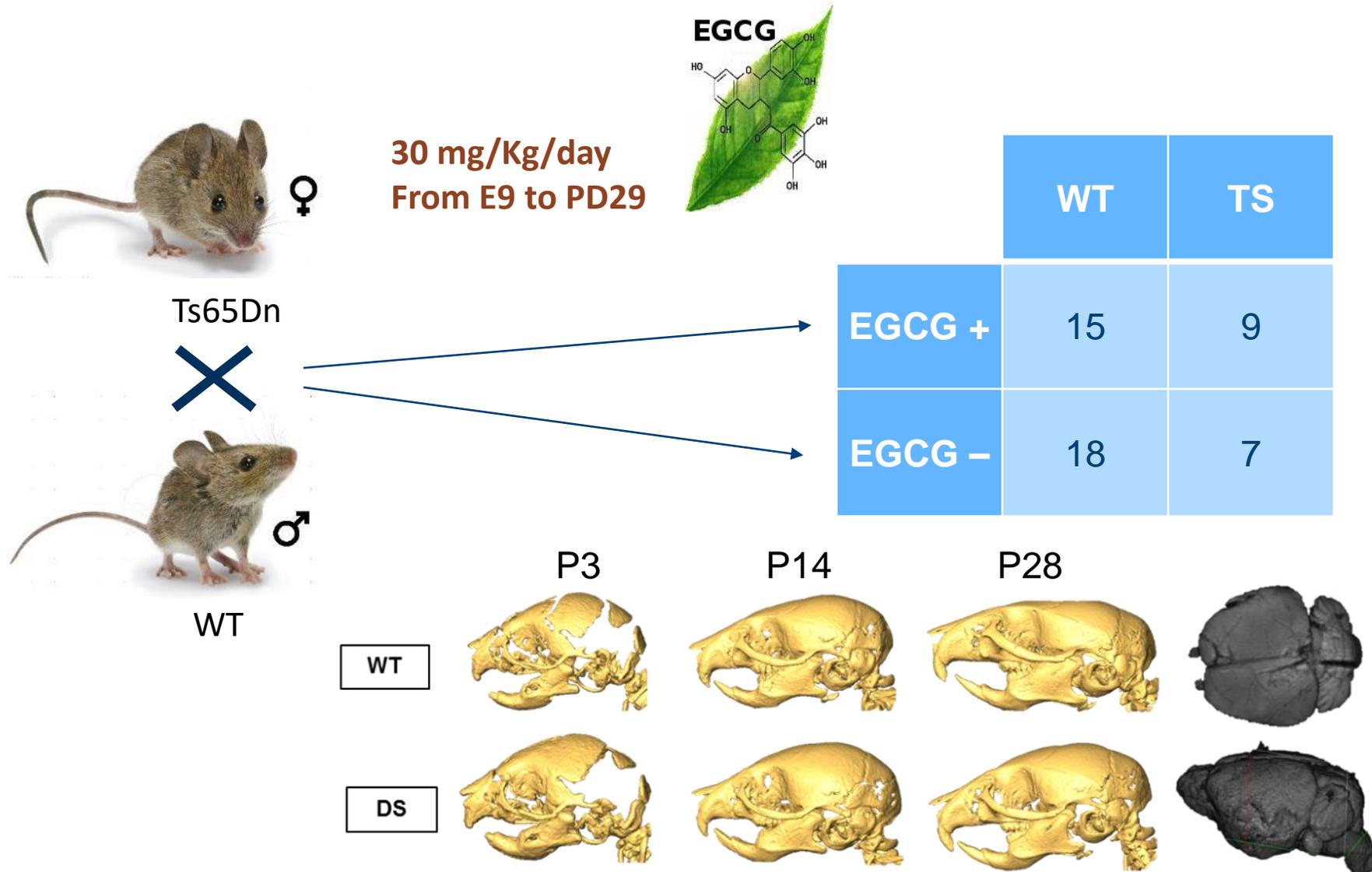
Quantify and compare **normal** and **disease-altered** brain and craniofacial face morphological shape over time.



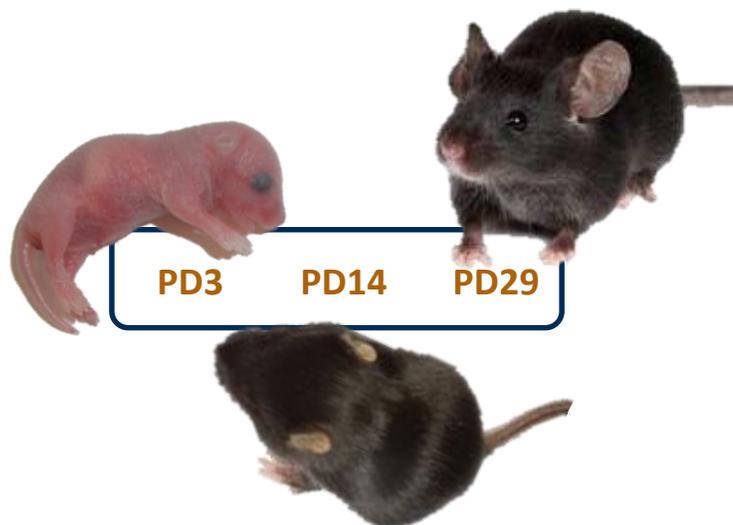
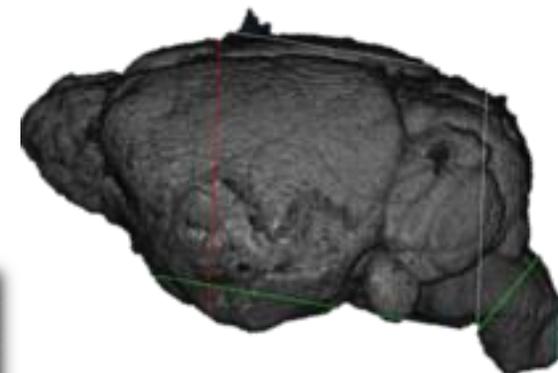
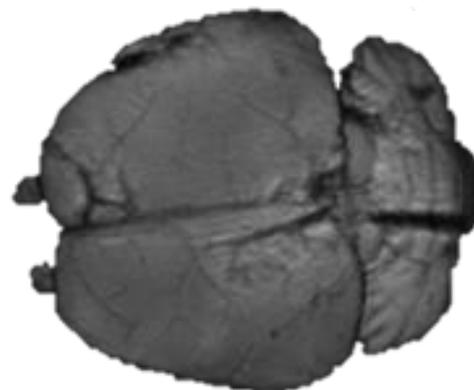
## Geometric morphometrics

Experimentally **modulate** Dyrk1A kinase activity using pharmacological agent (**EGCG**) affecting the development of the brain and the face in order to test its potential effect on their shape and integration pattern.

# The setup



# Brain analysis: MR imaging



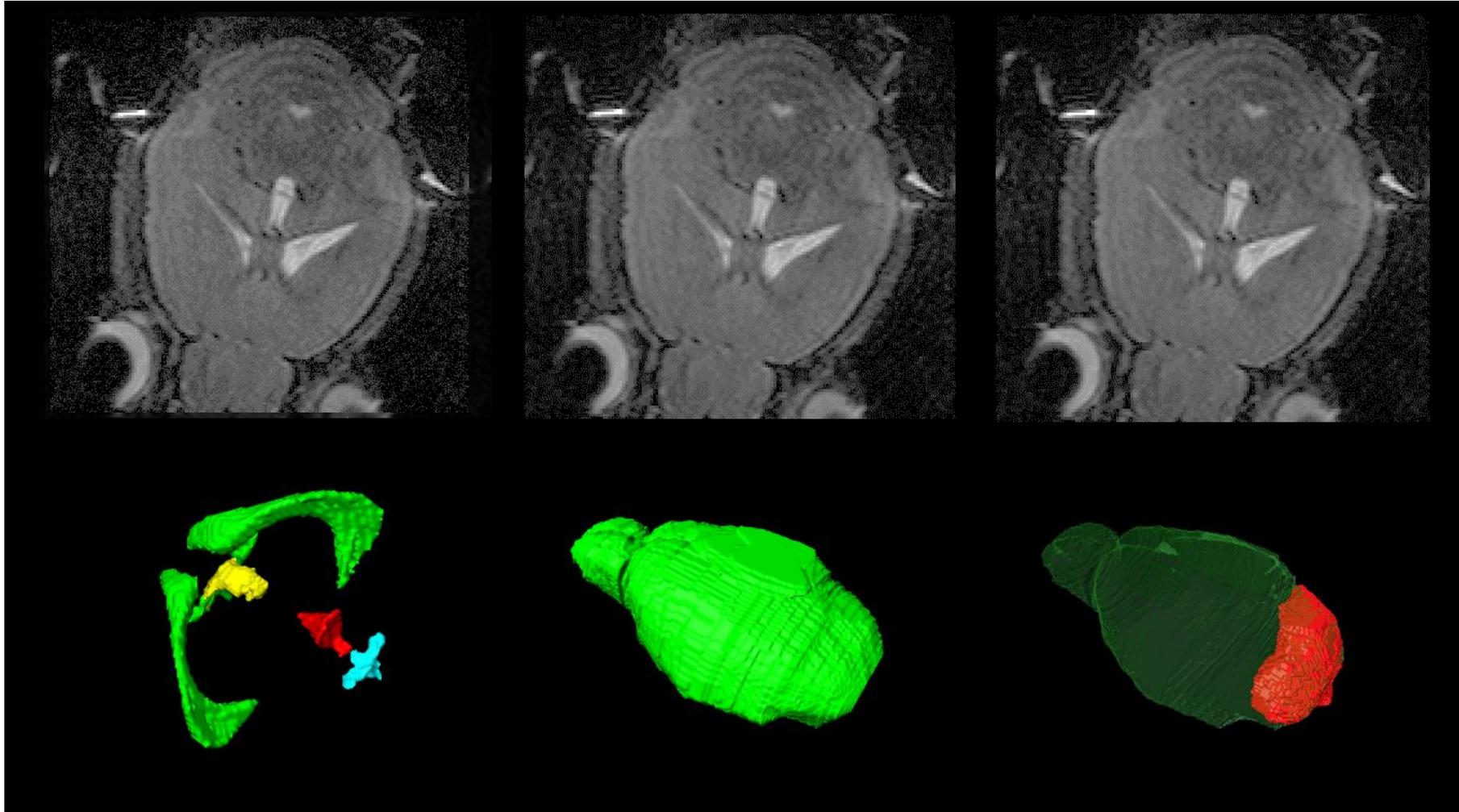
# Brain volume analysis

PD29

Ventricles

Whole brain

Cerebellum



# Brain shape analysis

J. Barbeito-Andrés et al. / Magnetic Resonance Imaging 34 (2016) 980-989

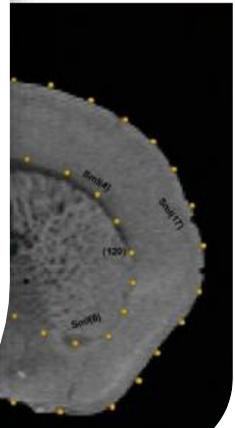
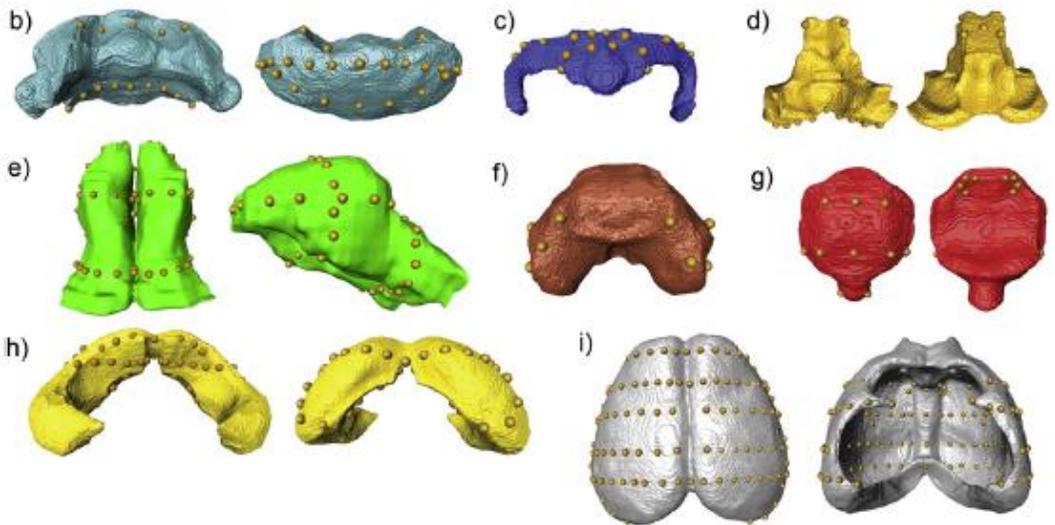
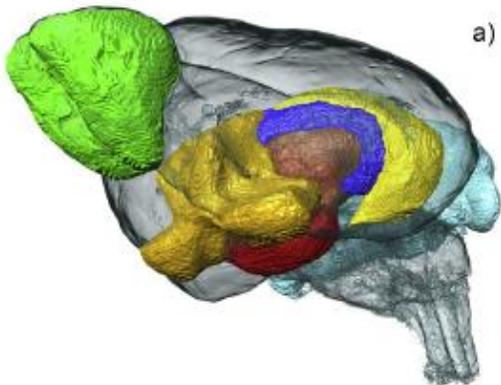
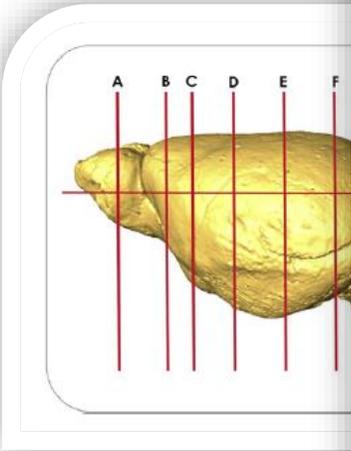
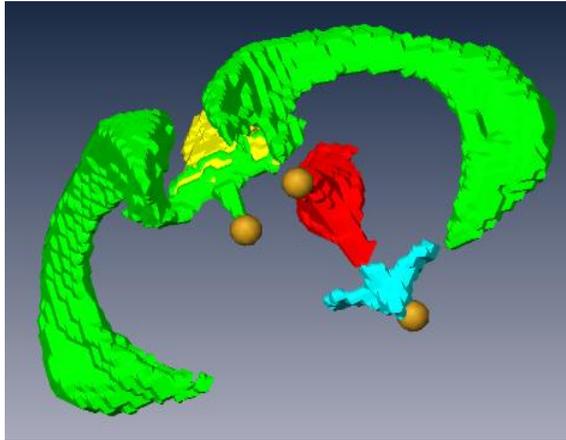


Fig. 3. 3D reconstruction of brain regions displaying the position of landmarks and semilandmarks digitized on A-H planes. Whole brain (a), cerebellum (b), fimbria (c), forebrain septum (d), olfactory bulbs (e), thalamus (f), hypothalamus (g), hippocampus (h) and (i) neocortex.

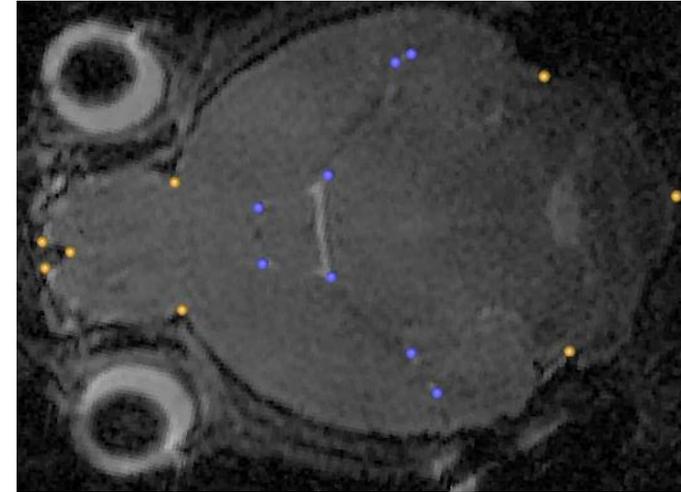
# Brain shape analysis: landmarking

PD29

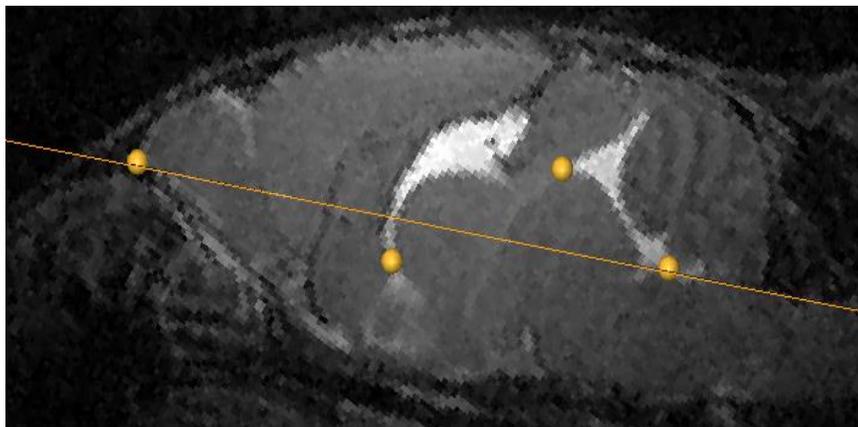
Positioning



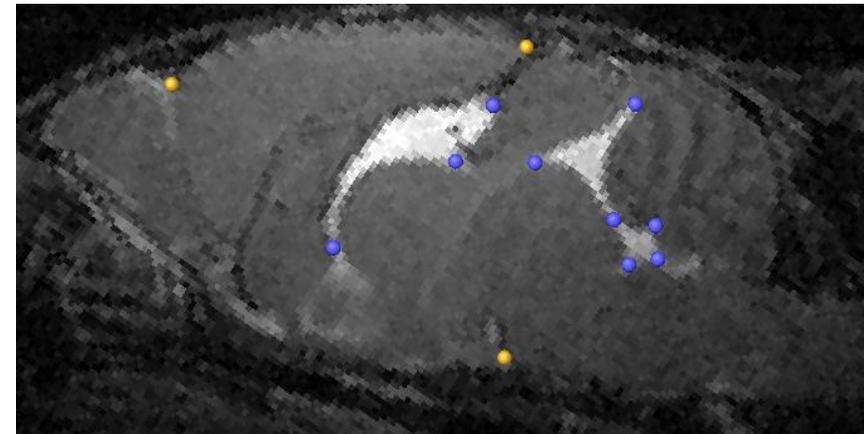
Axial



Sagittal + Axial



Sagittal



# Brain landmarking

PD29

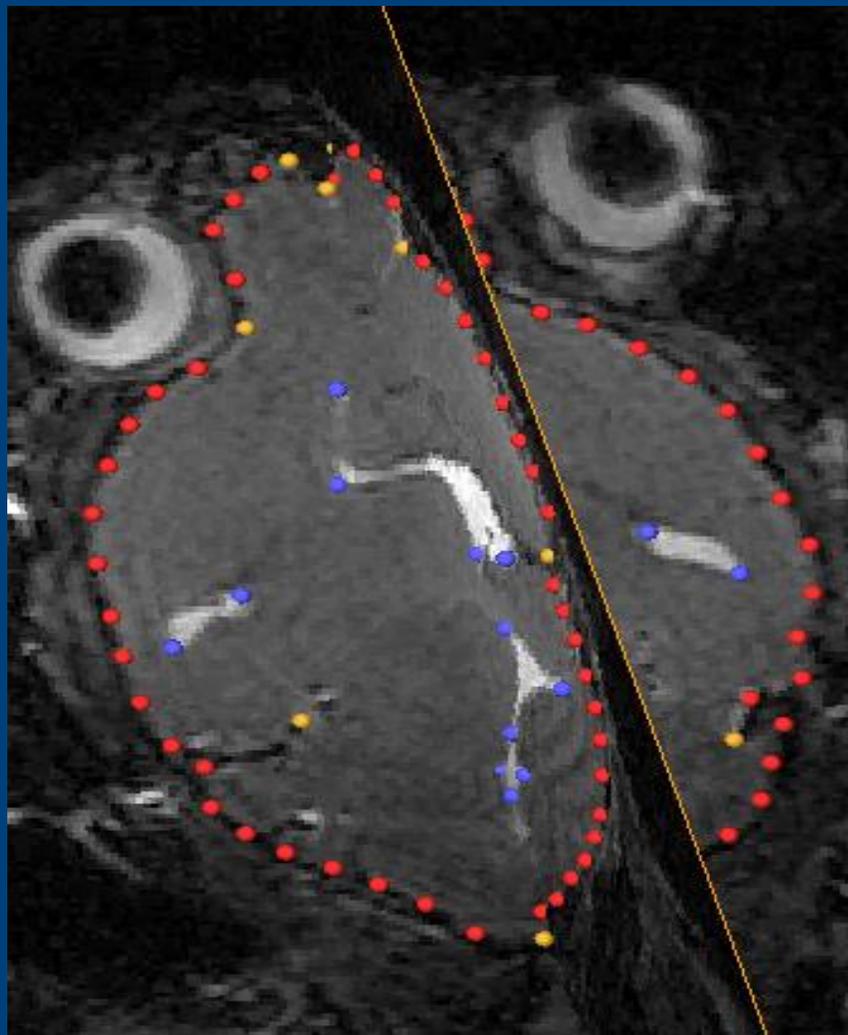
Anatomical landmarks  
external

Anatomical landmarks  
internal

Surface  
semilandmarks

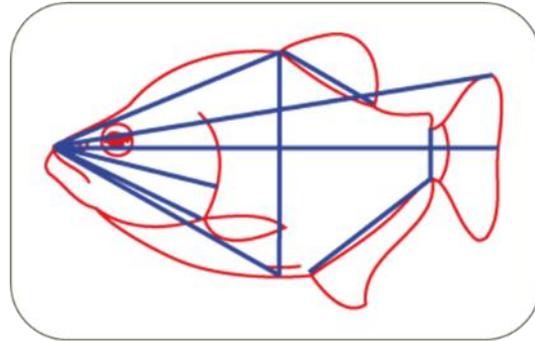
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270 landmarks

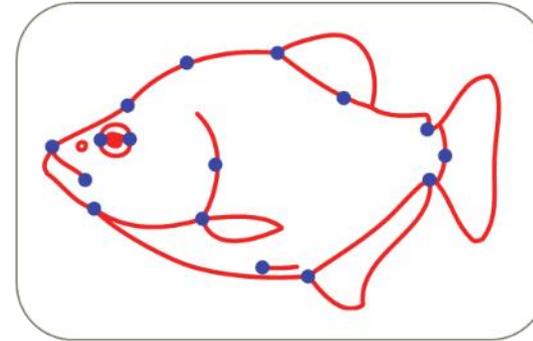


# Shape analysis: Geometric Morphometrics

How to describe the shape of an organism

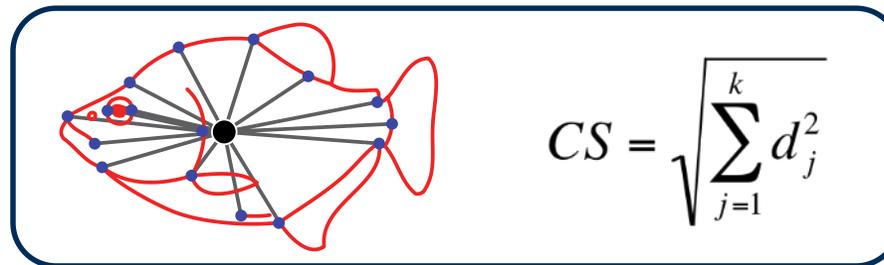


Linear measurements

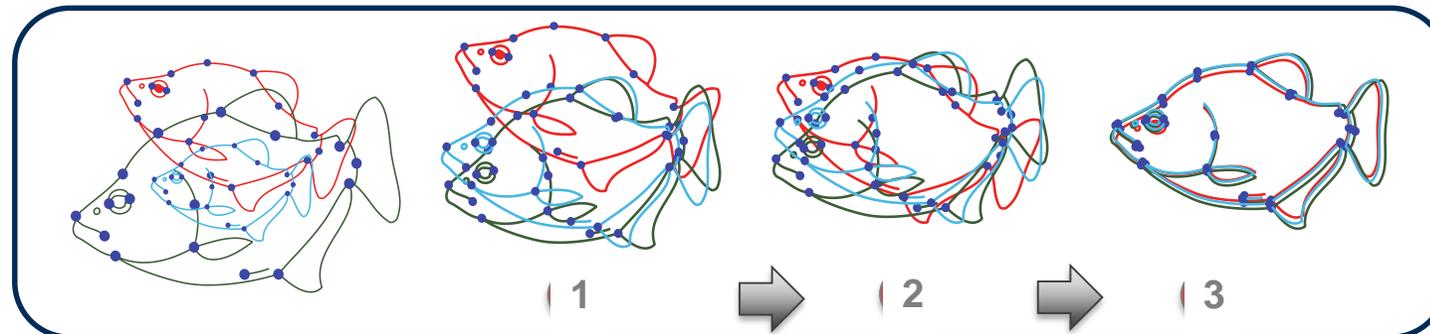


Anatomical landmarks

Centroid size



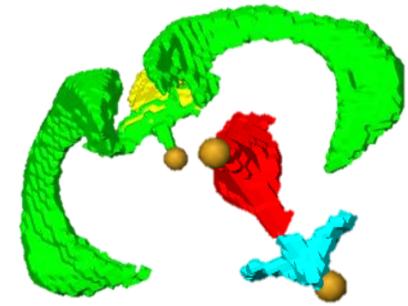
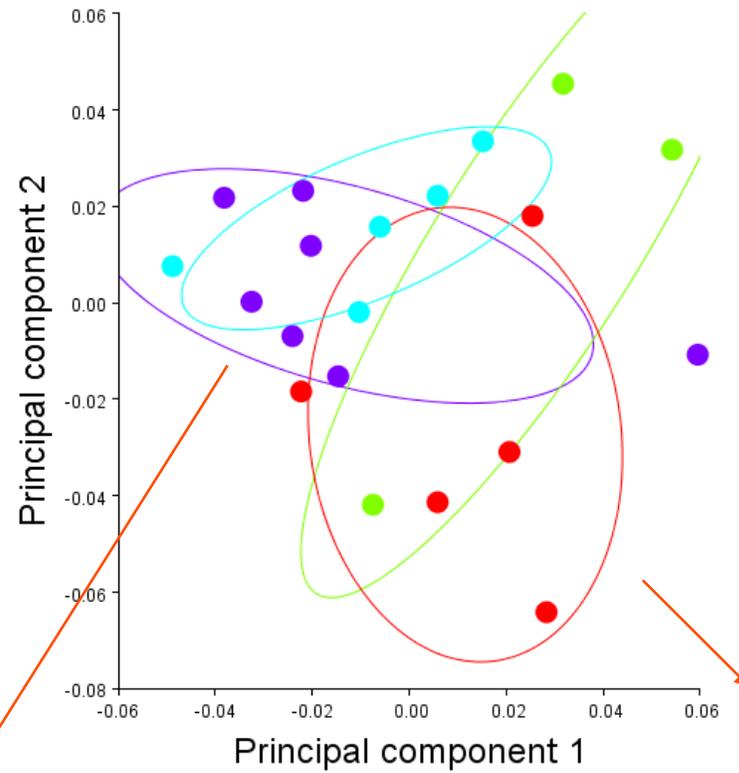
Procrustes fit



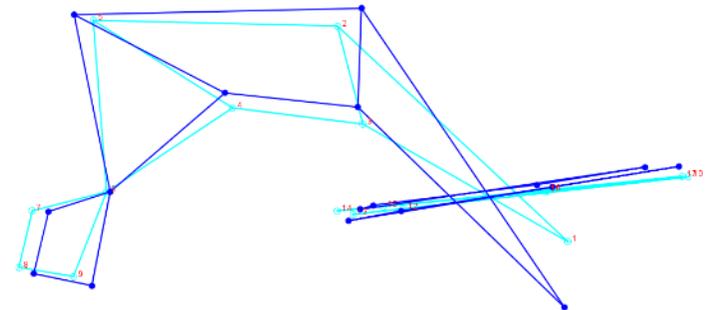
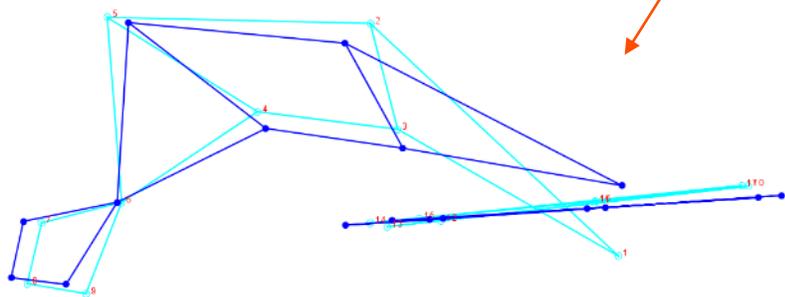
# Brain shape analysis

PD29

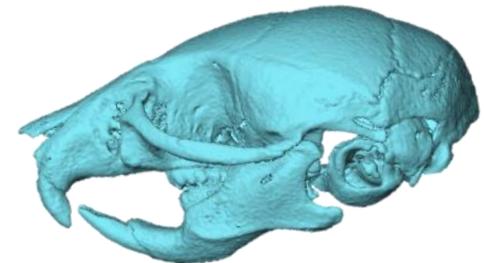
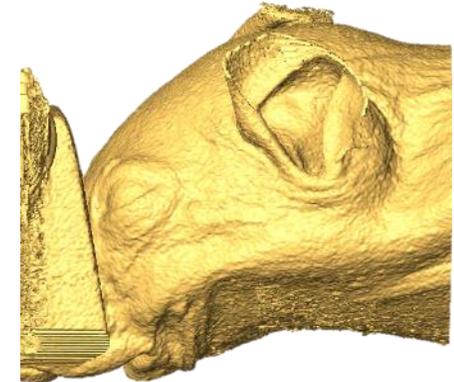
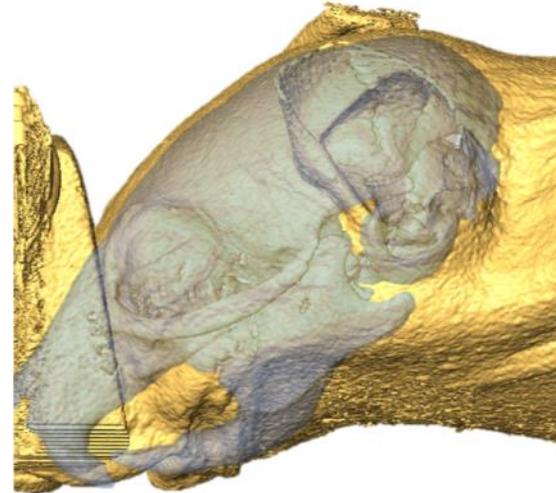
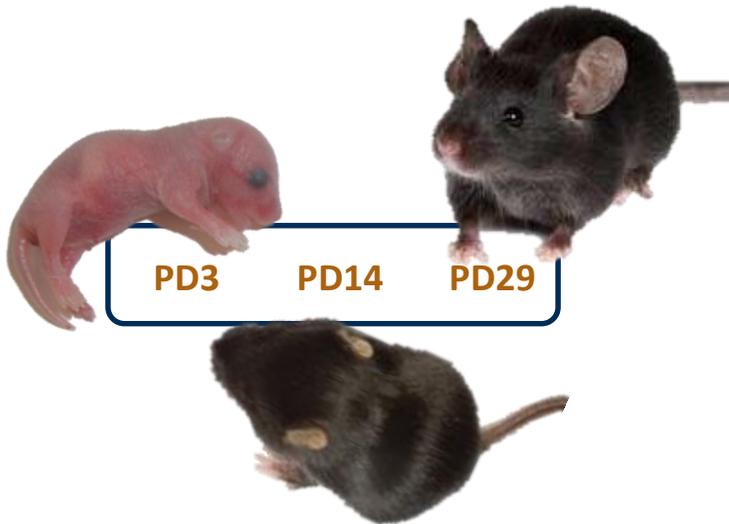
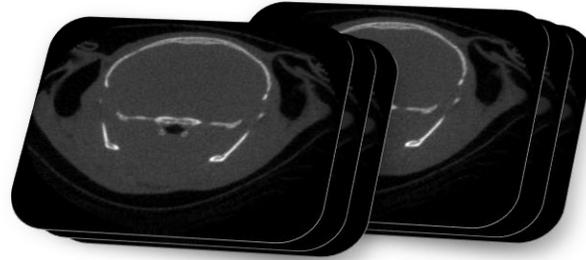
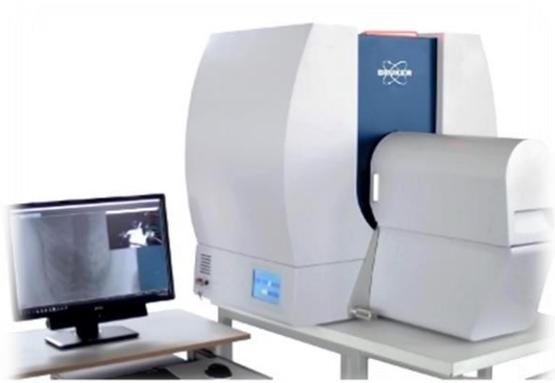
TS\_Treated  
TS\_Untreated  
WT\_Treated  
WT\_Untreated



17 landmarks



# Craniofacial analysis: micro-CT



# Craniofacial analysis: micro-CT

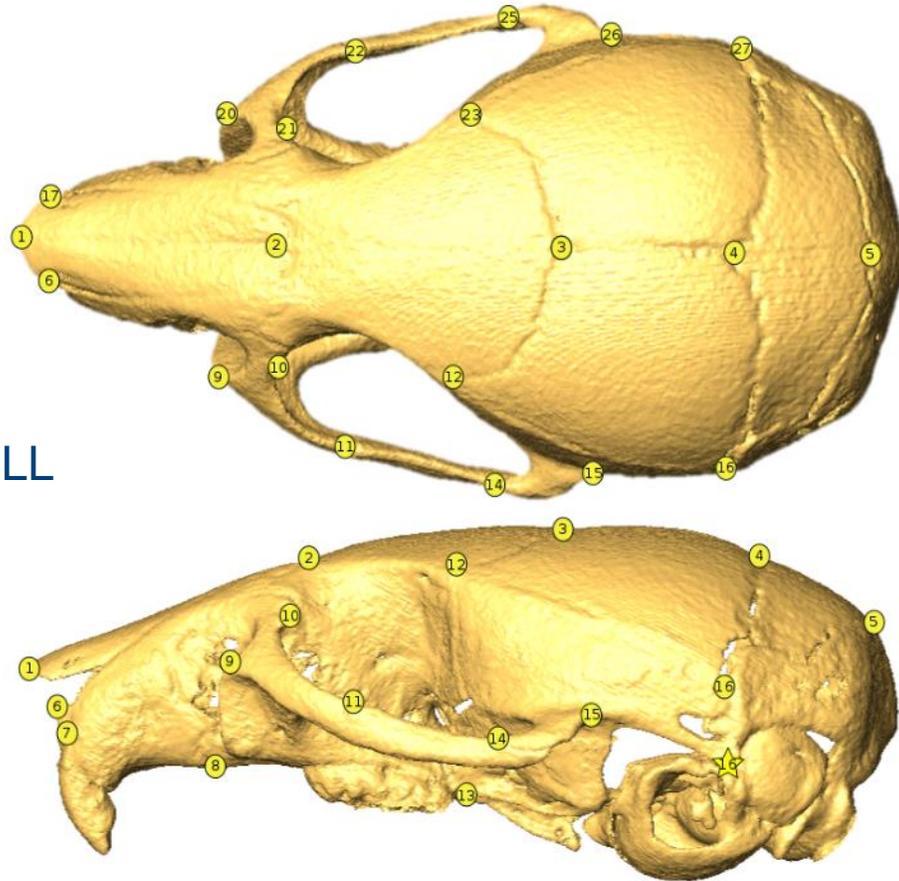
## SKELETAL ALTERATIONS IN EGCG-TREATED MICE



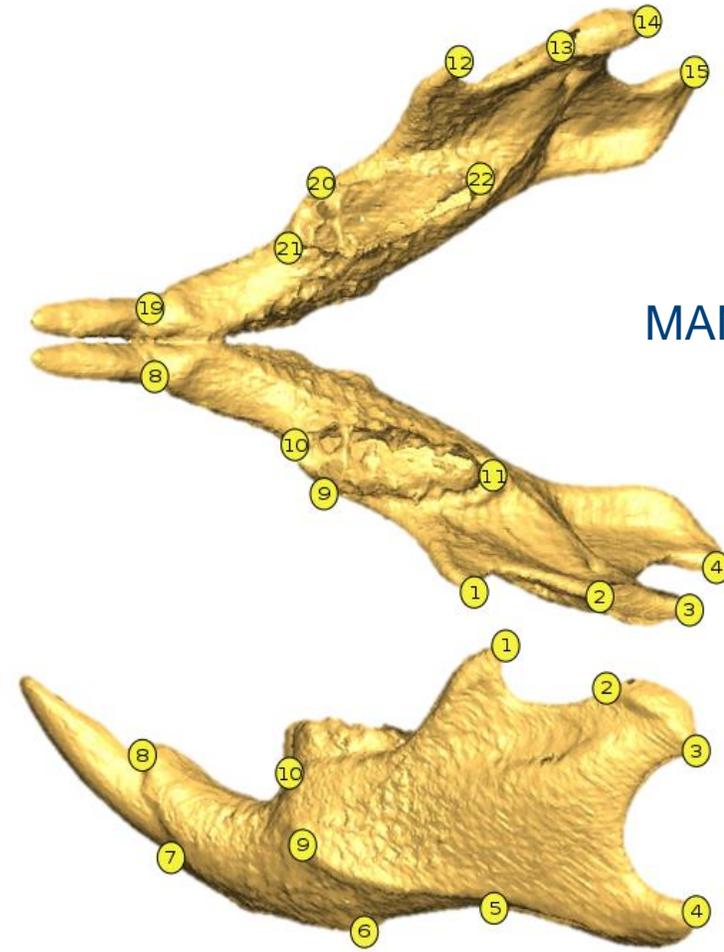
# Craniofacial landmarking

Set of 27 anatomical landmarks in the skull (34 at PD3) and 22 in the mandible

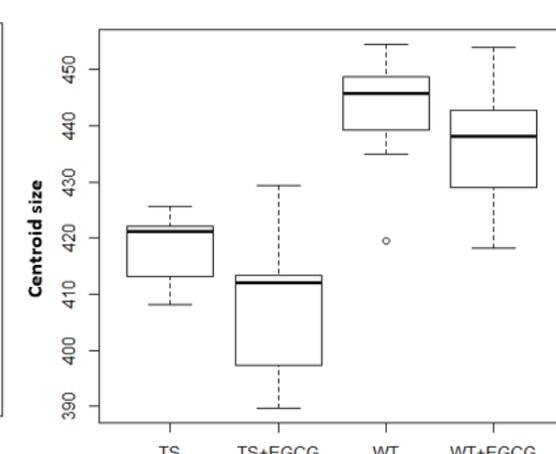
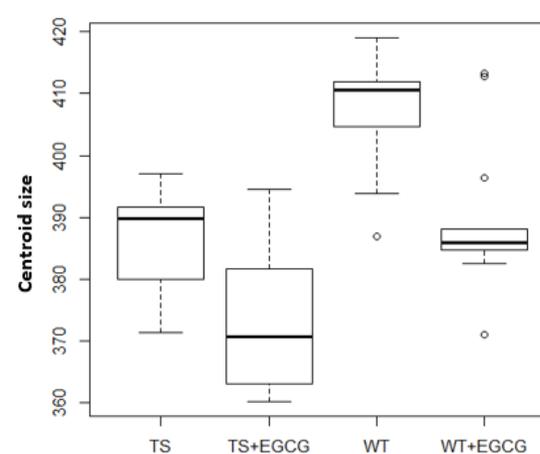
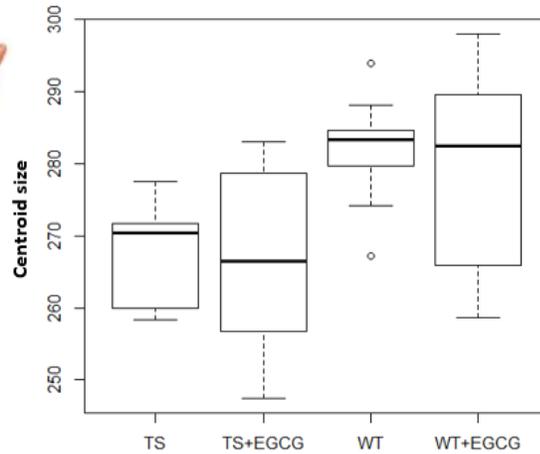
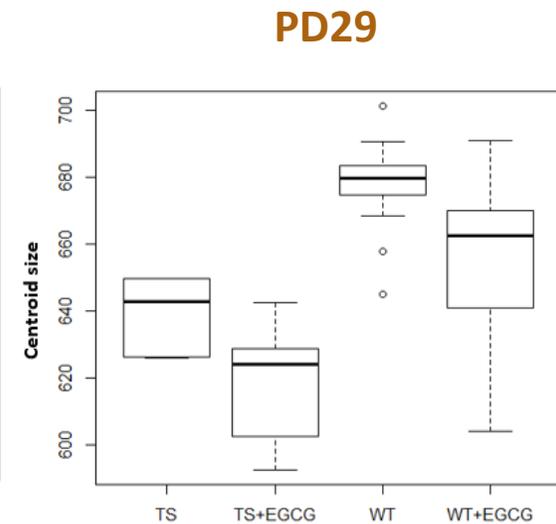
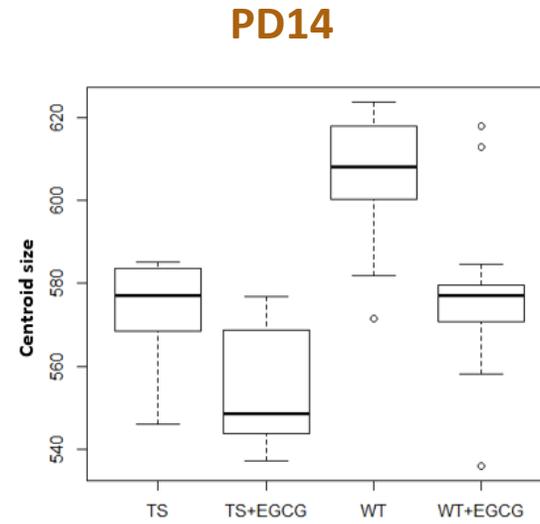
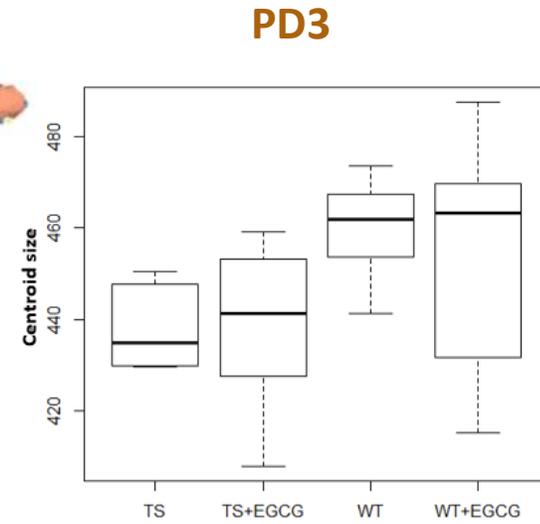
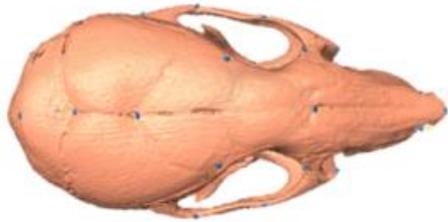
SKULL



MANDIBLE



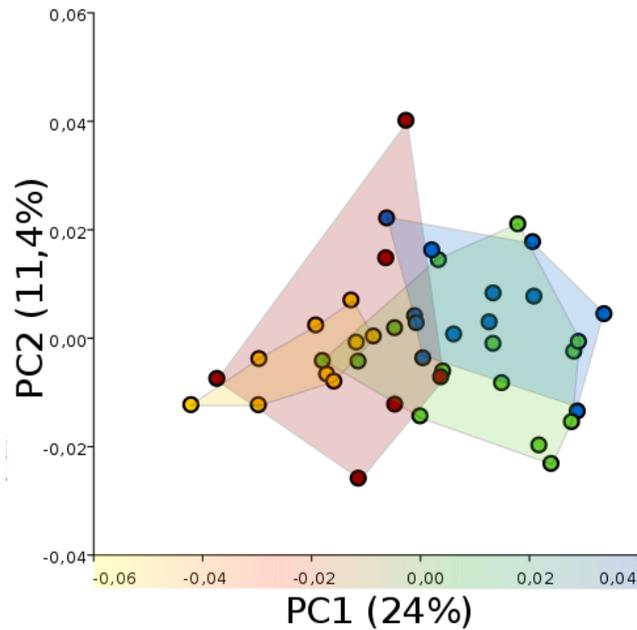
# Craniofacial size analysis



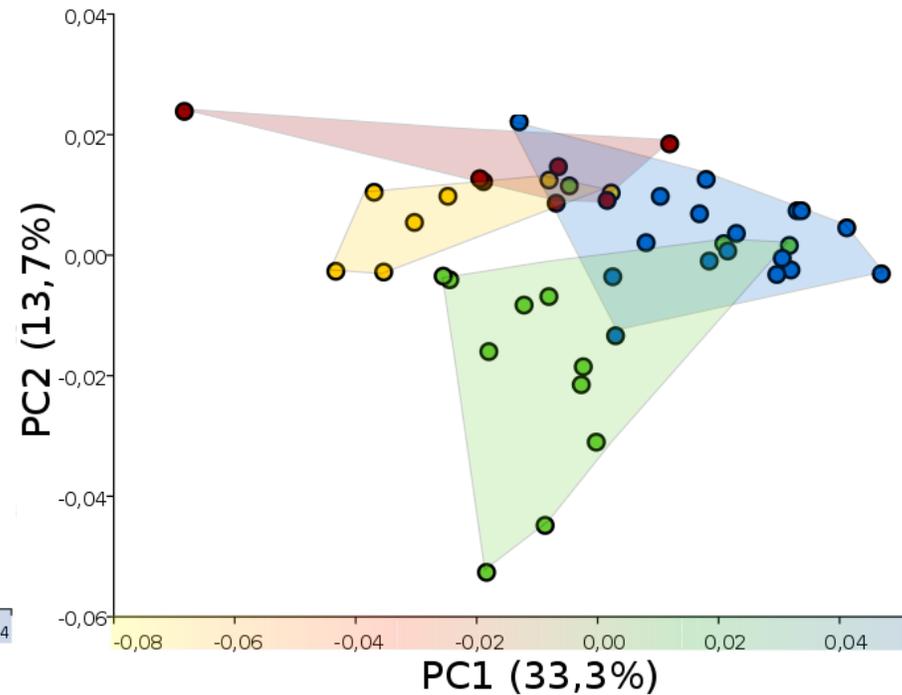
# Craniofacial *shape* analysis

## SKULL

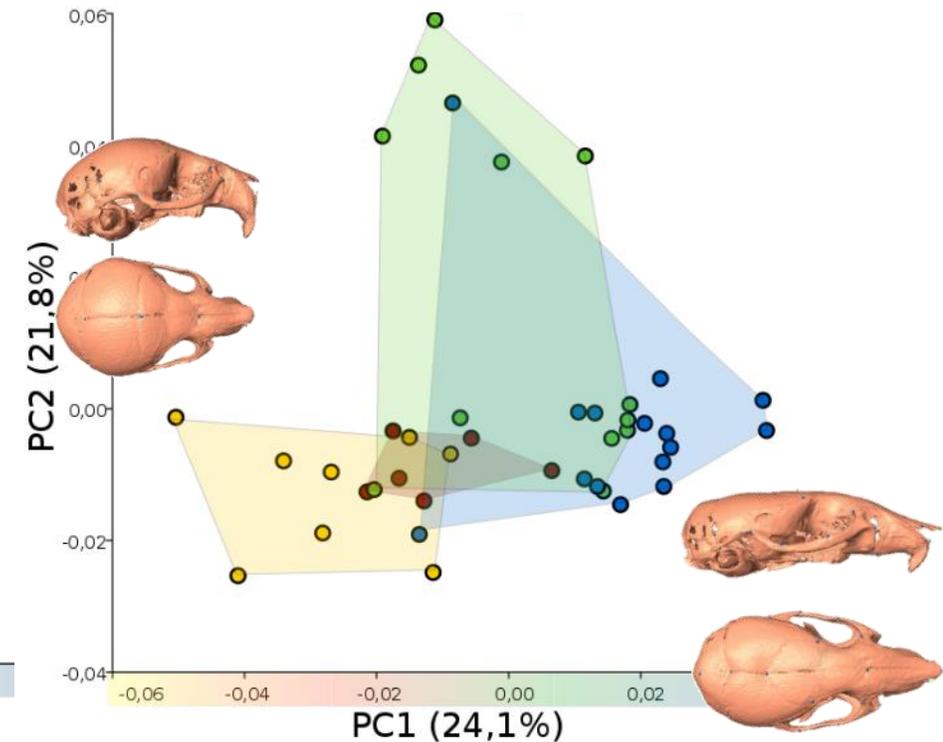
PD3



PD14



PD29



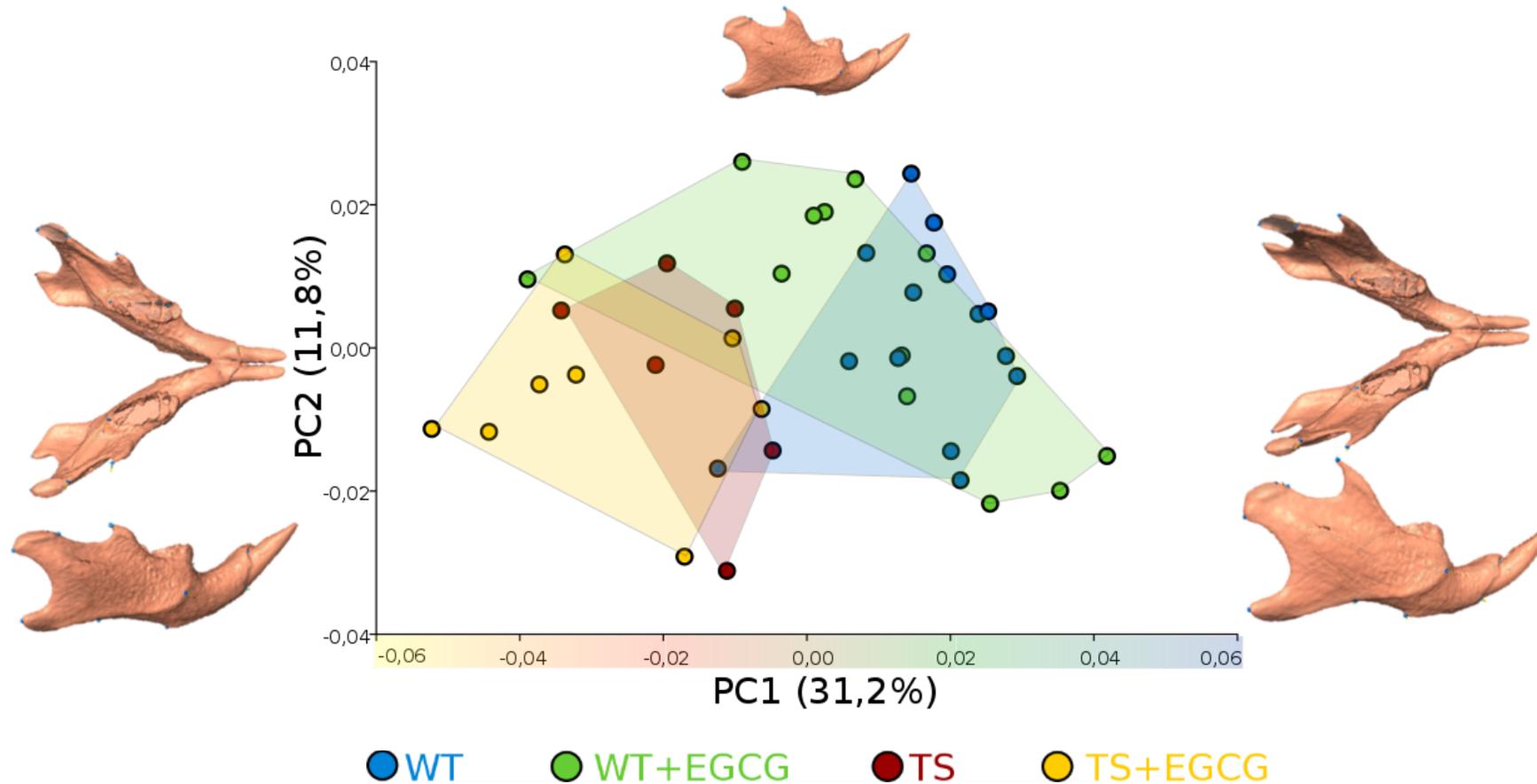
● WT ● WT+EGCG ● TS ● TS+EGCG



*EGCG-treatment (high-dose) tends to make craniofacial shape worse*

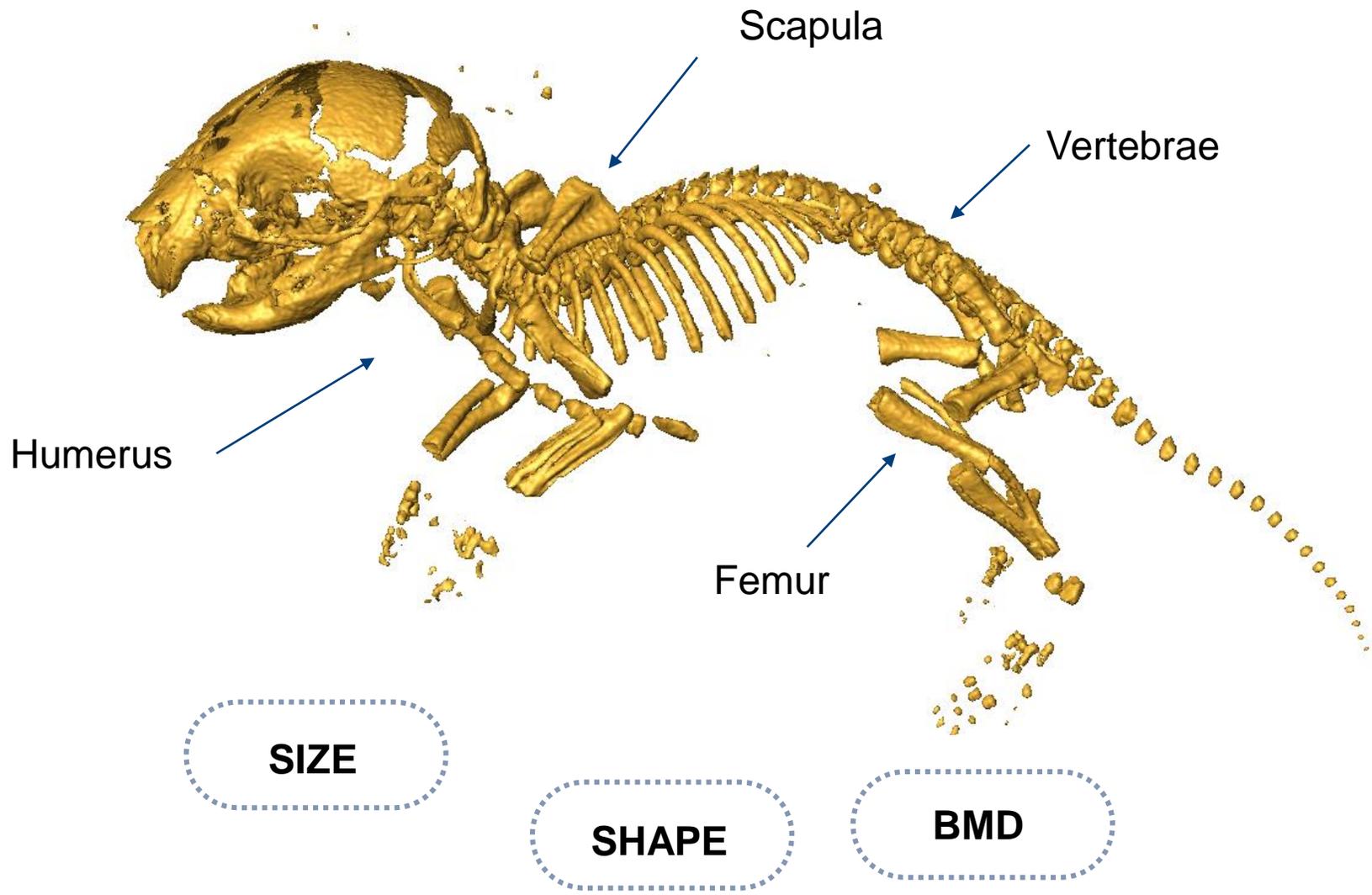
# Craniofacial *shape* analysis

MANDIBLE: PD29

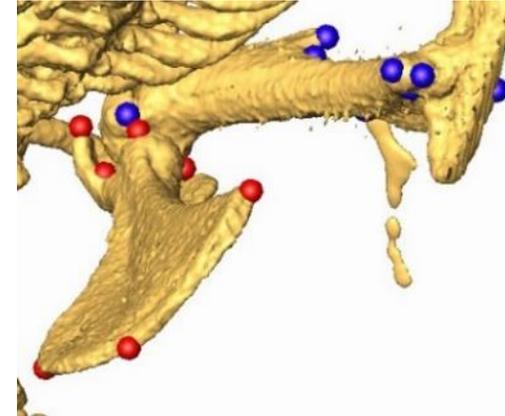
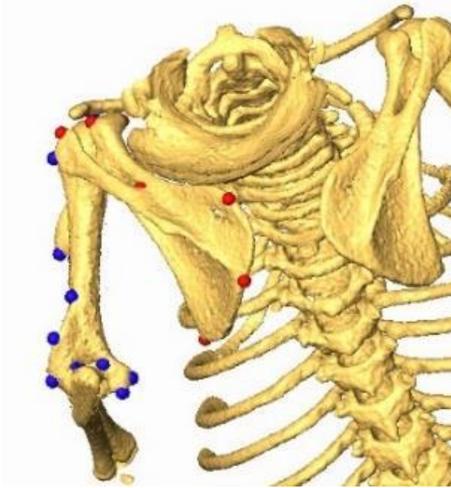
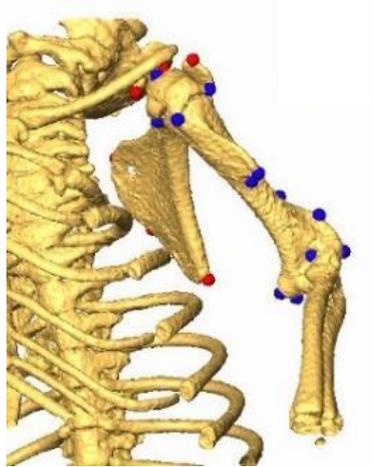


Read more & comment: [Epigallocatechin-3-gallate improves facial dysmorphology associated with Down syndrome. Starbuck JM et al. BioRxiv 2018, 276493.](#)

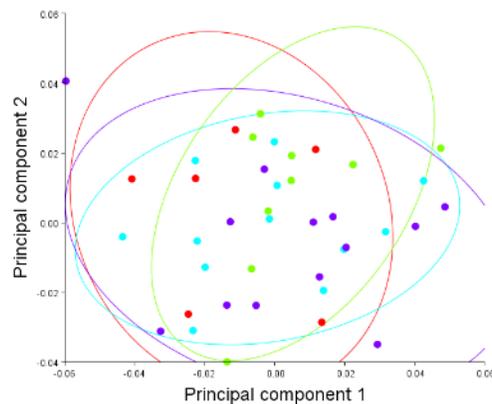
# Skeletal development in DS



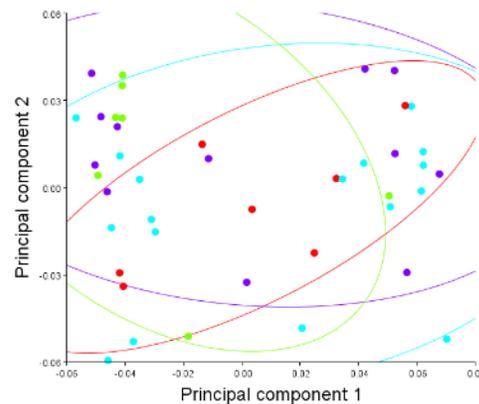
# Humerus & scapula *shape* analysis



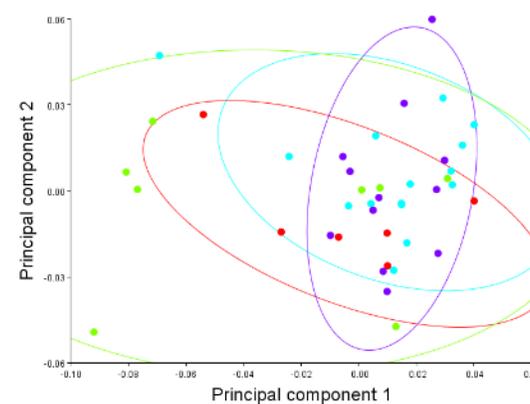
PD3



PD14



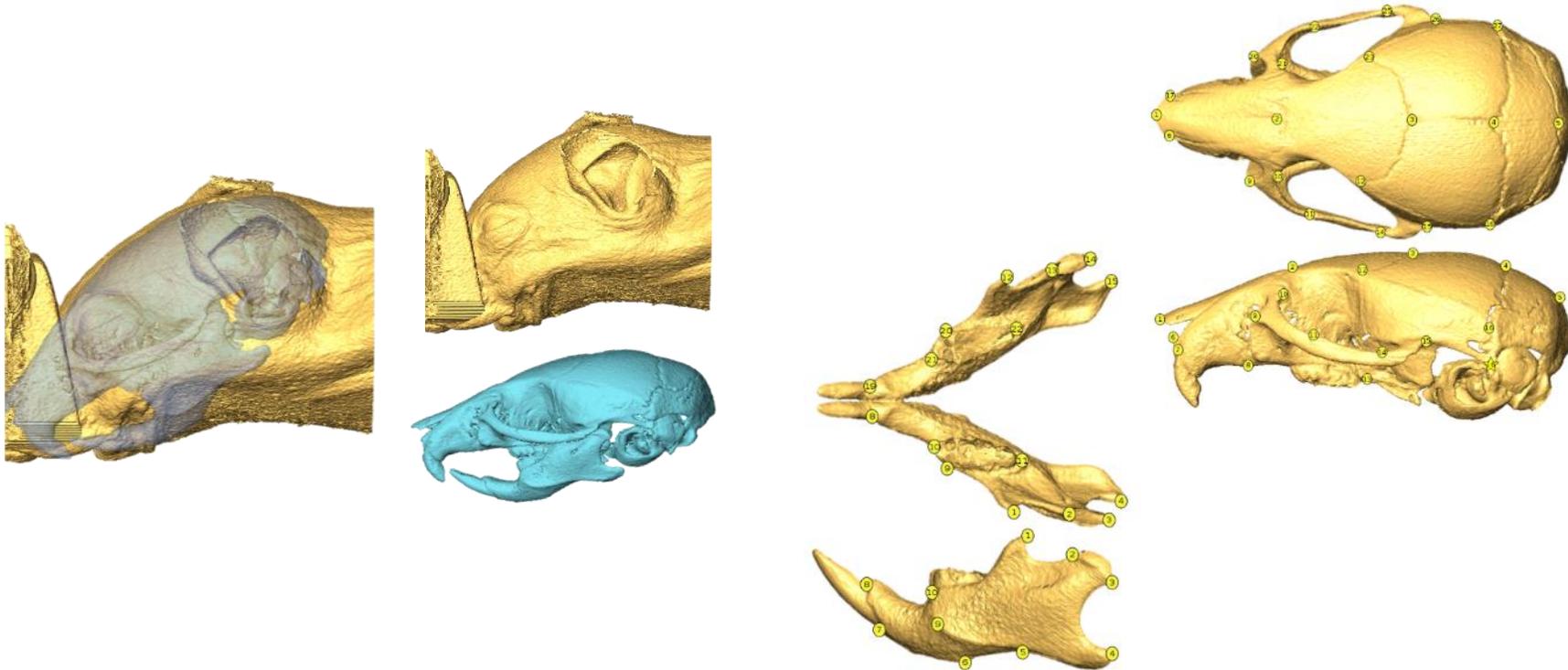
PD29



TS  
TS-EGCG  
WT  
WT-EGCG

# To wrap up: applications of *low-dose high-resolution micro-CT*

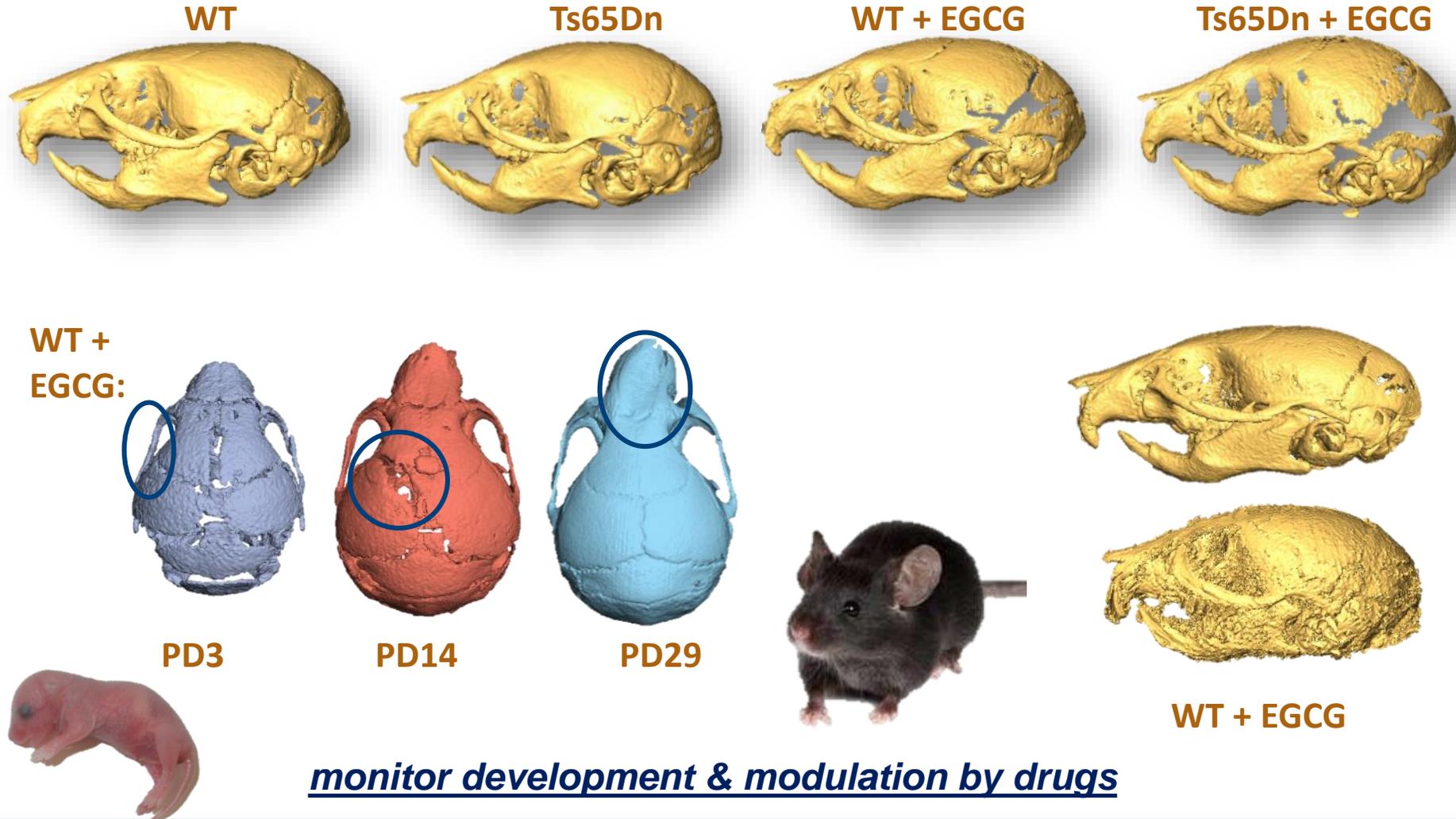
*With one single low-dose whole-body  $\mu$ CT scan we can do...*



***craniofacial landmarking & morphometry***

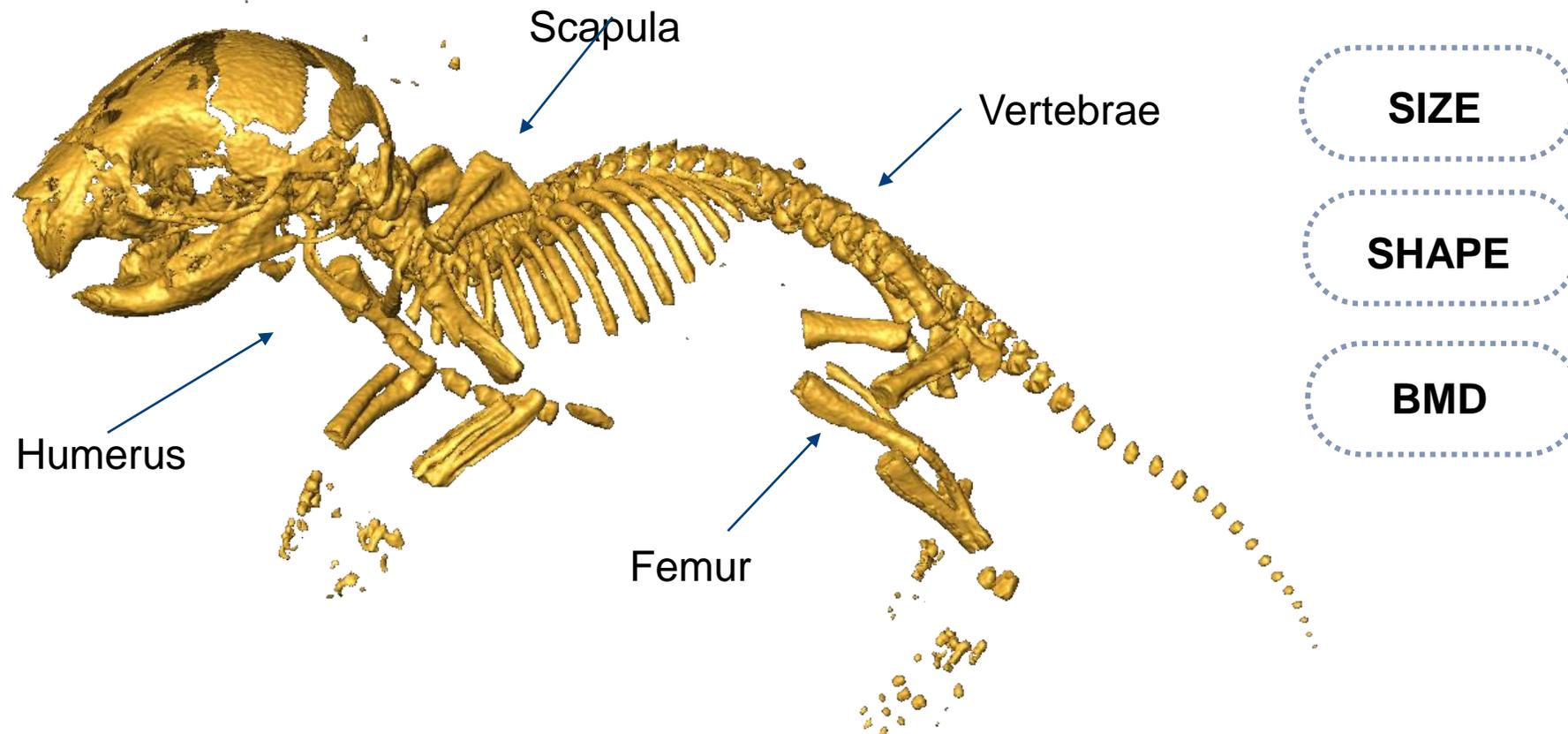
# To wrap up: applications of *low-dose high-resolution micro-CT*

*With one single low-dose whole-body  $\mu$ CT scan we can do...*



# To wrap up: applications of *low-dose high-resolution micro-CT*

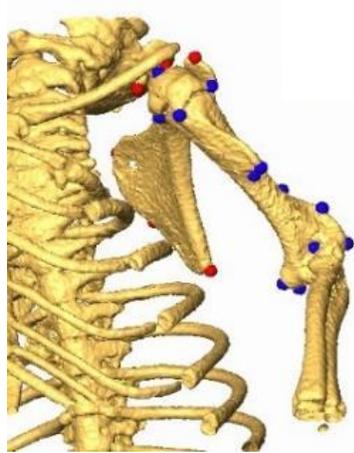
*With one single low-dose whole-body  $\mu$ CT scan we can do...*



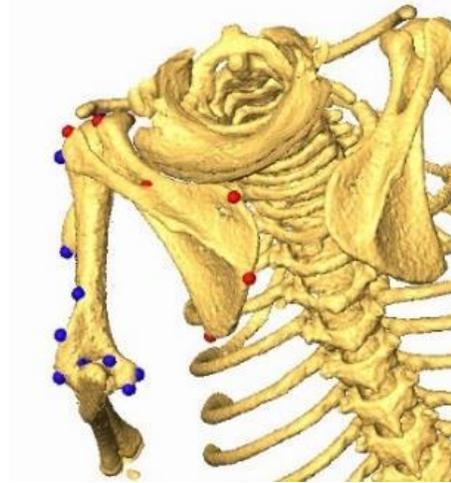
*monitoring skeletal development*

# To wrap up: applications of *low-dose high-resolution micro-CT*

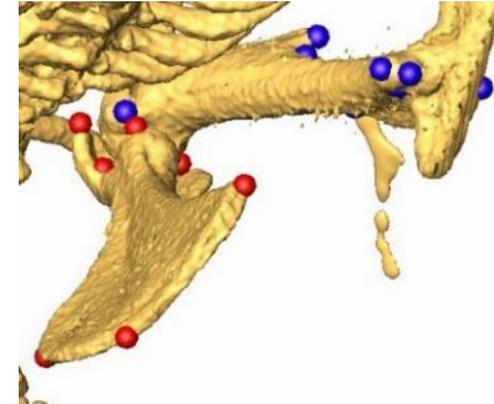
*With one single low-dose whole-body  $\mu$ CT scan we can do...*



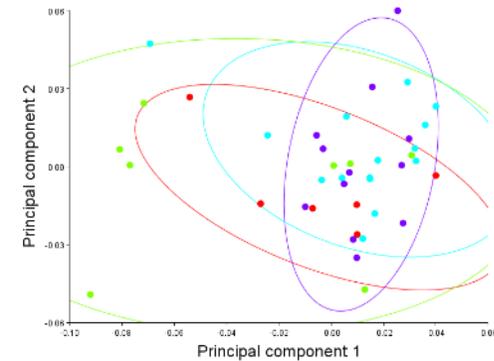
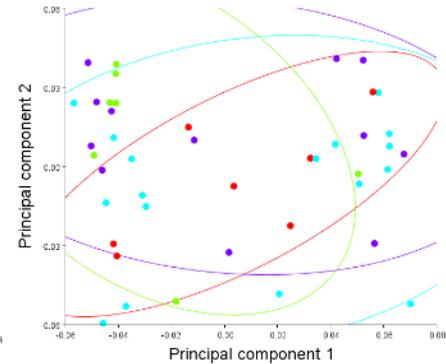
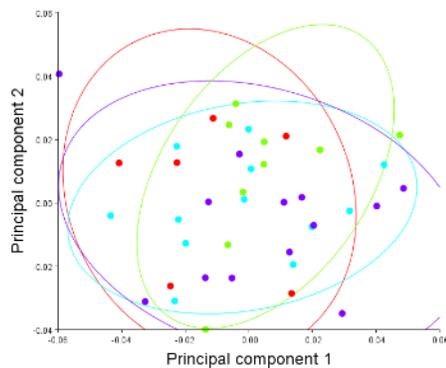
PD3



PD14



PD29



TS  
TS-EGCG  
WT  
WT-EGCG

**Longitudinal shape analysis**

# The people, the funding... THANKS !

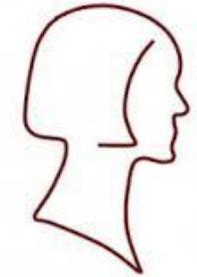
...and you!

Neus Martinez Abadias  
Julia Albaiges Rafoll  
Ruben Gonzalez Colon  
Jorge Roldán  
Mara Dierssen  
Rafael de la Torre  
James Sharpe

*Multicellular Systems Biology, CRG,  
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Sergi Llambrich Ferré  
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Jens Wouters  
Amy Hillen  
Willy Gsell  
Uwe Himmelreich  
Katrien Lagrou  
Jeroen Vanoirbeek  
Peter Hoet

*KU Leuven,  
Leuven, Belgium*



FONDS DE SOUTIEN - STEUNFONDS  
MARGUERITE - MARIE DELACROIX



**Bruker Biospin & Bruker microCT**  
*For support with implementation*



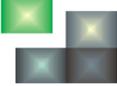
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*How about in vivo imaging applications for you?*

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*Greetje.VandeVelde@kuleuven.be*