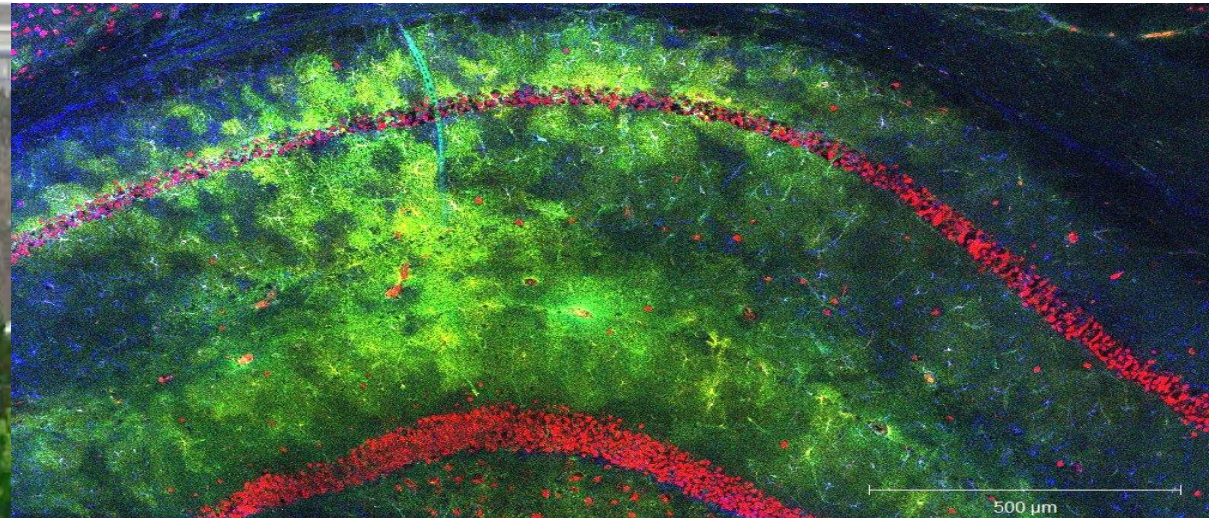


Novel targets and treatment strategies against neurodegeneration

MHH Cellular Neurophysiology
Hannover Medical School



Evgeni Ponimaskin



Our Projects

Astrocytes and Calcium Signalling



Protein Palmitoylation



Serotonin receptors in health and disease



The role of Serotonin in Myocardial infarction

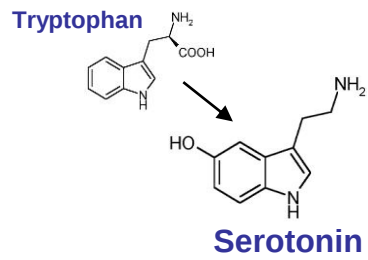


Quantitative Molecular Microscopy



Smartage





Serotonin helps regulate

Sleep



Appetite



Learning and memory



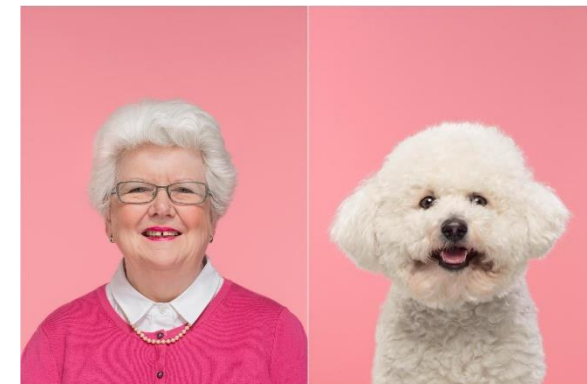
Agression



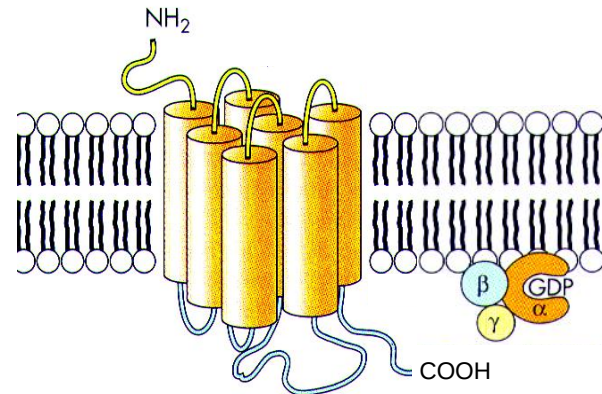
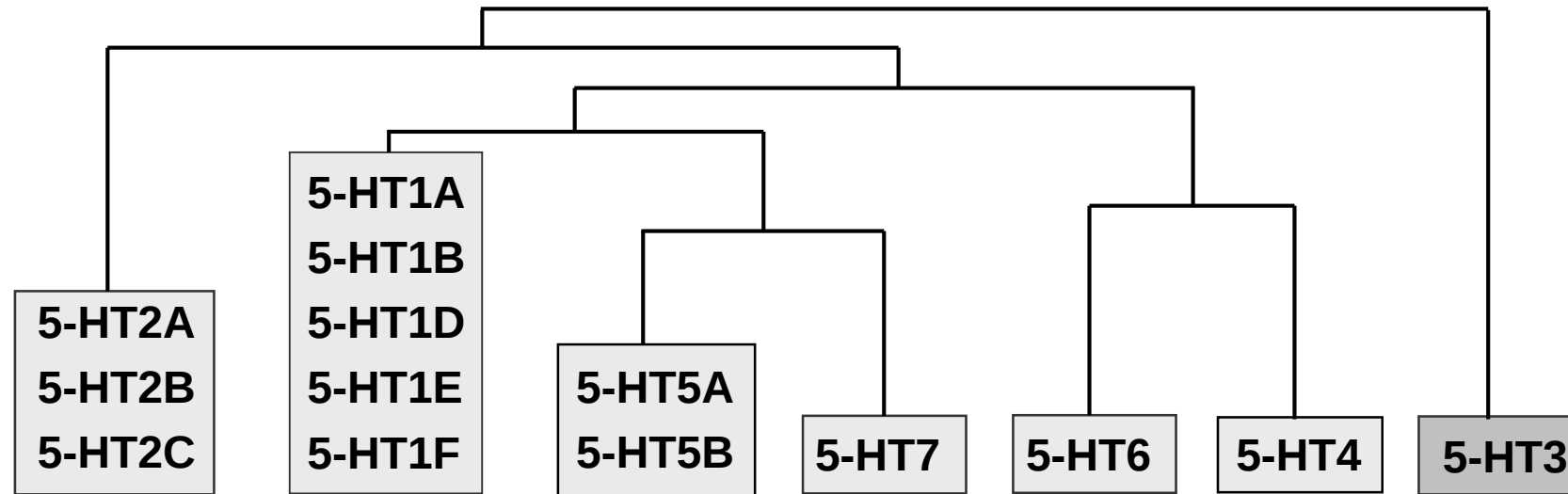
Sexuality



(good) Mood

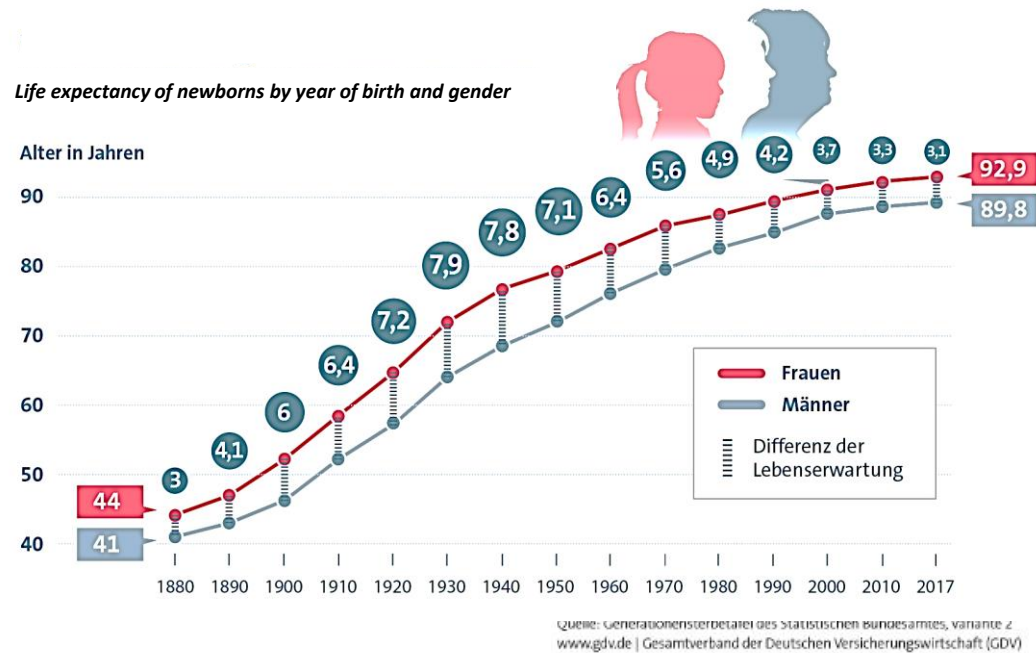


5-Hydroxytryptamine (5-HT or Serotonin) Receptors



Could the serotonergic system be a new target for the treatment of neurodegenerative disorders?

Demographic ageing and dementia



Prevalence for dementia

60-65	1.3%
80-85	13.1%
90+	40%

Annual incidence in Germany - 2.000

900 new cases per day

Nearly 7.9 million people in the EU have AD and related dementias (14.3 million in 2050)

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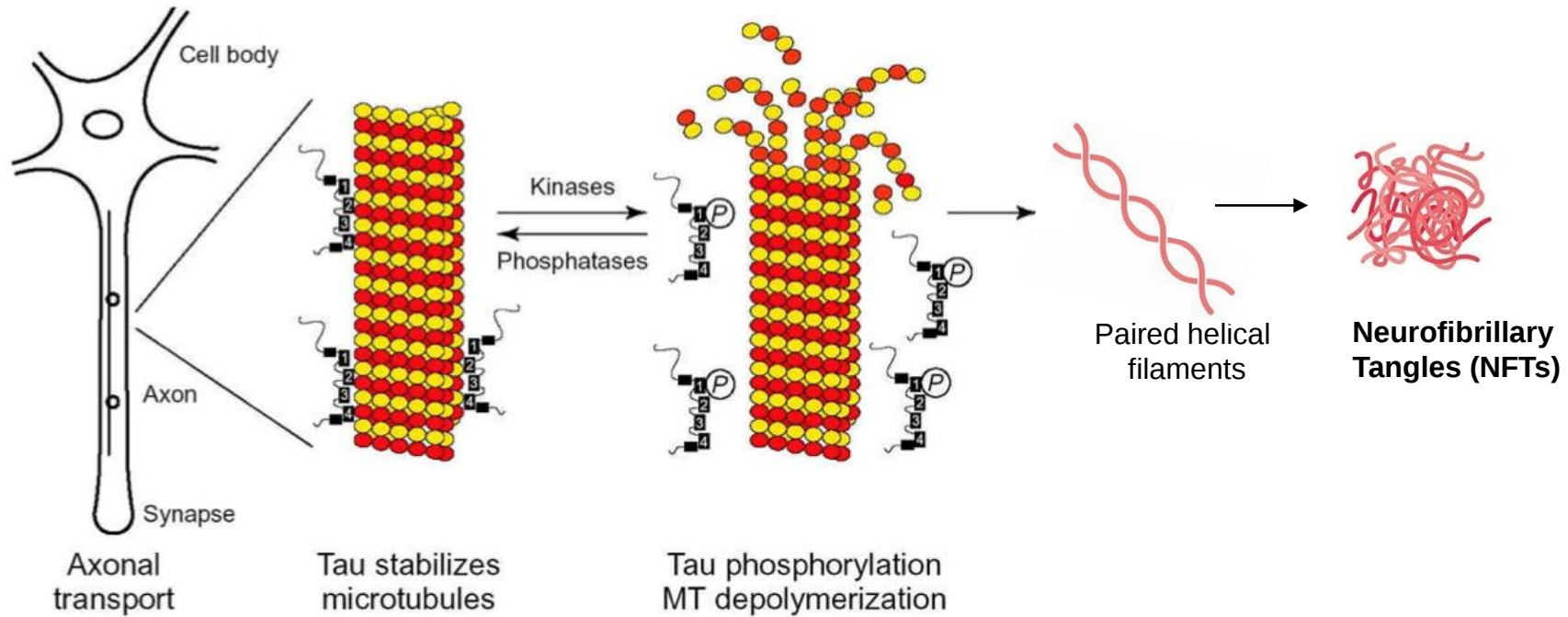
<https://www.lindau-nobel.org/blog-das-alternde-gehirn/>

Aggregopathy

Many neurodegenerative diseases are associated with the misfolding and aggregation of proteins

	Deposits of	Localisation
Alzheimer's disease	A β 42 and Tau	extra- and intracellular, cerebral cortex
Parkinson's disease	α -Synuclein	intracellular, substantia nigra
ALS	SOD1, TDP-43	intracellular, 1° and 2° motoneurons

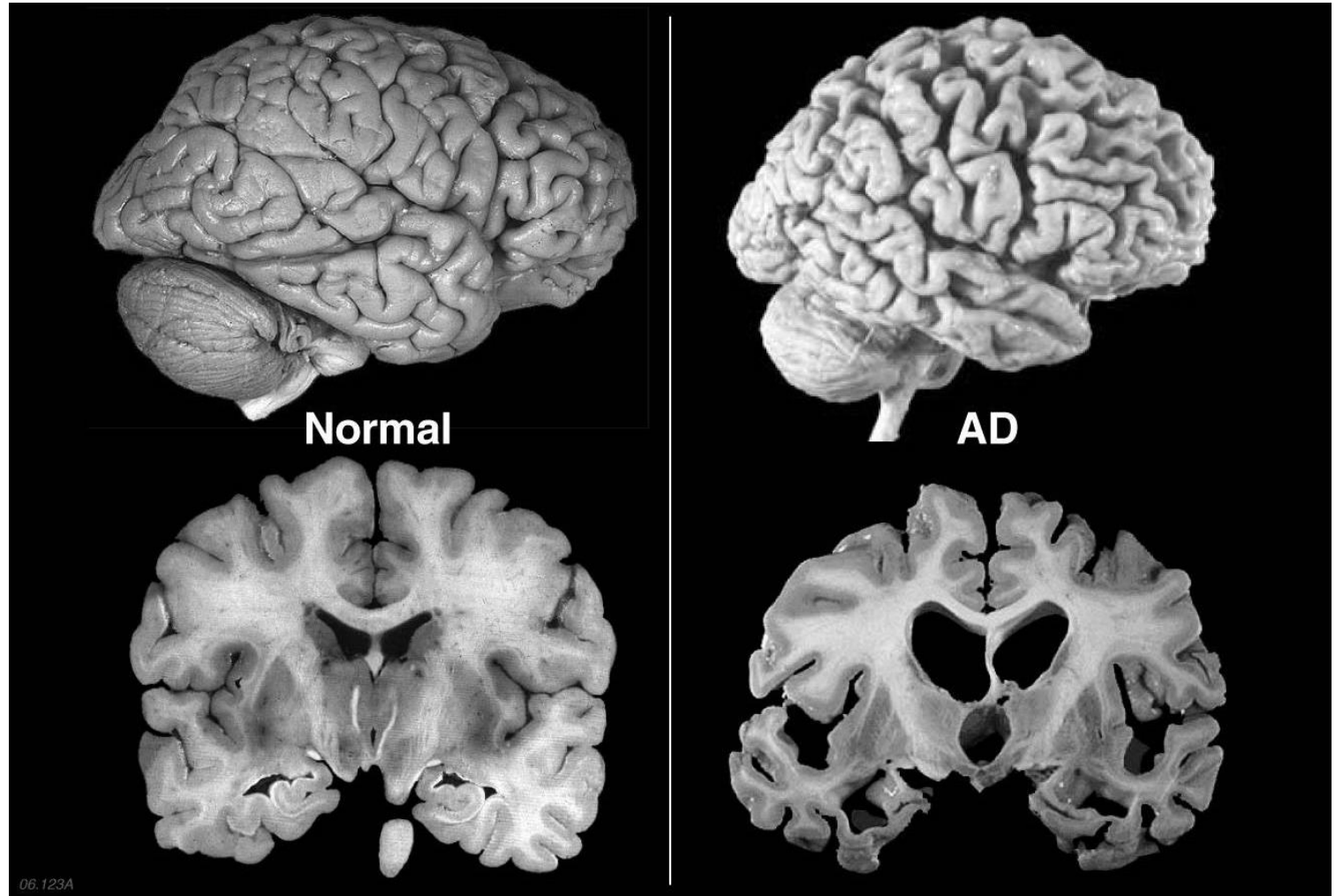
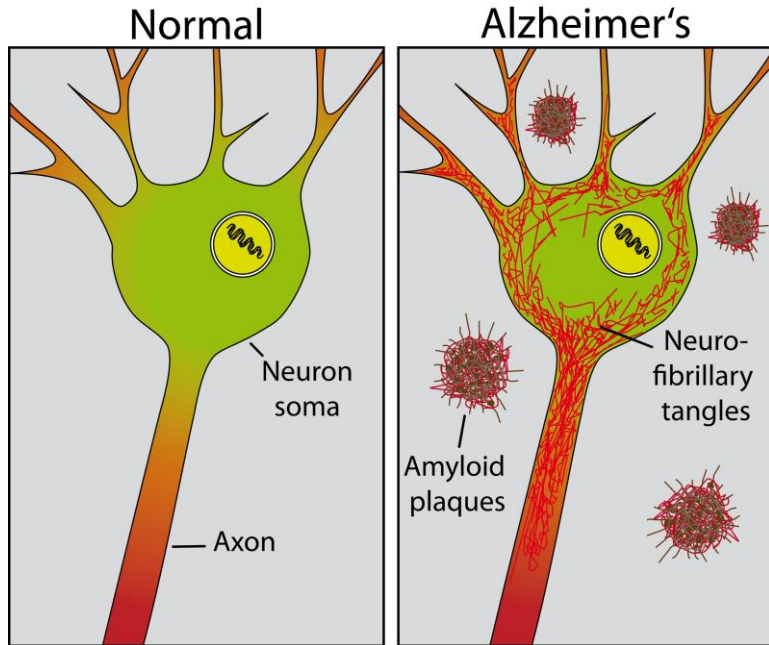
Tauopathy



Aggregated Tau is hallmark of multiple neurodegenerative disorders:

- **Alzheimer's disease (AD)**
- Argyrophilic Grain Disease (AGD)
- Primary age-related tauopathy (PART)
- Progressive supranuclear palsy
- Corticobasal degeneration (CBD)
- Chronic traumatic encephalopathy (CTE)
- Frontotemporal dementia with parkinsonism (FTDP-17)

Brain atrophy in advanced Alzheimer's disease

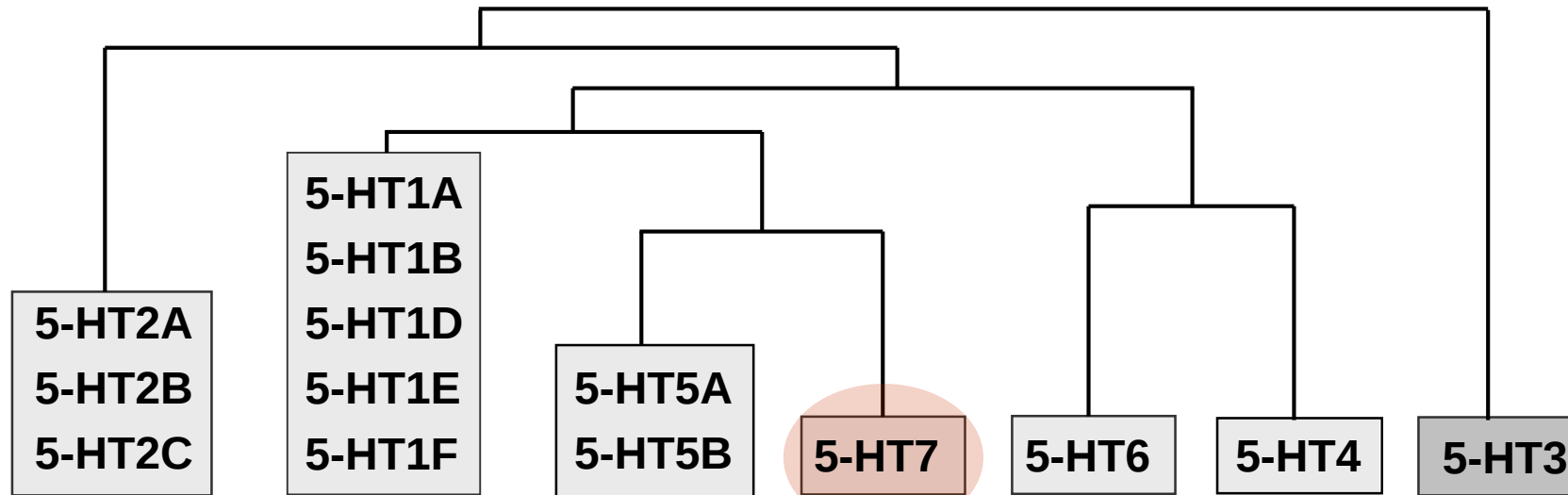


Bagad et al., Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013

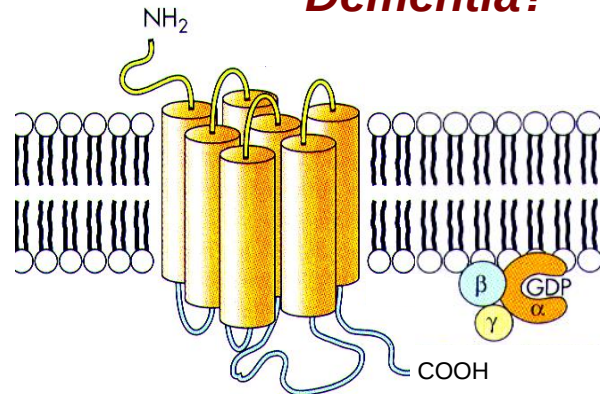
Lecanemab (monoclonal antibody against amyloid plaques) – is only the AD drug approved by EMA in April 2025

Could the serotonergic system be a new target for the treatment of dementia?

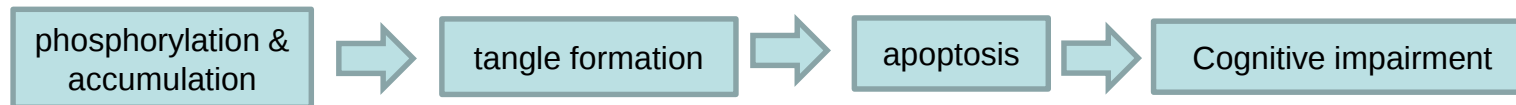
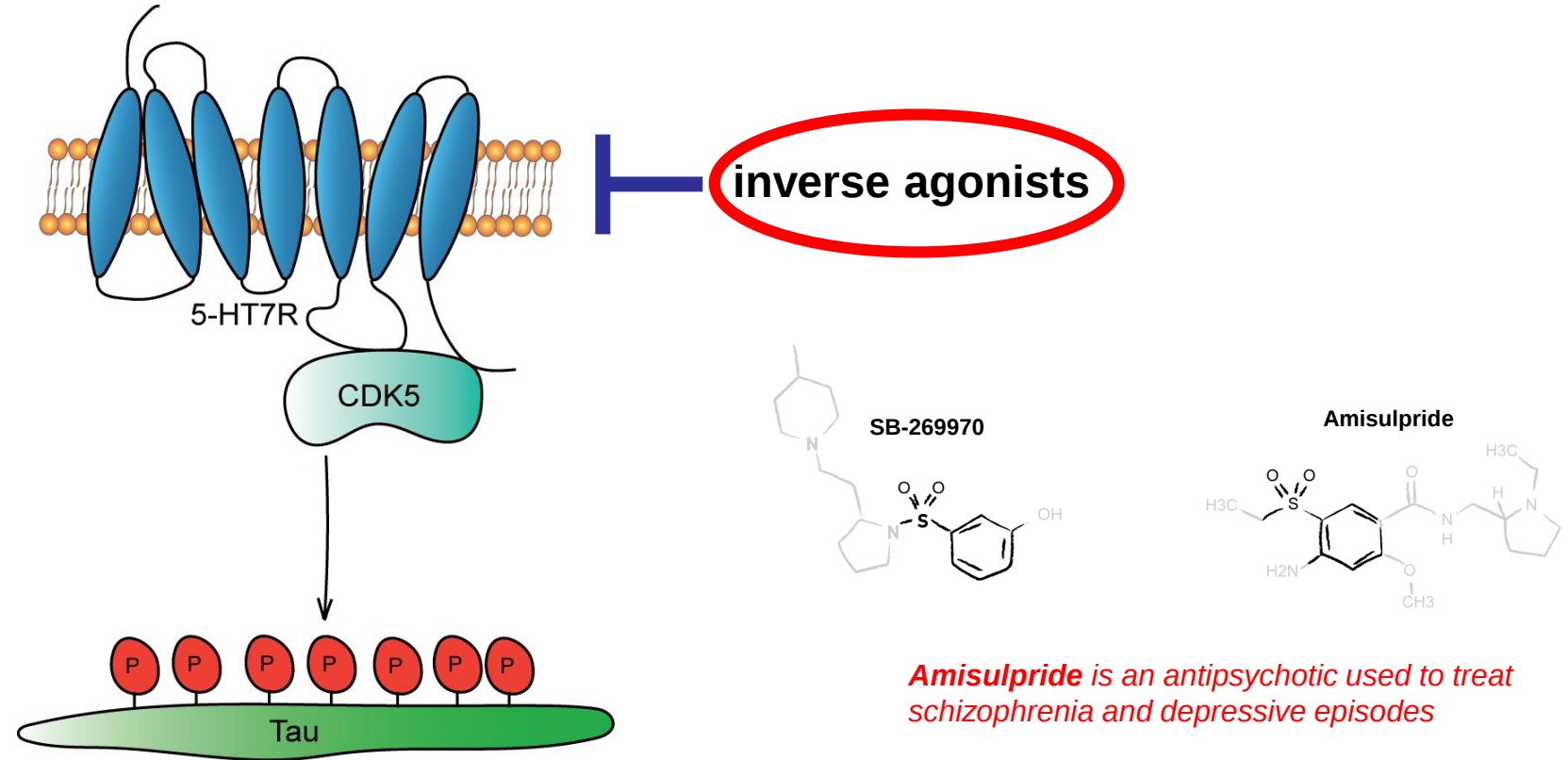
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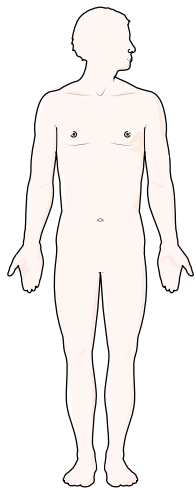


Circadian rhythm and sleep
Body temperature
Regulation of mood
Autism Spectrum Disorders
Depression
Dementia?



Blockade of constitutive 5-HT₇R activity ameliorates Tau pathology





Amisulpride treatment and occurrence of dementia

Epidemiological analysis (AOK health insurance data 2004-2016)

Occurrence of dementia for patients treated with Amisulpride vs. Tiapride

Treatment	Dementia Cases	No Dementia Cases
Amisulpride <i>(5-HT7R inverse agonist)</i>	24	31.801
Tiapride <i>(not a 5-HT7R blocker)</i>	55	31.770

Fisher's exact test: **p = 0.037**

Individuals treated with Amisulpride had a significantly lower risk of developing dementia (1.75-fold)

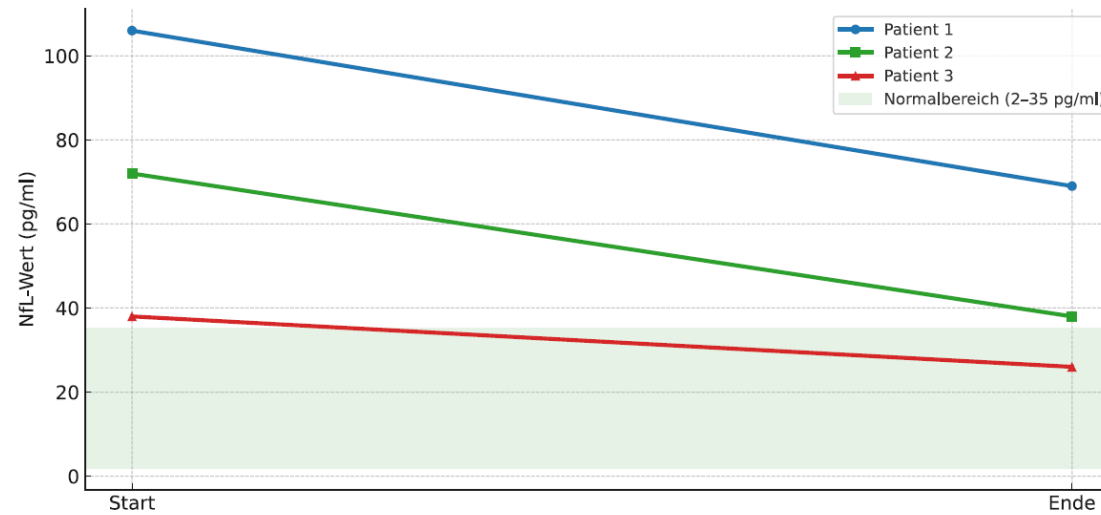
Amisulpride treatment by 3 patients with FTLD

- Start of treatment: December 2023
- Duration: **10 months**
- Blood marker: **NfL** (*Neurofilament Light Chain*) – Indicator of neuronal damage
- Reference range: **2 – 35 pg/ml**



Dr. Péter Körtvélyessy
Neurologie
Charité Berlin

Patients	Before the treatment	After 10 months	Trend
Patient 1	106 pg/ml	69 pg/ml	↓ clear
Patient 2	72 pg/ml	38 pg/ml	↓ clear
Patient 3	38 pg/ml	26 pg/ml	↓ normal range

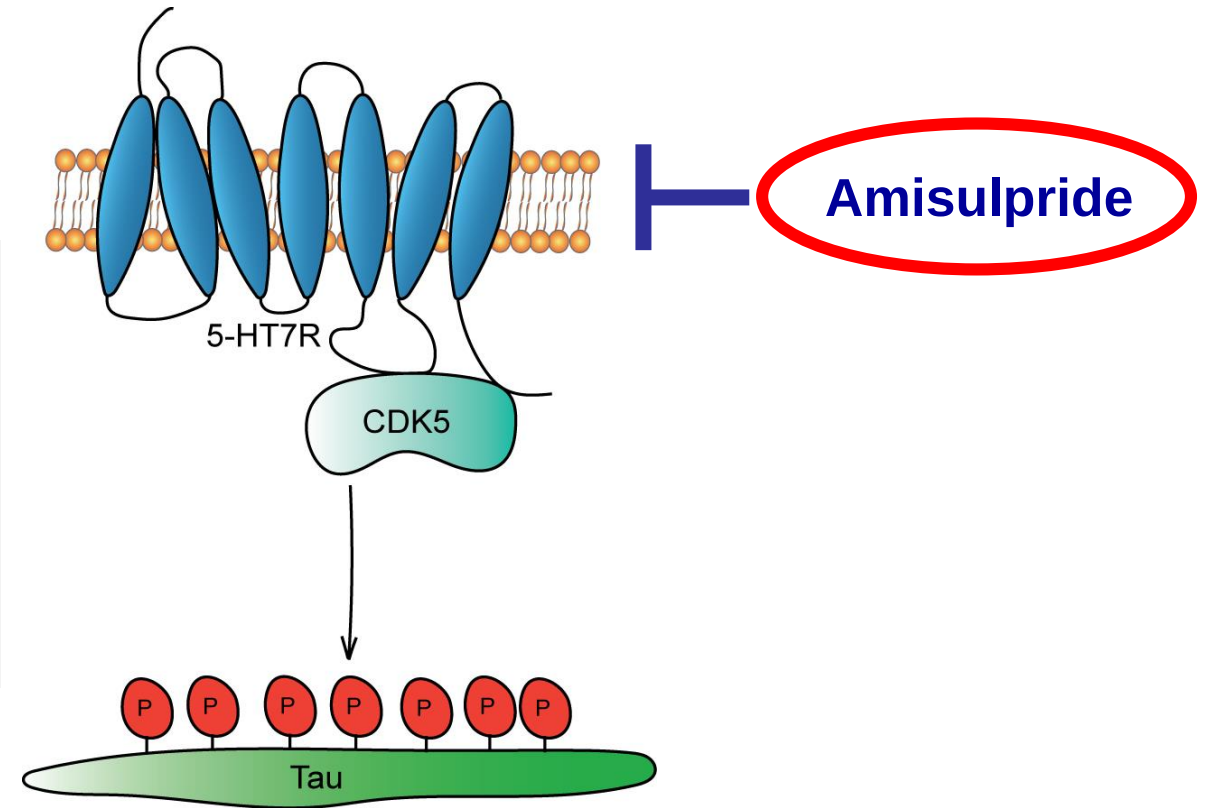


In all three patients, the NfL value decreased - an indication of a potential improvement of neuronal health

Novel strategy to treat tauopathy

Our expertise

- Cellular models of tauopathy and ALS
- Patient's iPSC-derived neurons and astrocytes
- Drosophila and mouse models of tauopathy
- Access to human samples



phosphorylation & accumulation

tangle formation

apoptosis

Cognitive impairment

Our Projects

Astrocytes and Calcium Signalling



Protein Palmitoylation



Serotonin receptors in health and disease



The role of Serotonin in Myocardial infarction



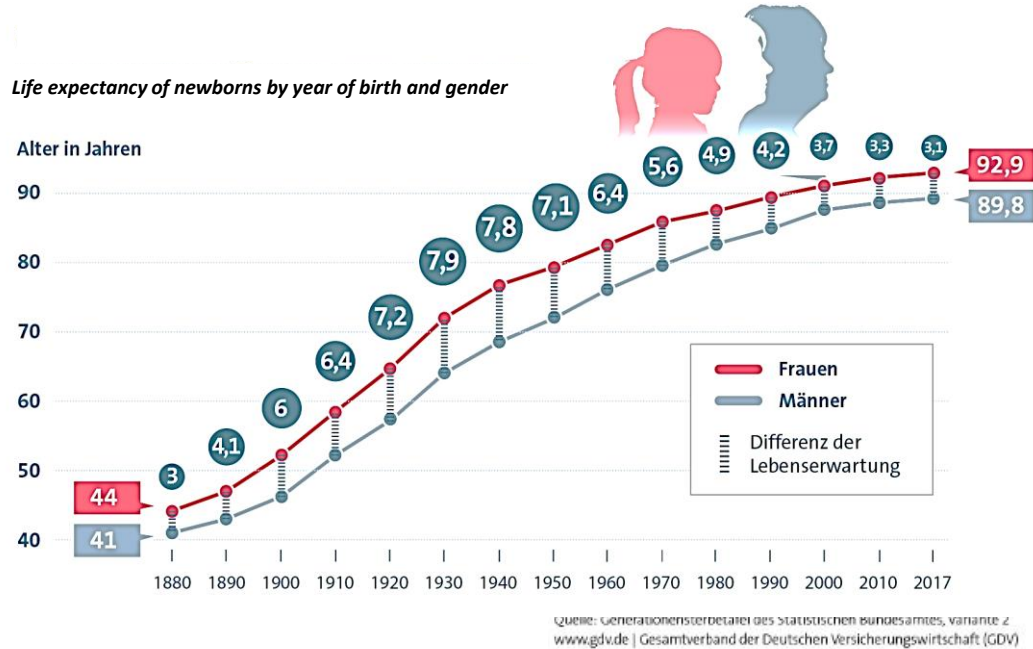
Quantitative Molecular Microscopy



Smartage



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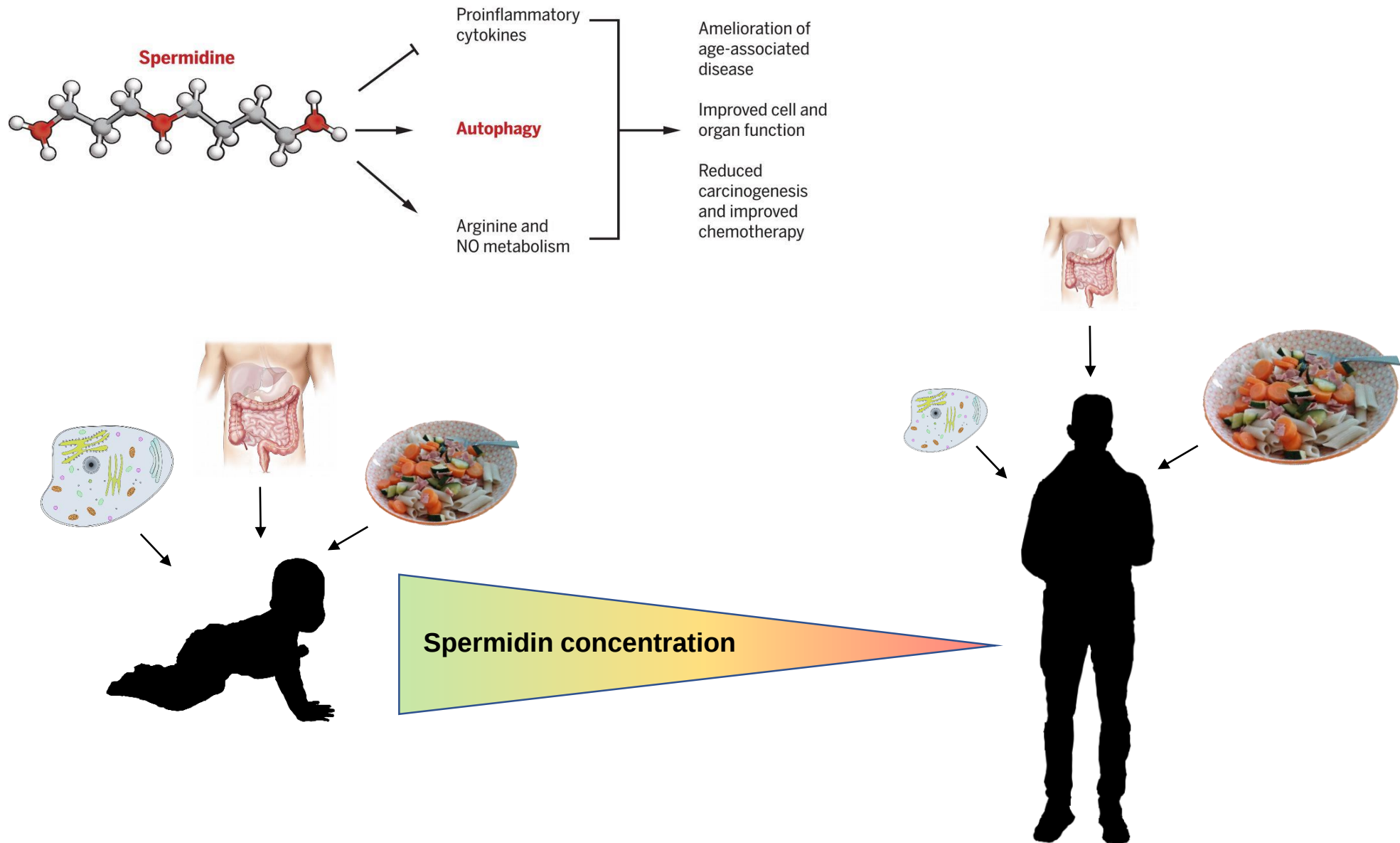
“Dementia robs millions of people of their memories, independence and dignity, but it also robs the rest of us of the people we know and love”

Dr. Tedros Ghebreyesus, Director-General of the WHO



<https://www.lindau-nobel.org/blog-das-alternde-gehirn/>

Spermidine: A Small Molecule with Potent Geroprotective and Anti-Aging Properties



Smartage

Young control



male C57Bl/6J
5 months
normal water

Old control



male C57Bl/6J
17 months
normal water

Late-in-life treatment



male C57Bl/6J
17 months
water suppl. with 3mM Spd⁺

final experiments



5

7



3mM spermidine *ad libidum*

17

age (months)

final experiments

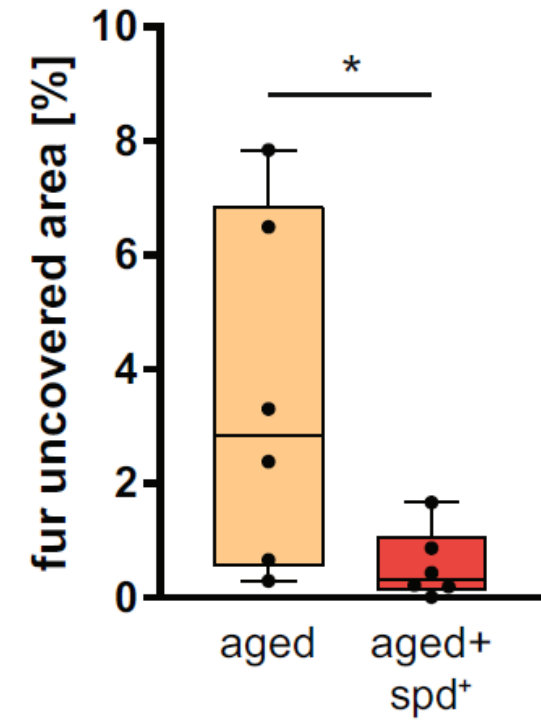
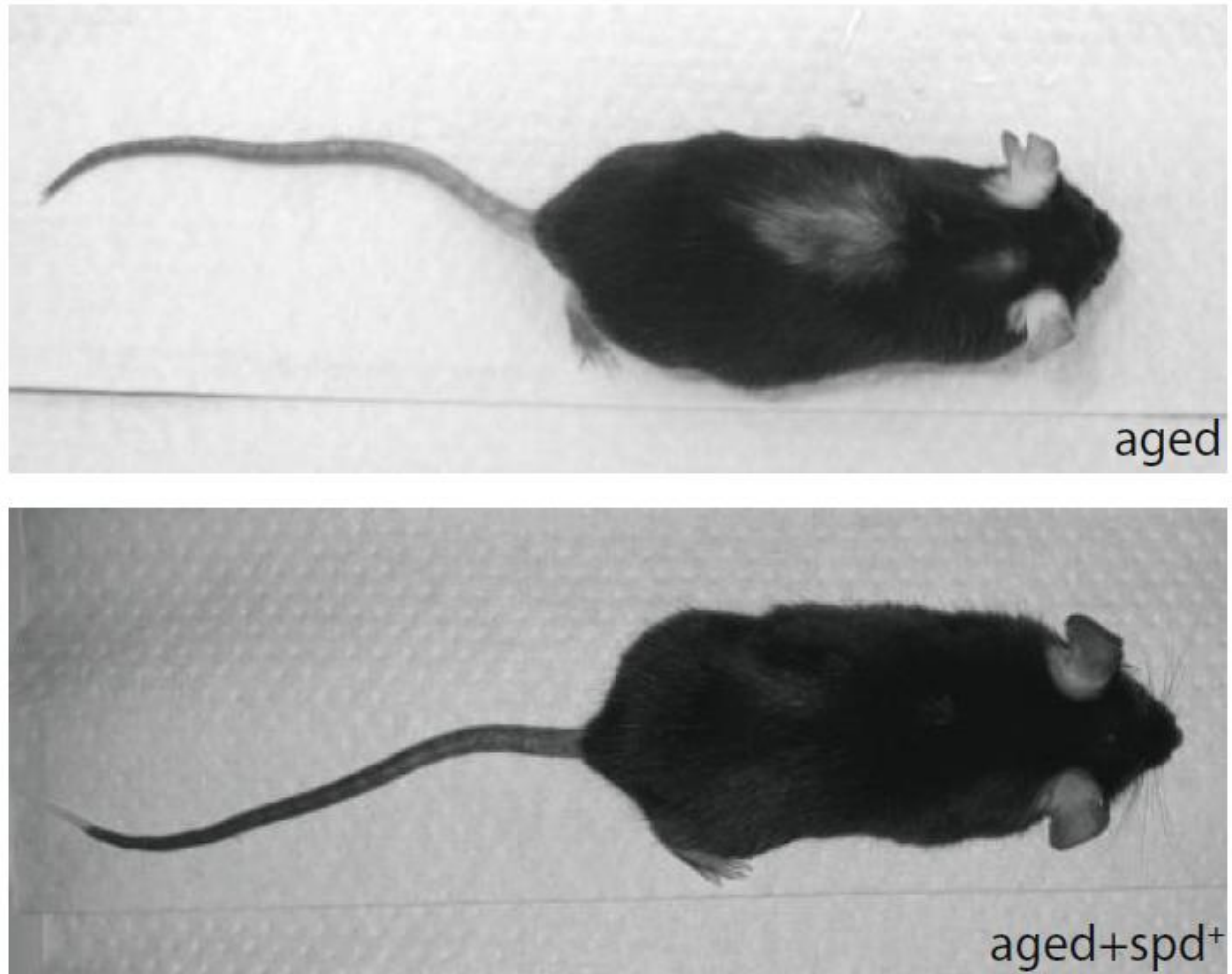


23

24

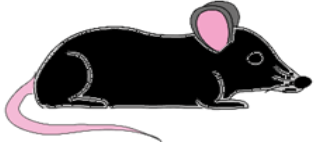


Spermidine and ageing-induced hair loss



Smartage

Young control



male C57Bl/6J
5 months
normal water

Old control

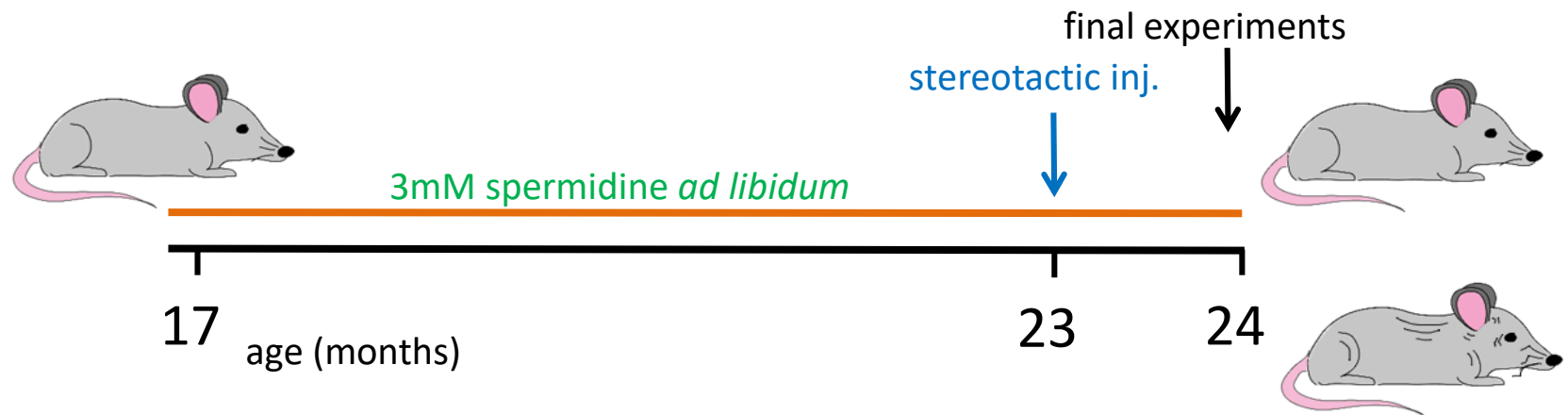
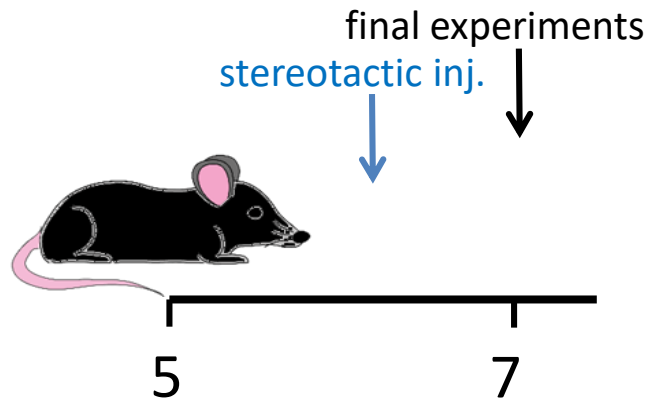


male C57Bl/6J
17 months
normal water

Late-in-life treatment



male C57Bl/6J
17 months
water suppl. with 3mM Spd⁺

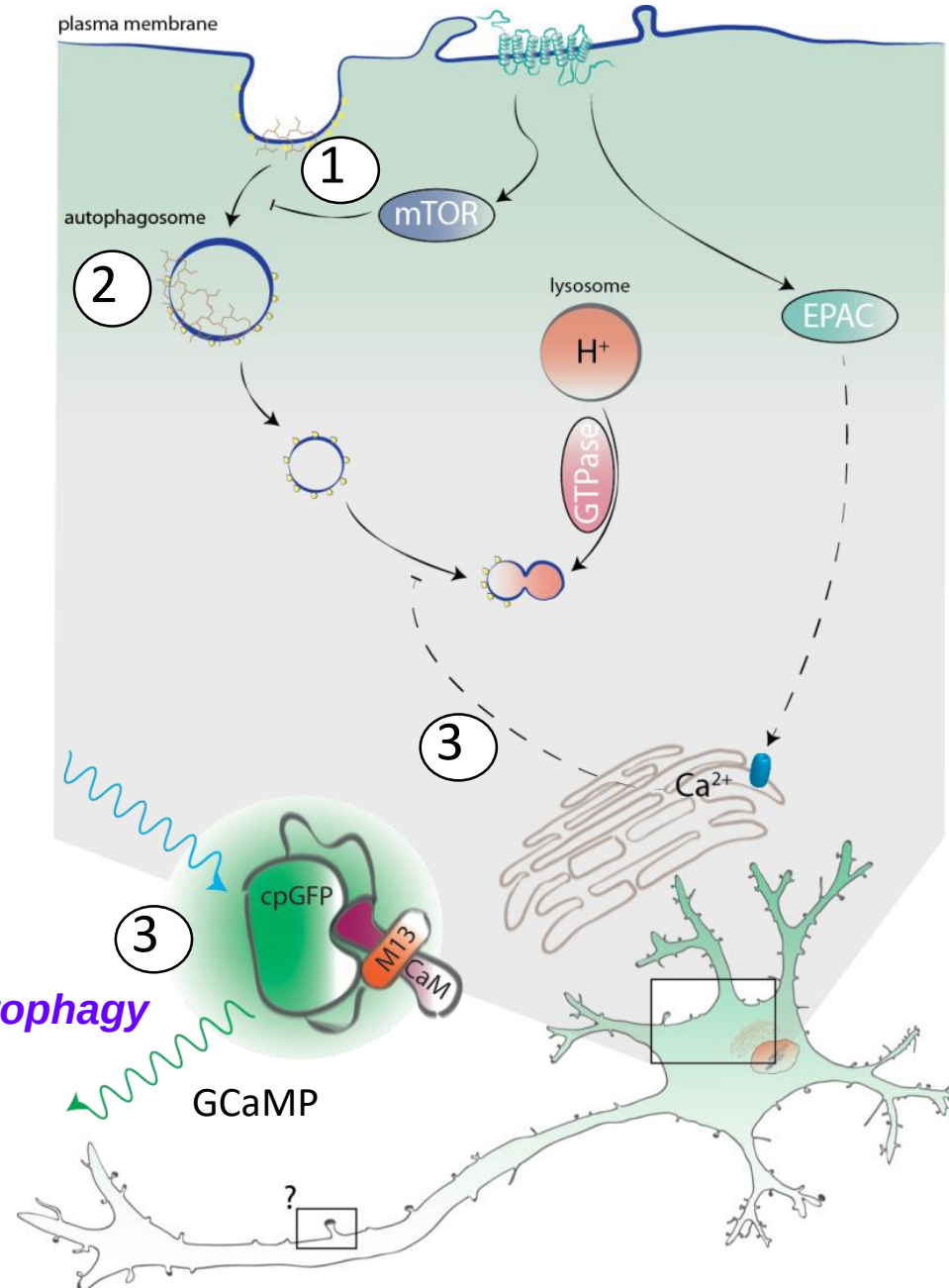


Biosensors used in Smartage project

Injection of AAV-
encoded sensors

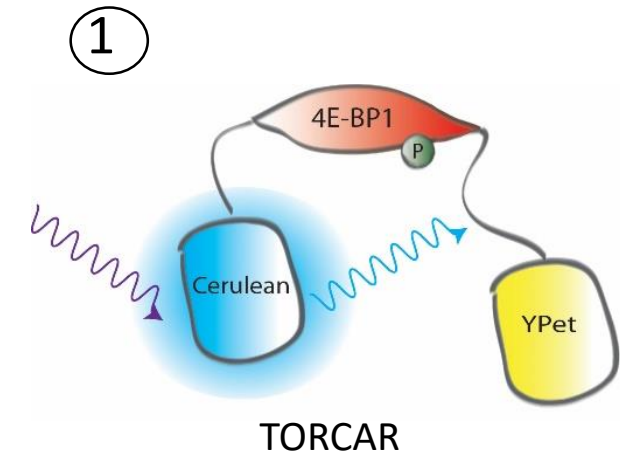


Microscopic
analysis,
Proteomics

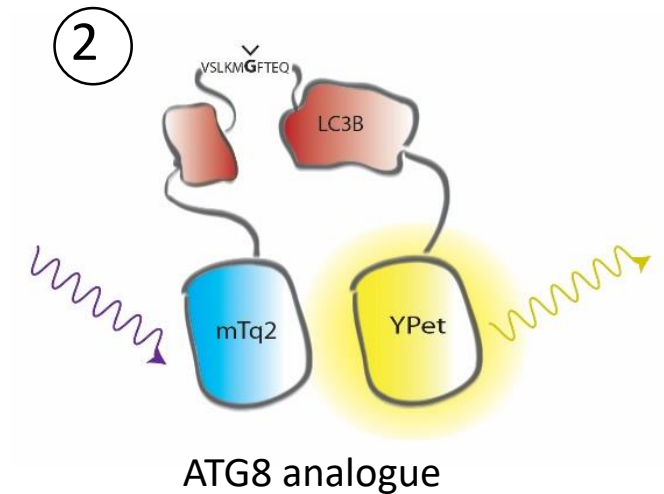


Modulation of autophagy

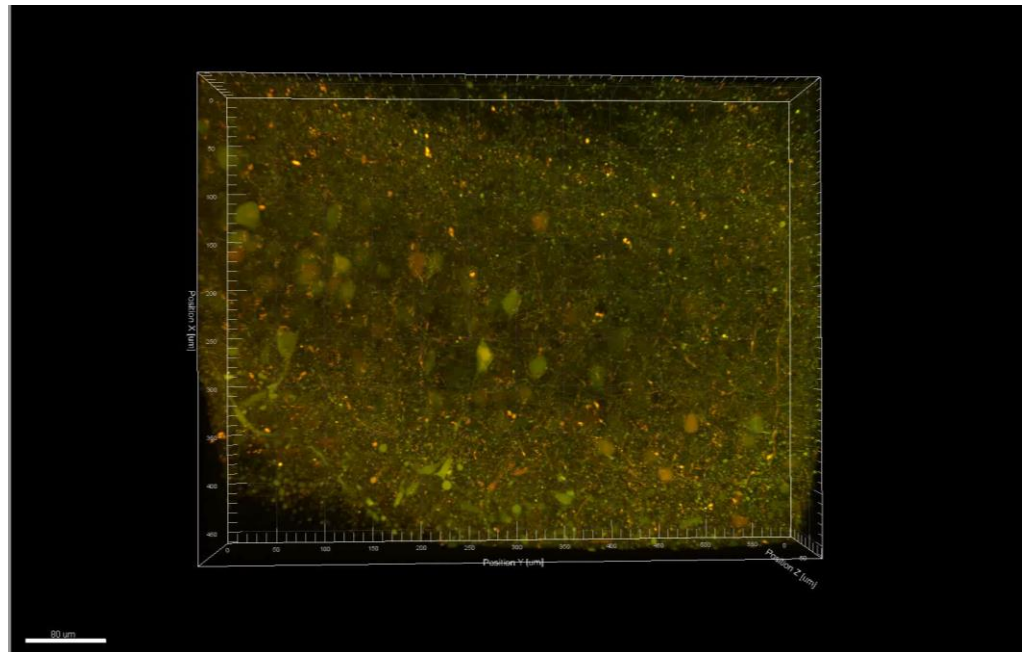
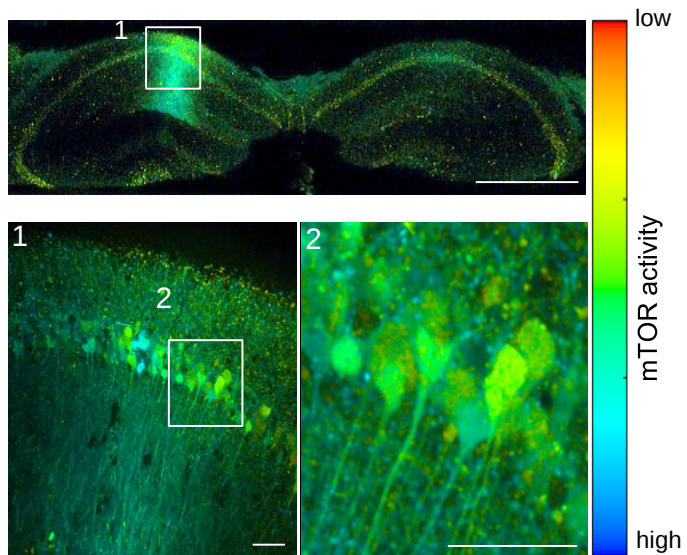
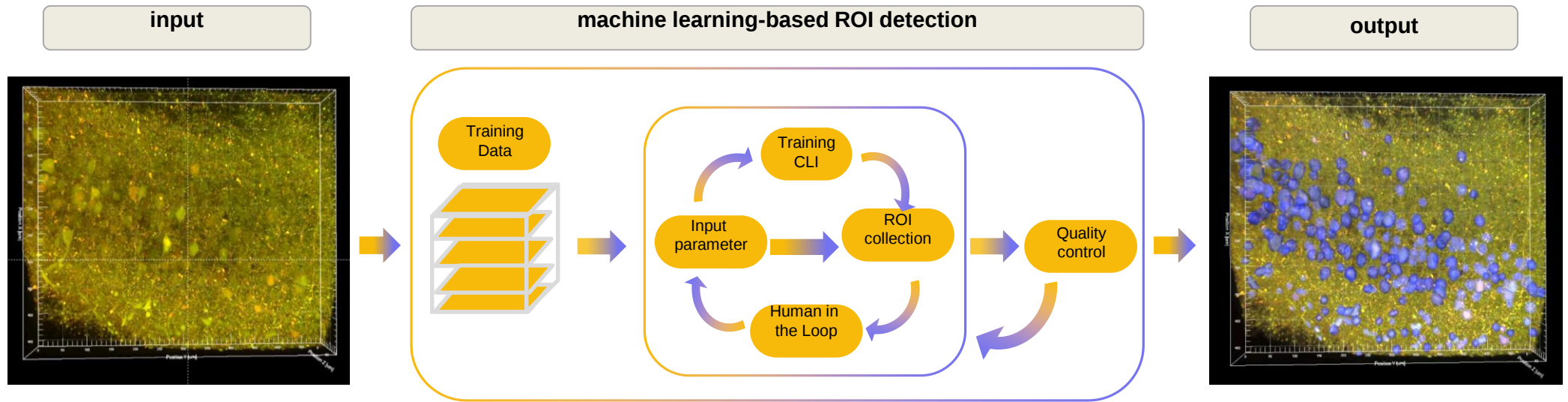
Initiation of autophagy



Formation of autophagosomes

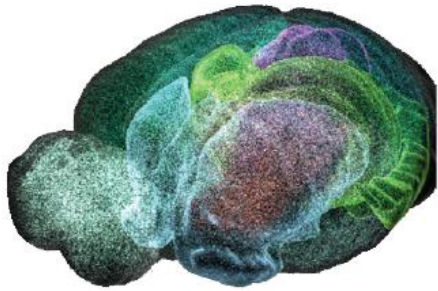


Smartage: Big data analysis



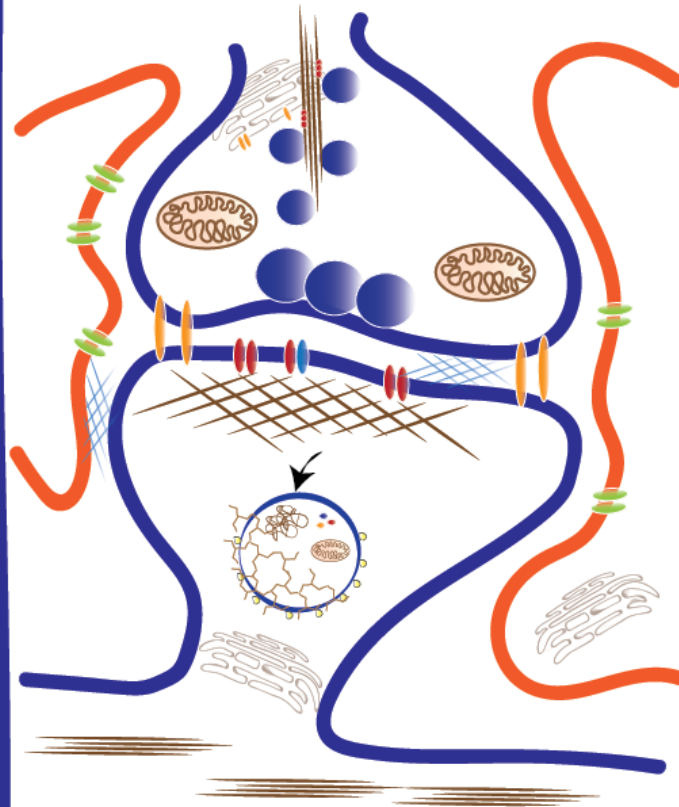
Synaptosomal proteomics in Smartage mice

Brain tissue

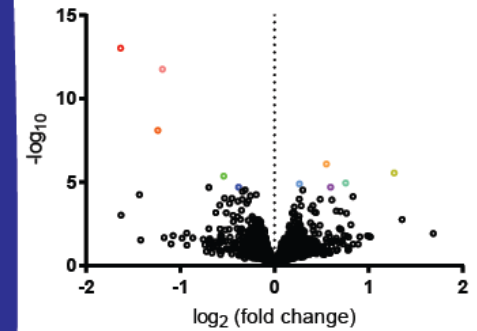
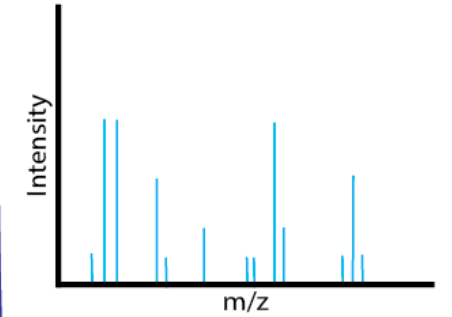


Cortices from young, aged
and aged+spd⁺ mice

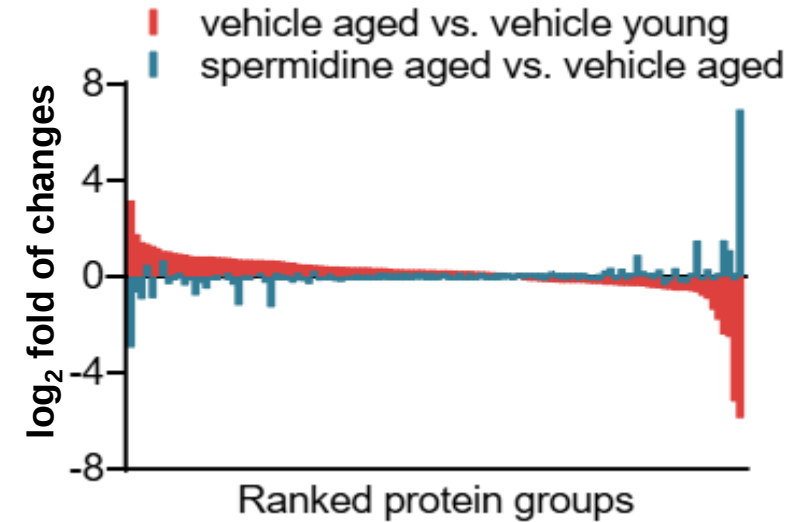
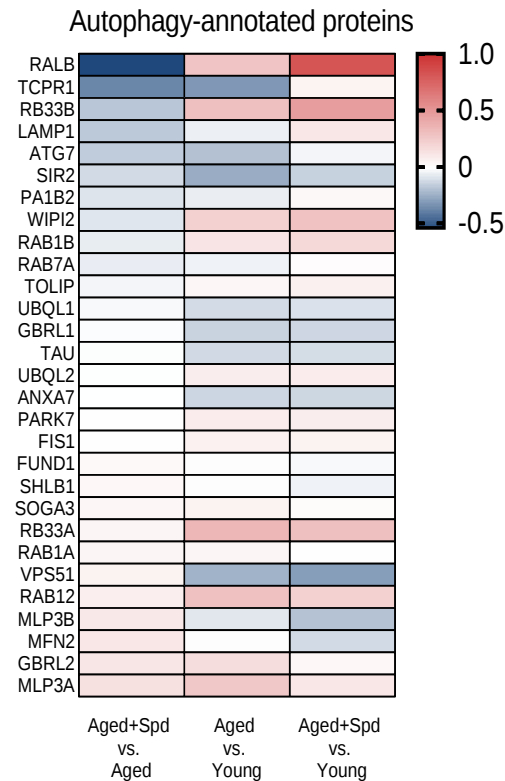
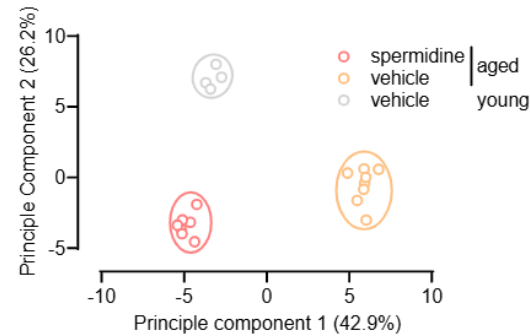
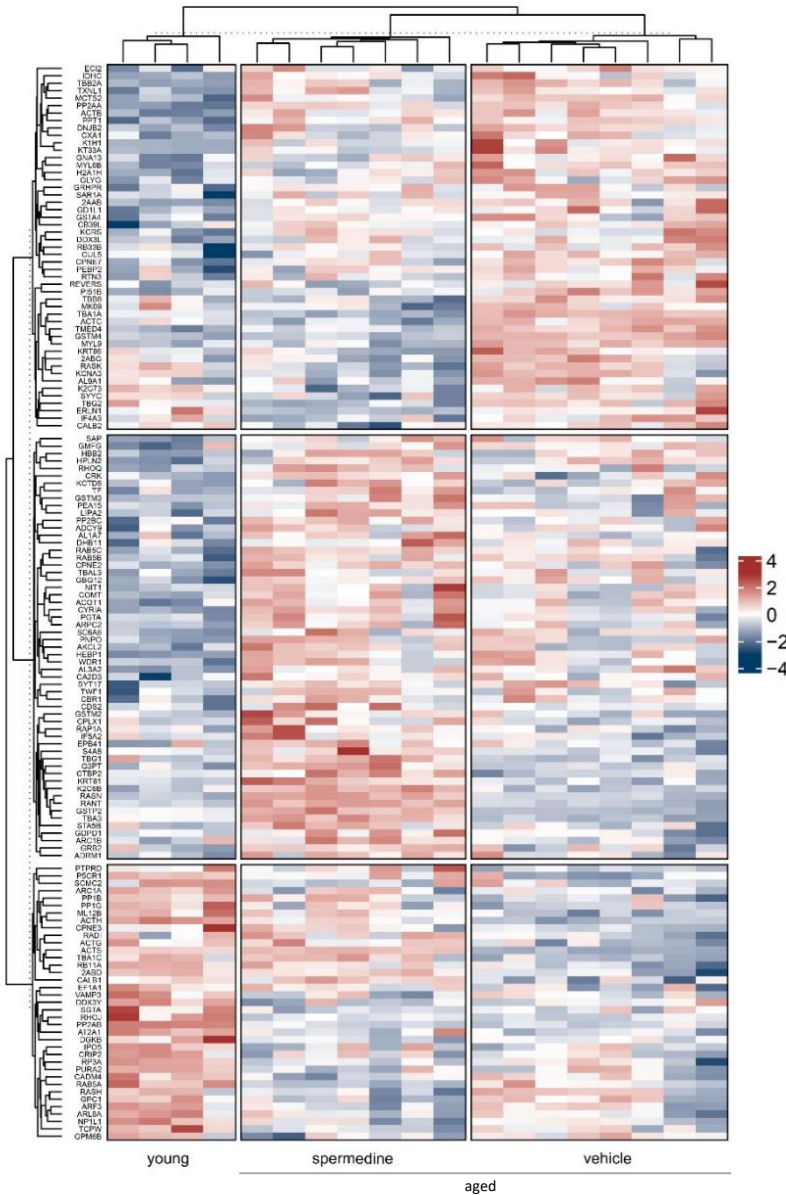
subcellular fractionation



LC-MS/MS analyses



Spermidine modulate multiple signalling pathways in the brain



Our expertise

- Mouse model of ageing
- Drosophila model of ageing
- Set of biosensors for *in vivo* analysis
- State-of-the-art imaging
- Proteomics
- AI- and ML-based big data analysis

Our Projects

Astrocytes and Calcium Signalling



Protein Palmitoylation



Serotonin receptors in health and disease



The role of Serotonin in Myocardial infarction



Quantitative Molecular Microscopy

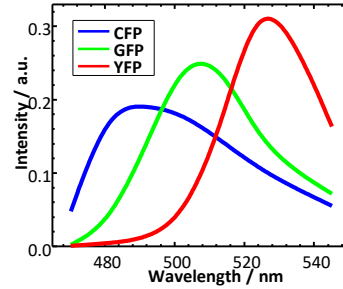


Smartage

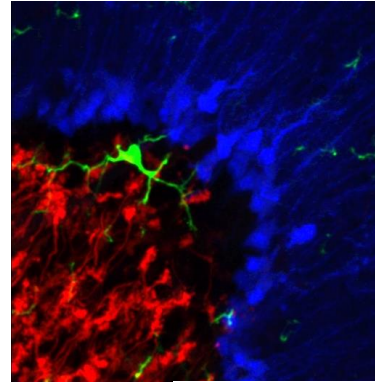


Quantitative Molecular Microscopy

1. Zeiss LSM 780 META + el. Physiol.



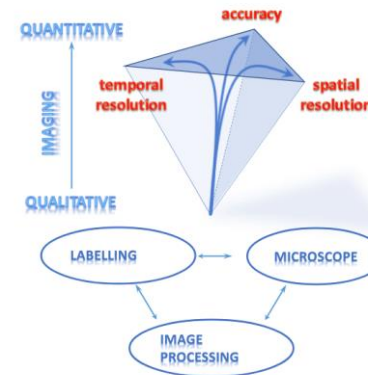
eCFP: Bergmann-Glia
eGFP: Microglia
eYFP: axon terminals



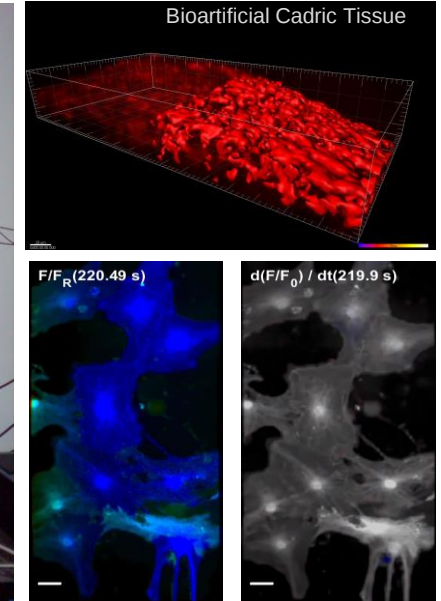
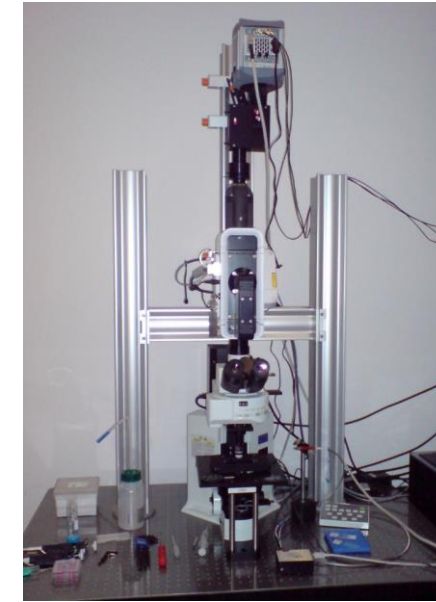
Labelling: Collection of fluorescence-based biosensors (cAMP, small GTPases, LC3, mTOR, MMP9, glutamate, Ca²⁺, voltage sensors, etc.)

Image Processing:

- Big data analysis by HPC cluster
- Own MATLAB scripts for denoising and FRET analysis
- MTED (multi-threshold event detection) analysis of multidimensional data
- AI-based 3D analysis of cell morphology

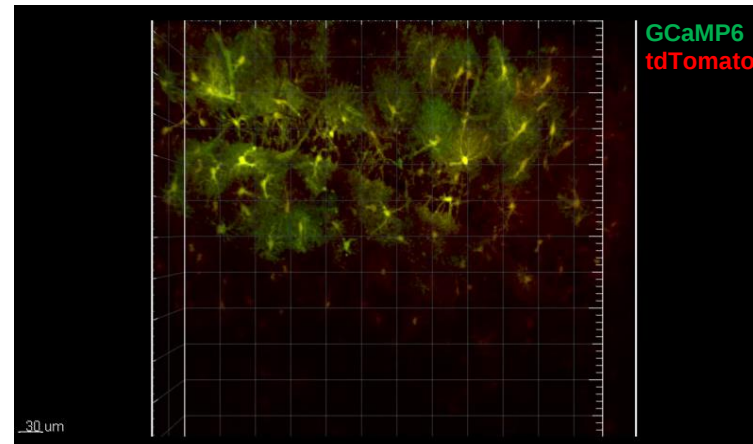


2. Andor Spinning Disk + el. Physiol

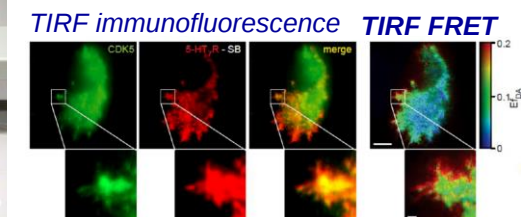
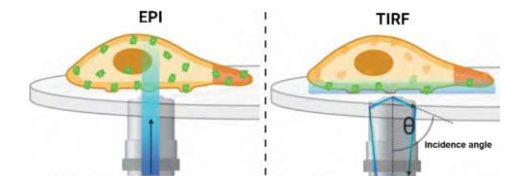


5. Inverses Zeiss LSM 980 mit AiryScan und Multiplex

4. Multiphoton Leica TCS SP8 DIVE (Deep In Vivo Explorer) with FALCON (FASt Lifetime CONtrast)



3. iMic TIRF/FRET



Possible subject: **Innovative Approaches to Treat Neurocognitive Disorders**

Possible scope: **HORIZON-HLTH-2025-03-DISEASE-02-two-stage**

According to the ICD-11 classification, this also includes neurocognitive disorders (6D70-6E0Z), which cover different types of dementia.

Our Team *(open for any suggestions)*

