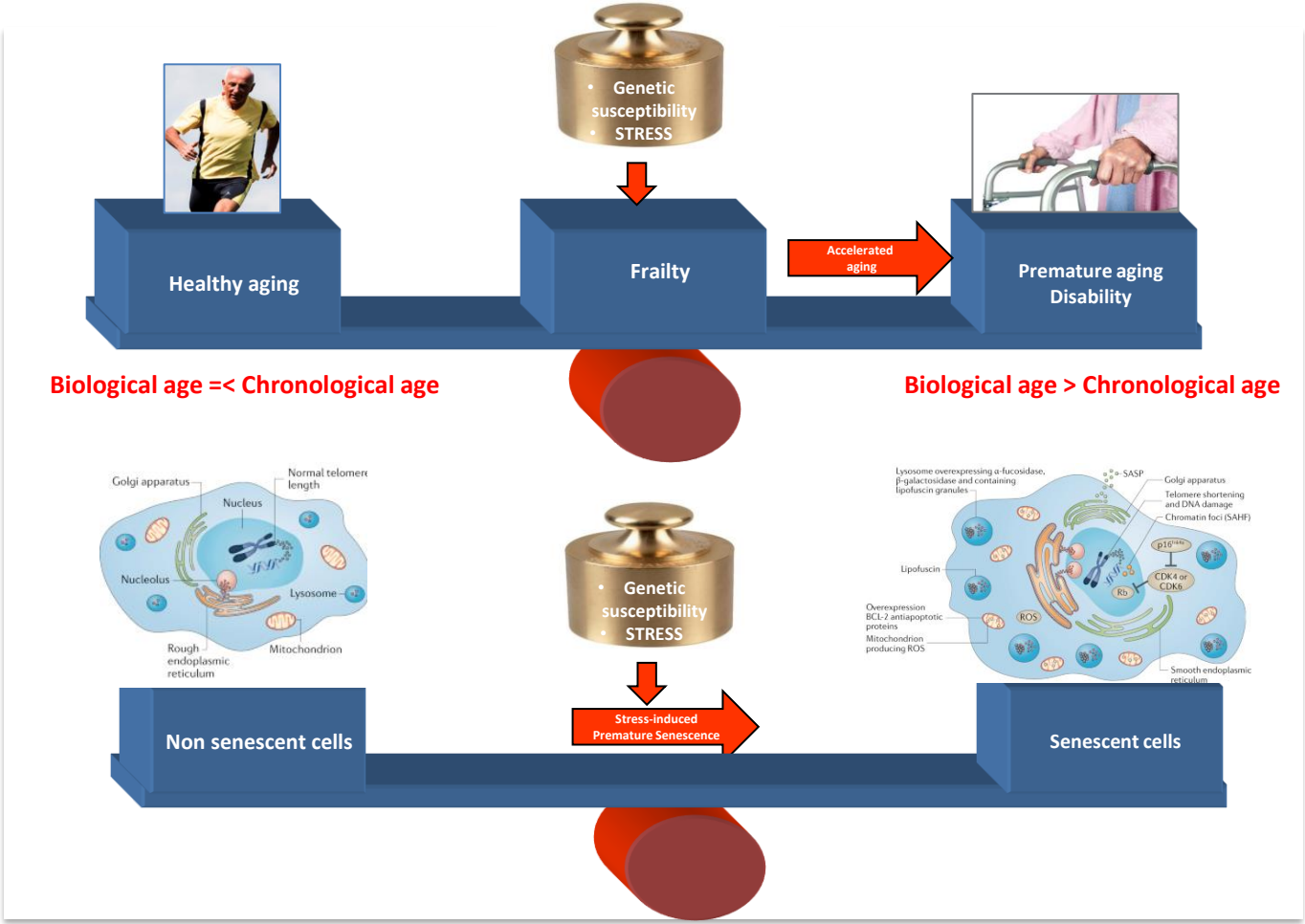
The Inspire mouse cohort: where we are and where we plan to go

Angelo PARINI/ Yohan Santin

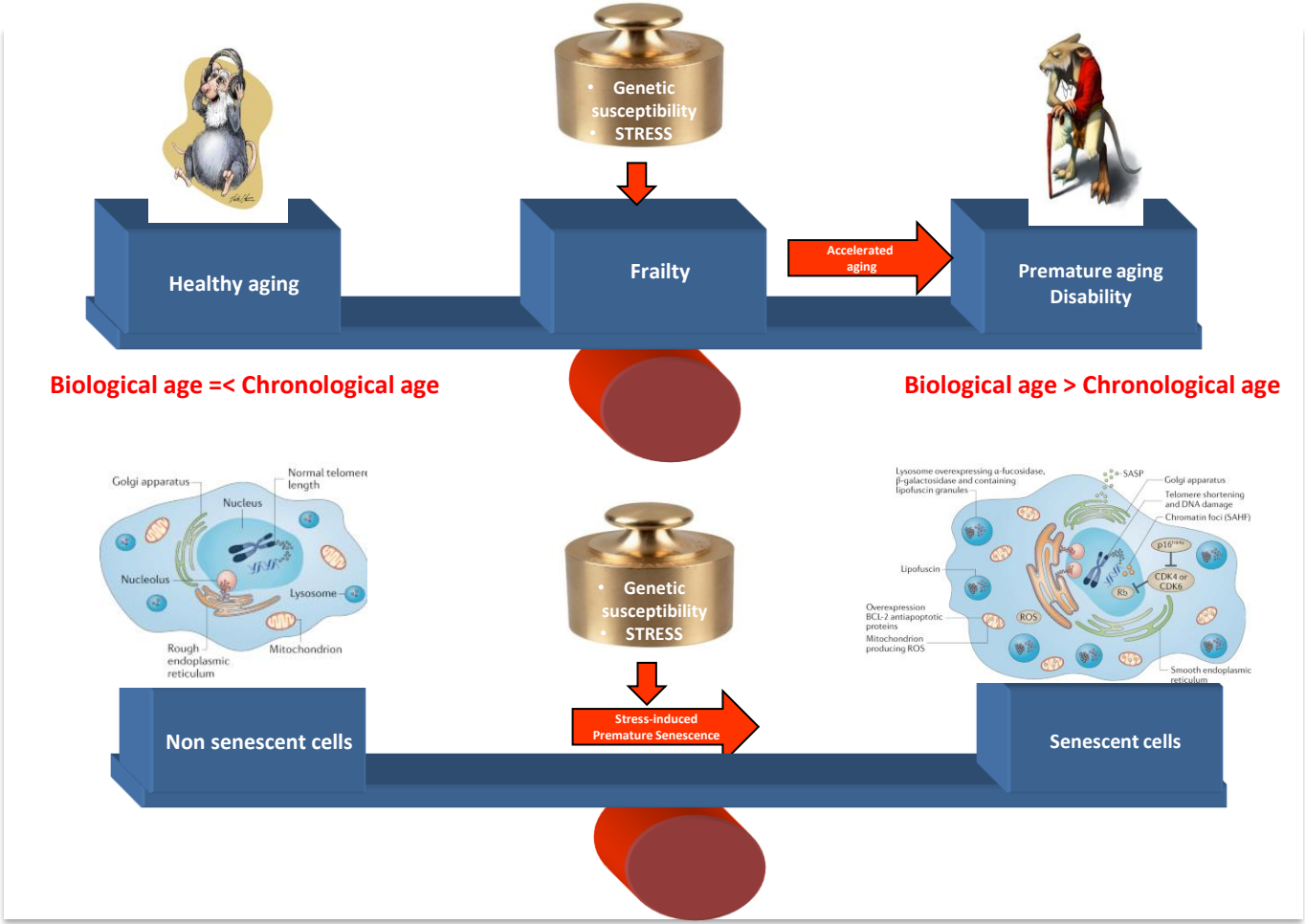
INSPIRE: SAB Meeting

October 4th-5th, 2021

Accelerated aging and cell senescence

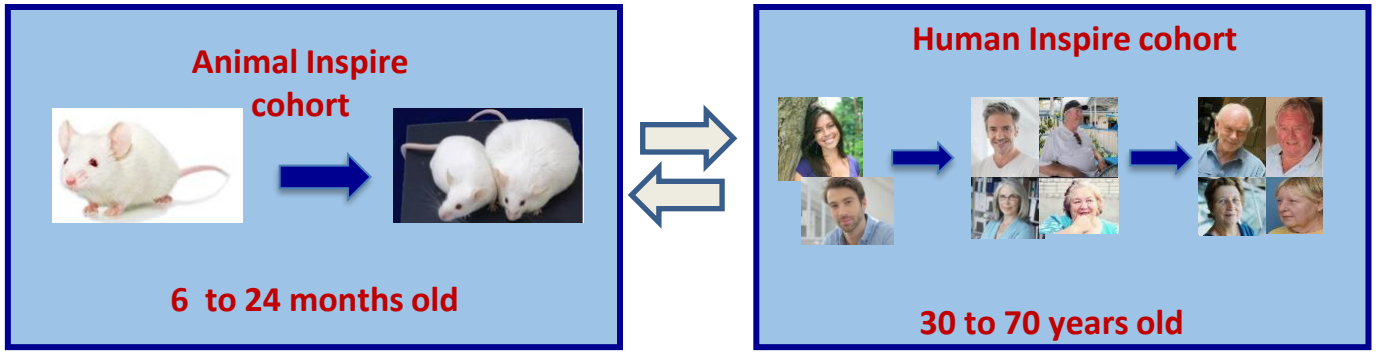


Accelerated aging and cell senescence



STRATEGY

The Inspire Bio-resource Research Platform for Healthy Aging



A unique “mirror” Human and Animal cohort
(health status and chronological age)

Normalization and optimization of clinical and biological parameters
Common dataset with equivalent clinical tests (eg, cognitive function, mobility), and biological tests
New techniques/technologies *(eg, lymphocytes’ profiling, imaging..)*

Cross-talks between humans and animal investigations
Discovery : biomarkers associated with functional loss / identification of causal mechanisms/ development of new therapeutic strategies

Translation into routine clinical care (monitor and prevent the loss of ICs)

Goals of the INSPIRE animal cohort (September 2019-August 2022 period)

- **GENERAL GOAL:**

  Define the relationship between frailty/accelerated aging and cell premature senescence

  ***(without a priori, semi a priori*, hypothesis-driven approaches)**

- **SPECIFIC GOALS:**
- **Define an appropriate animal model of frailty/accelerated aging.**
- **Combine multiple functional and biological parameters**
  - **i) to extend the concept of « frailty index »**
  - **ii) to evaluate the role of different organ dysfunction in the onset and progression of frailty/accelerated aging**
- **Create body fluid, faeces and tissues biobanks.**
- **Define biomarker profiles predicting normal and accelerated aging**

Define an appropriate animal model of frailty/accelerated aging.

Overweight and Sedentary lifestyle

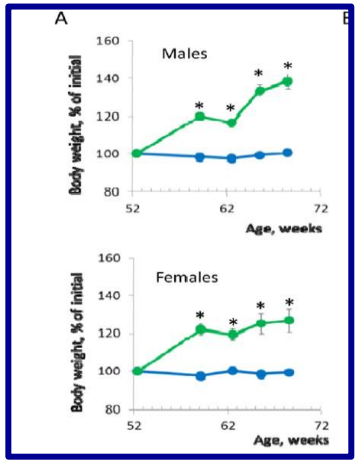
- **WHY ?**
  - Sedentary lifestyle and obesity are known risk factors of frailty in humans
  - As compared to others experimental approaches, sedentary lifestyle and overweight are particularly suitable to promote progressive/long-term frailty in mice.
  - The INSPIRE research teams have international reputation in the field of metabolic diseases.

Cohort organization

SWISS mice

Study design	Cross-sectional study				Longitudinal study
Arms	**6 months**	**12 months**	**18 months**	**24 months**	
Control	80 mice (40M/40F)	80 mice (40M/40F)	100 mice (48M/48F)	136 mice (68M/68F)	120 mice (60M/60F)
HFHS diet	--	80 mice (40M/40F)	112 mice (64M/48F)	180 mice (112M/68F)	
Voluntary Activity (VA)	--	80 mice (40M/40F)	100 mice (48M/48F)	136 mice (68M/68F)	
HFHS diet + VA	--	80 mice (40M/40F)	112 mice (64M/48F)	180 mice (112M/68F)	
TOTAL	80 mice	320 mice	416 mice	632 mice	120 mice

Overweight: High fat/High sucrose diet



(Antoch et al. Aging 2017)

Modified western diet

ssniff Spezialdiäten GmbH	Control diet (2)	High Fat / High Sucrose
Energy (Atwater) MJ/kg	14.7	18.9
kcal% Protein	20	20
kcal% Fat	10	40
Sucrose %	5.800	25.368

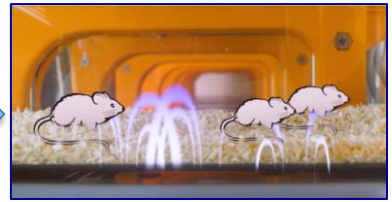
Appropriate animal model of frailty/accelerated aging: sedentary lifestyle vs voluntary physical activity

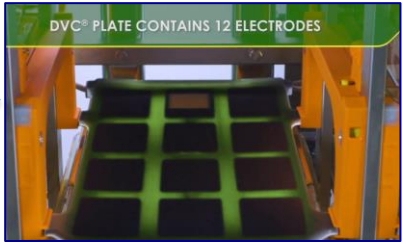
Tecniplast Connected Digital Ventilated Cages (DVC)

The system is composed by three main components:

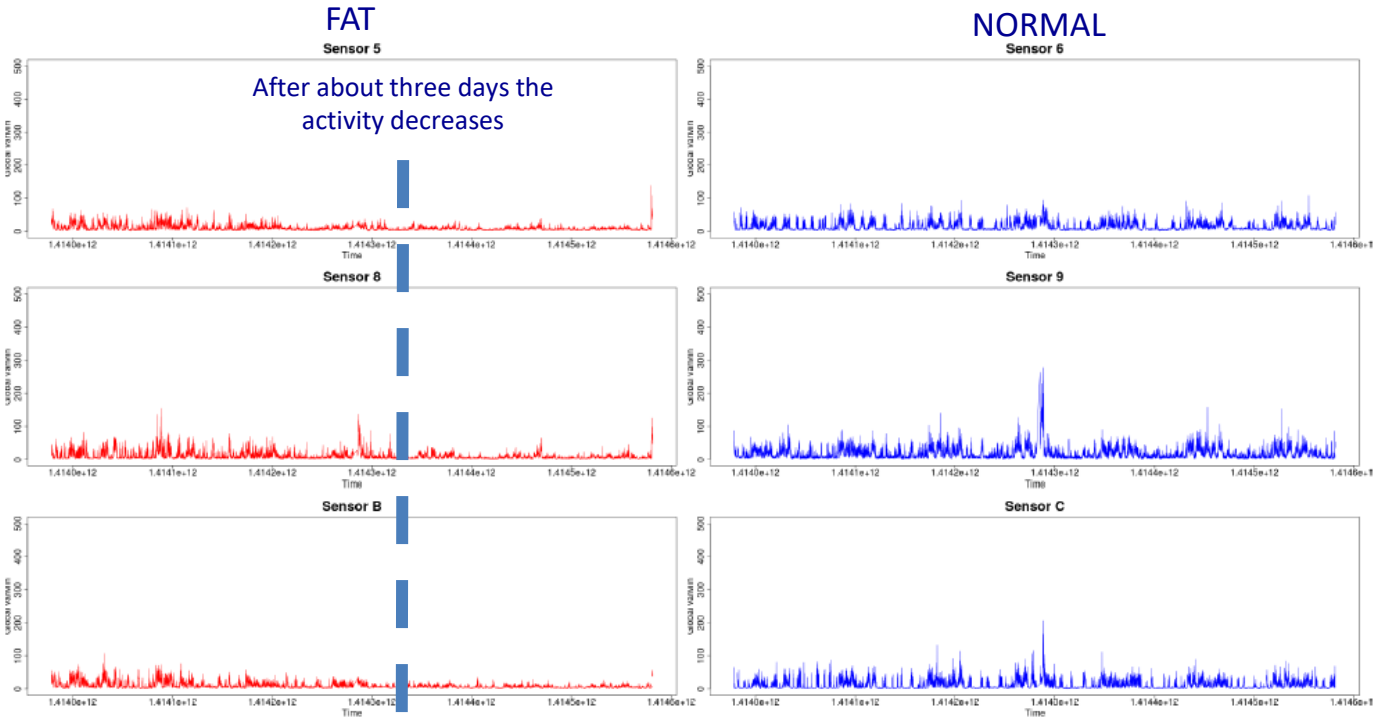
- an Infrared Tracking system for water and food consumption.
- the plate (an integral part of the rack, positioned in correspondence of each cage slot) for recording of spontaneous movement.
- the hardware and the software.

It allows recording and analysis of spontaneous physical activity 24 hours a day and during 2 years





Analysis of spontaneous movement during high-fat diet



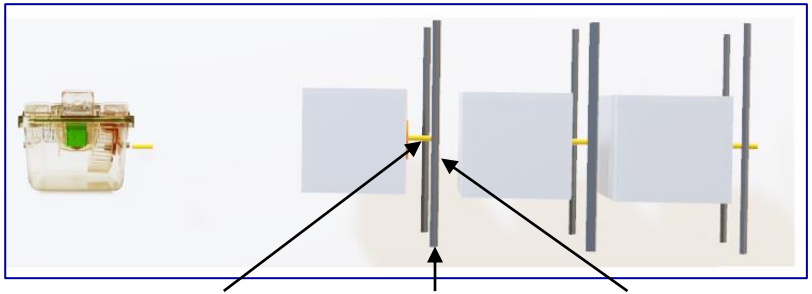
Appropriate animal model of frailty/accelerated aging: sedentary lifestyle vs voluntary running-wheel (RW) access

- Mice are housed 4 per cage.
- Wheels activity will be continuously recorded and then analyzed by the DVC software (time, speed)
- Problem:
  - Among the 4 mice of each cage, which one will run on the wheel ? How long ? What speed ?
- Project:
  - Design a “pay toll-like” detection system for measuring the activity of each mouse on the wheel.
  - Integrate the data in the DVC Analityc software.

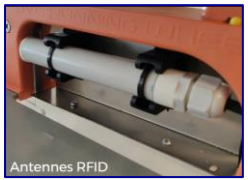
PHYSICAL ACTIVITY: INDIVIDUAL DETECTION SYSTEM

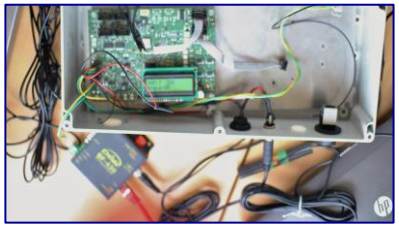
Collaboration with Biolog-ID and Tecniplast

Goal : to allow individual detection (via RFID microchips) of mice using a running wheel in real time > number of revolutions and rotation speed
> creation of a database



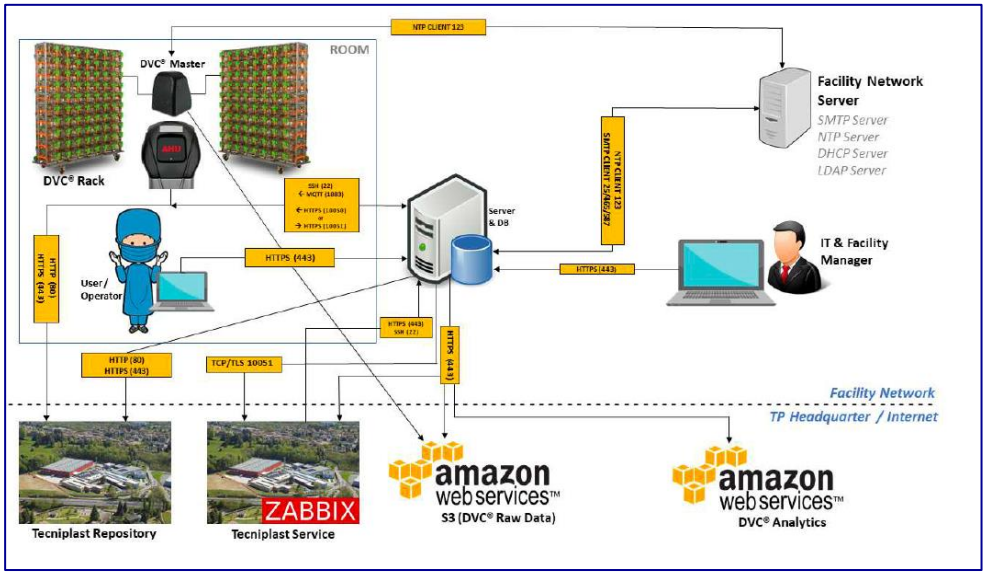
Antenna Rack Shield





➢ ***Patent: February 2021***

DVC Network Diagram to record data on spontaneous and voluntary physical activities



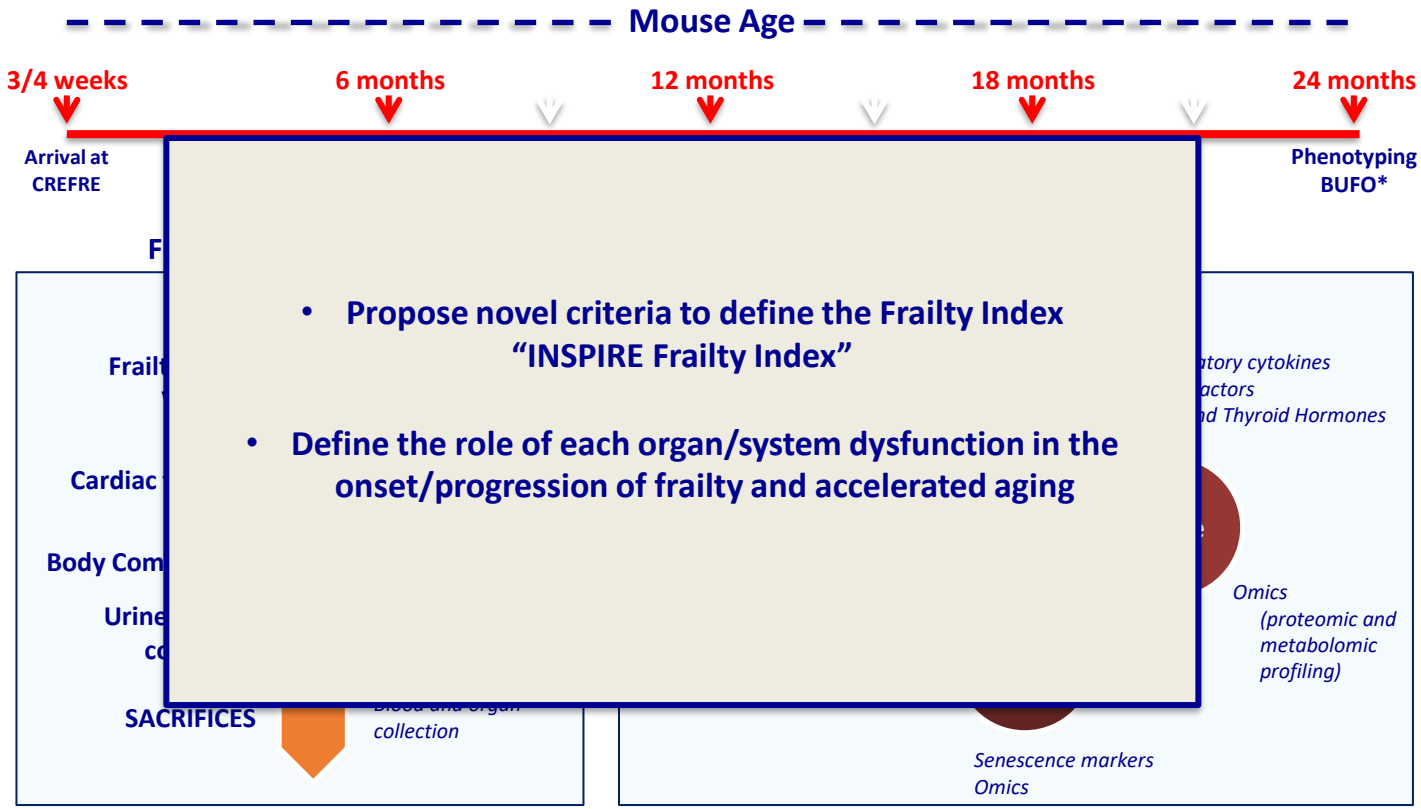
Between 133,000 and 532,000 points/day

Between 97 millions and 388 millions points/2 years

Continuous recording and analysis of spontaneous and voluntary physical activities 24 hours a day throughout the INSPIRE project

1. Collaboration with Tecniplast and Dr. Brun Ulfhake, Karolinska Institute, Stockolm, Sweden (Analysis of DVC data variability in Outbred mice depending on housing conditions).
2. In progress: European Networking of DVC users for collaborative and R&D projects

Combine multiple functional and biological parameters to define the onset and progression of frailty: Definition of Frailty Index (FI)



BUFO : Blood, Urine, Feces and organ collection

Schedule


Mice arrival
(October 2020)
3-4 weeks
6
months
12 months
18
months
24
months
PHENOTYPING
18 Jan 2021
05 Mar 2021
30 Aug 2021
10 Dec 2021
17 Jan 2022
06 May 2022
18 Jul 2022
08 Dec 2022
SACRIFICES
01 Mar 2021
12 Mar 2021
11 Oct 2021
17 Dec 2021
28 Feb 2022
13 May 2022
29 Aug 2022
16 Dec 2022

Frailty

Fried Score		Valencia Score
Unintentional Body Weight Loss	⇔	*Unintentional Body Weight Loss*
Slow Walking Speed	⇔	*Running Speed*
Self-reported Exhaustion	⇔	*Running Time*
Weakness	⇔	*Grip Strength*
Low Physical Activity	⇔	*Motor Coordination*

Fried et *al.*, 2001

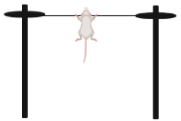
Martinez de Toda et *al.*, 2018

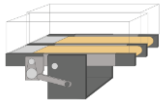
Six months old mice: some results

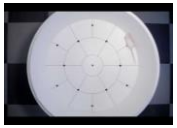
« BASIC FRAILTY PHENOTYPING » (Valencia Score) *Martinez et al., 2018: Journal of Gerontology*

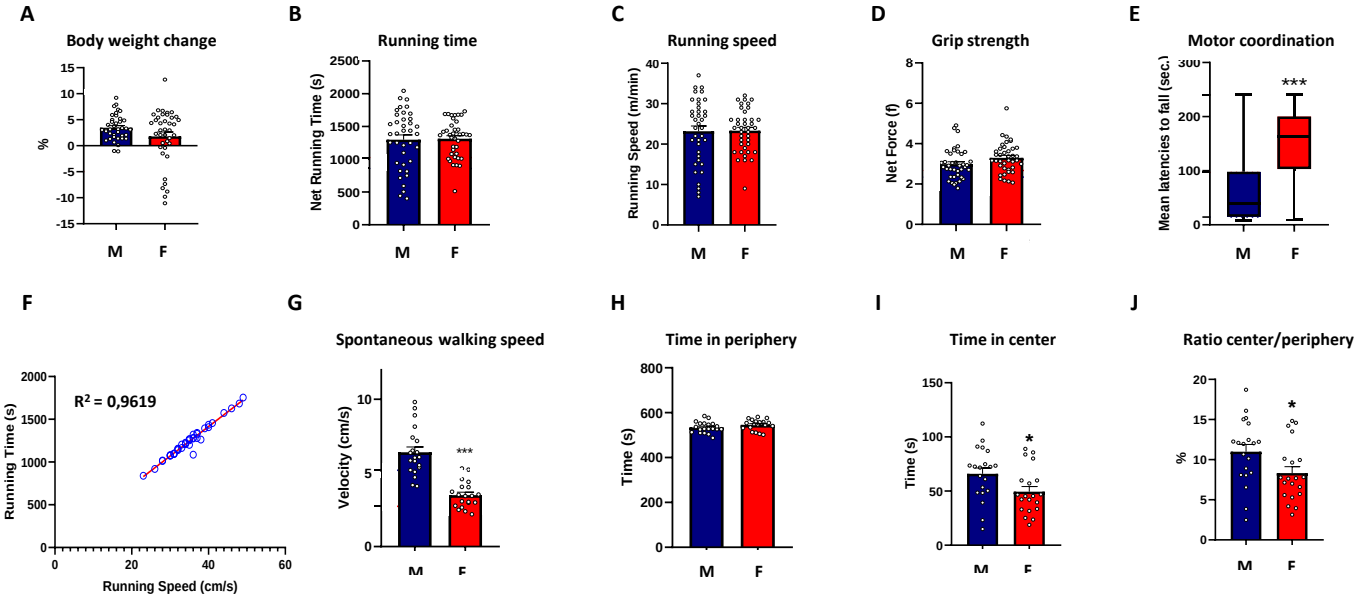

Ymaze


Grip

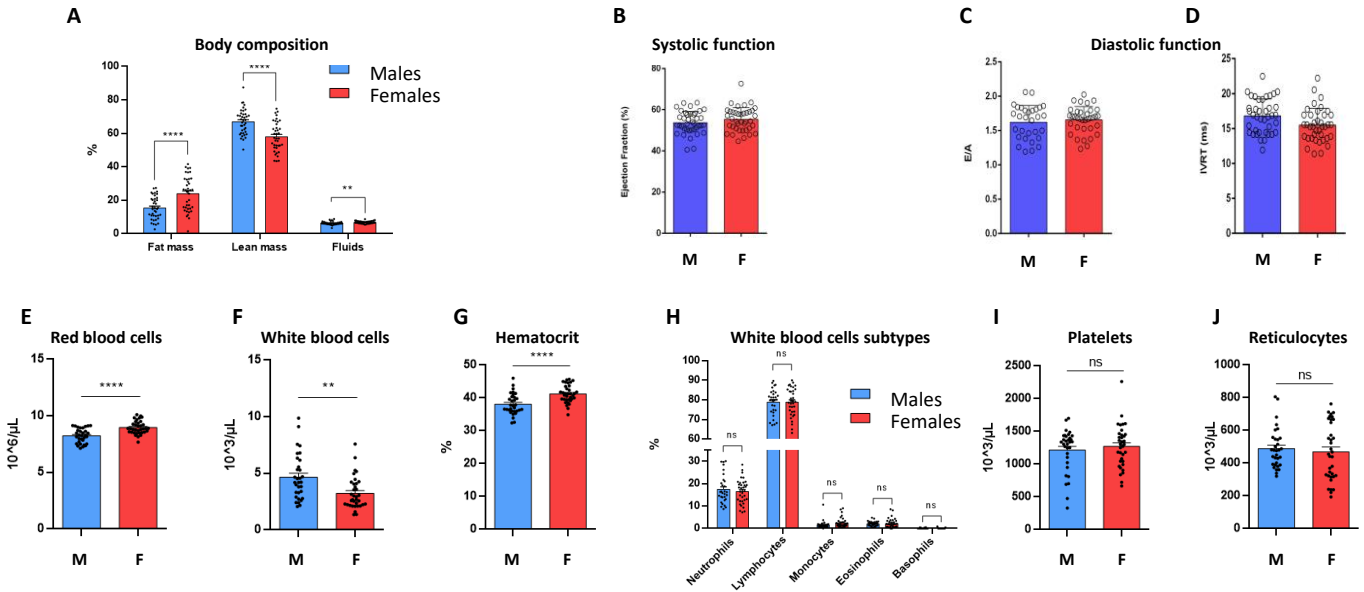

Tight-rope


Treadmill

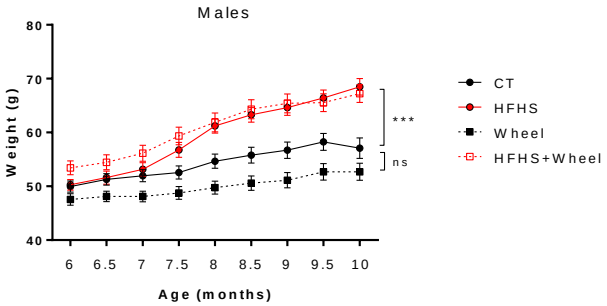

Open field

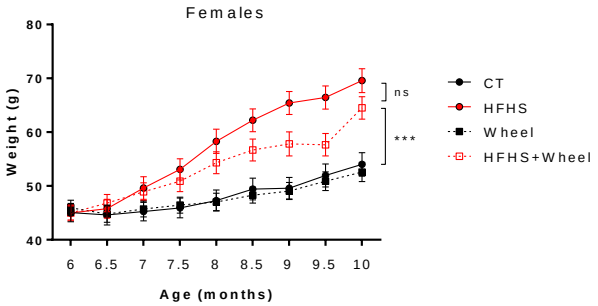


Six months old mice: some results



Weight gain


Males
Weight (g)
80
70
60
50
40
6
6.5
7
7.5
8
8.5
9
9.5
10
Age (months)
***
ns
CT
HFHS
Wheel
HFHS+Wheel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Weight (g)
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40
6
6.5
7
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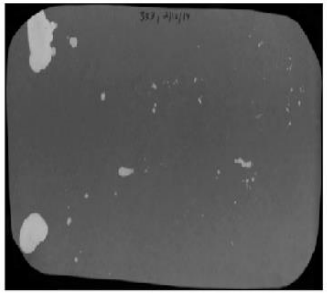
8
8.5
9
9.5
10
Age (months)
ns
***
CT
HFHS
Wheel
HFHS+Wheel

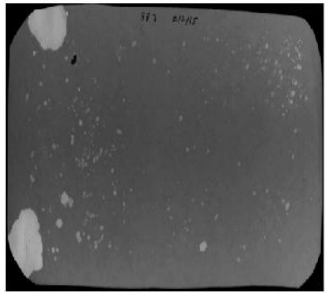
Voiding Spot Assay (urinary incontinence)

UV illuminate and Image

2-3 Months Old



13-14 Months Old



Organ sampling

SALIVARY GLANDS

BAT

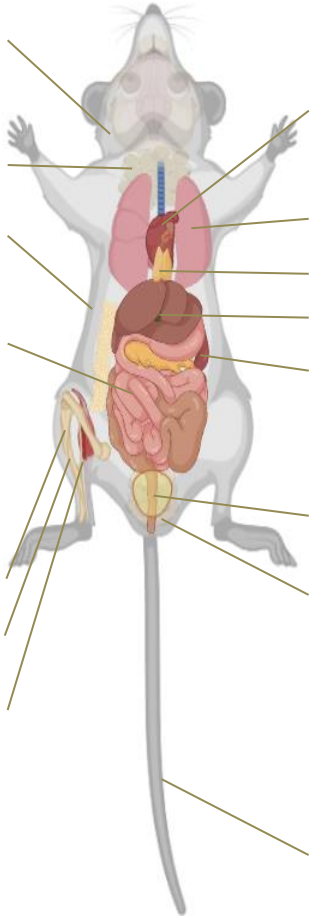
WAT
- Inguinal (sub-cutaneaous)

DIGESTIVE TRACT
- Stomach
- Duodenum
- Jejunum
- Caecum
- Colon

BONES

BONE MARROW

MUSCLE
- gastrocnemius



HEART
- Atria
- Ventricles

LUNGS

THYMUS

LIVER

SPLEEN

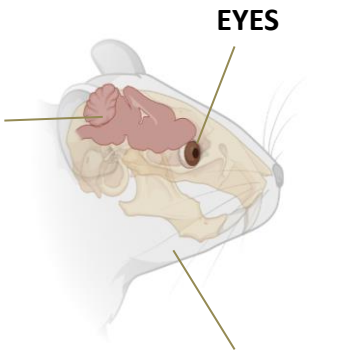
KIDNEYS

BLADDER

WAT
- Perigonadal (visceral)

TAIL

BRAIN
- hemisphere (left)
- hypothalamus
- hippocampus
- cortex
- optic nerves



EYES

JAWS
- maxillaries
- mandibles

Sample storage and biobanking

- **Number of samples:**
  - **Blood: 14,500**
  - **Urine: 1,500**
  - **Feces: 6,000**
  - **Tissues: 75,000 (anatomopathology and pulverization)**
  - **Tails: 1,500**

Total: 98,500

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

Biological Resource Centre - Cancer

Director : **Pr Anne Gomez-Brouchet**

Quality Engineer **Sophie Périès-Bataille**

Location : **Institut Universitaire du Cancer Toulouse**

•Administrative structure of attachment: CHU

Quality : Certified **AFNOR NF-S 96 900** since March 2014

Website : http://www.chu-toulouse.fr/-centre-de-ressources-biologiques

Biological resource management software : Tumorotek

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- **Define biomarker profiles predicting normal and accelerated aging**

INSPIRE Team

Biostatistics

Ignacio Gonzalez-Fuentes

Storage and tracking of samples

Cindy Pierson

Caring of mice and sacrifices

Pilar Oreja Fuentes

Fraha Haidar

Aurore Moreau

Axelle Le Mouel

Mégane Guardia

Lucas Lemmel

Phenotyping

Amélie Alfonso

Sandra Bonnal

Yosra Doghri

Rana Zahreddine

Project management and coordination

Angelo Parini

Yohan Santin

What next ?

- **Biostatistic analysis of functional data** *(completed in Juin 2023)*
- **Multiomics on body fluids and tissues** *(Priority to Body fluids; Questions : mouse groups or entire cohort ? ; selection of tissues?)*
- **Biostatistic analysis and correlation of functional/biological data in mice; comparison with data from human T cohort.**
- **Novel longitudinal and interventional colonies**