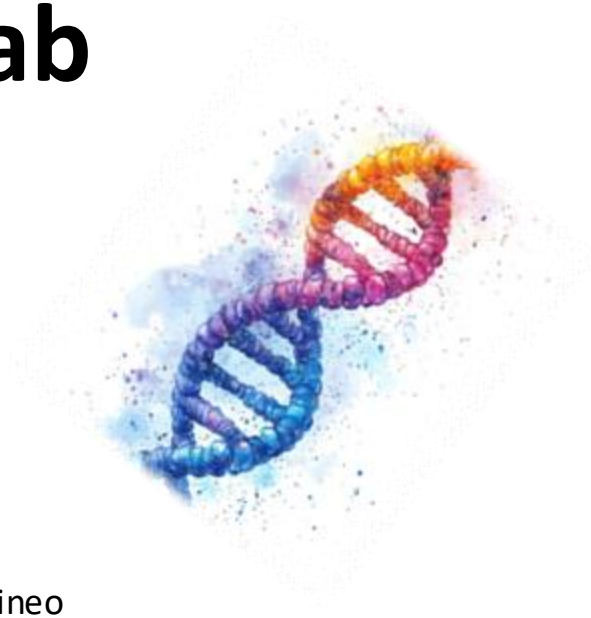
Department of Life Sciences
International Master's Degree in Neuroscience
Corso di Laurea Magistrale in Neuroscienze

LAB PRESENTATIONS

Pharmacogenomics and Molecular Pharmacology Lab



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Speakers: Dr. Giulia Zudeh, Dr. Luca Messineo

Pharmacogenomics and Molecular Pharmacology Lab

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DIPARTIMENTO DI SCIENZE DELLA VITA

Biomarker Identification

Discovery of pharmacogenomic indicators that predict drug response.

Patient-specific Cellular Model Development

Establishing 2D and 3D patient-derived models to simulate in vivo conditions.

Drug Discovery

Screening potential therapeutic compounds on personalized cellular models.

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Pharmacogenomics laboratory

Projects related to **neuroscience**:

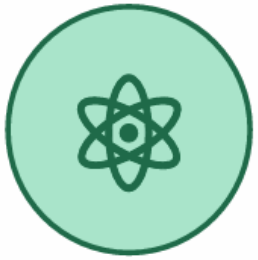
- Pharmacoepigenomics of ketamine;

- Induced pluripotent stem cell (iPSCs)- derived neurons as a model for pharmacological studies in primary immune deficiencies, such as Aicardi-Goutières Syndrome.

Study of the pharmacoepigenomics of ketamine

SEDATIVE, ANALGESIC AND ANESTHETIC AGENT

PROCEDURAL SEDATION IN EMERGENCY DEPARTMENT



N-METHYL-D-ASPARTATE (NMDA) GLUTAMATE RECEPTOR ANTAGONIST IN THE CENTRAL NERVOUS SYSTEM

VOMITING AND RECOVERY AGITATION

DOSE- AND AGE-DEPENDENT EFFECT

Predict the onset of **ketamine-induced adverse effects** in pediatric patients

SCAN ME

Study of the pharmacoepigenomics of ketamine

PATIENTS

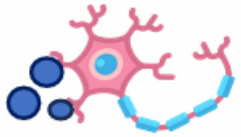
50 pediatric patients

ketamine

44% ADR

56% non-ADR

SAMPLES



neuron-derived extracellular vescicles (NDEVs)

ANALYSES

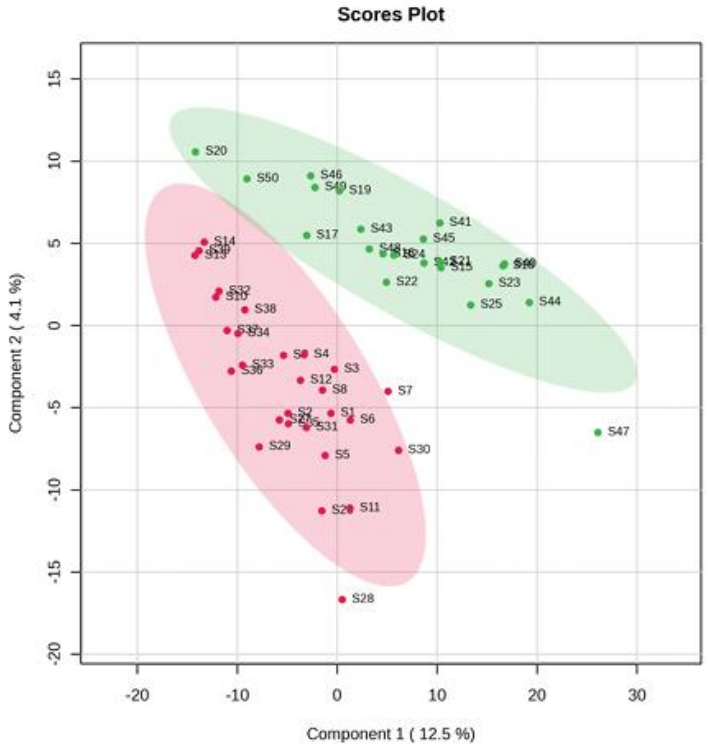
miRNA sequencing

predictive modelling (PLSDA)

differentially expressed miRNAs

gene target and functional analyses

Study of the pharmacoepigenomics of ketamine



miRNA	logFC	FDR
hsa-miR-484	0.51	0.02
hsa-miR-25-3p	0.72	0.025
hsa-miR-486-5p	0.97	0.037
hsa-miR-107	0.63	0.039
hsa-miR-92a-3p	0.64	0.039
hsa-miR-425-5p	0.50	0.05
hsa-miR-363-3p	0.64	0.05
hsa-miR-19b-3p	0.41	0.05
hsa-miR-144-3p	0.74	0.05
hsa-miR-126-3p	−0.37	0.05
hsa-miR-660-5p	0.61	0.05
hsa-miR-19a-3p	0.38	0.05
hsa-miR-15a-5p	0.65	0.05
hsa-miR-451a	0.71	0.05
hsa-miR-24-3p	−0.31	0.05
hsa-miR-144-5p	0.59	0.05

Positive logFC indicates upregulated miRNAs, while negative logFC indicates downregulated miRNAs.

NO
YES

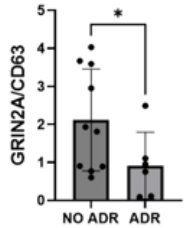
ADR ~ miR-18a-3p +miR-484

miR-484 + miR-107 + miR-19b-3p

up miRNA

- 1670 target genes ("inhibited")

GRIN2A, BDNF, MECP2 (**NMDAR-related genes**)



- Glutamatergic synapse
  Long-term potentiation (LTP)
  Neurotrophin signalling
  Dopaminergic synapse
  Cholinergic synapse

GRIN2A, encoding for the **glutamate ionotropic receptor NMDA** type subunit 2A, **is a target of miR-484, miR-107, and miR-19b-3p**

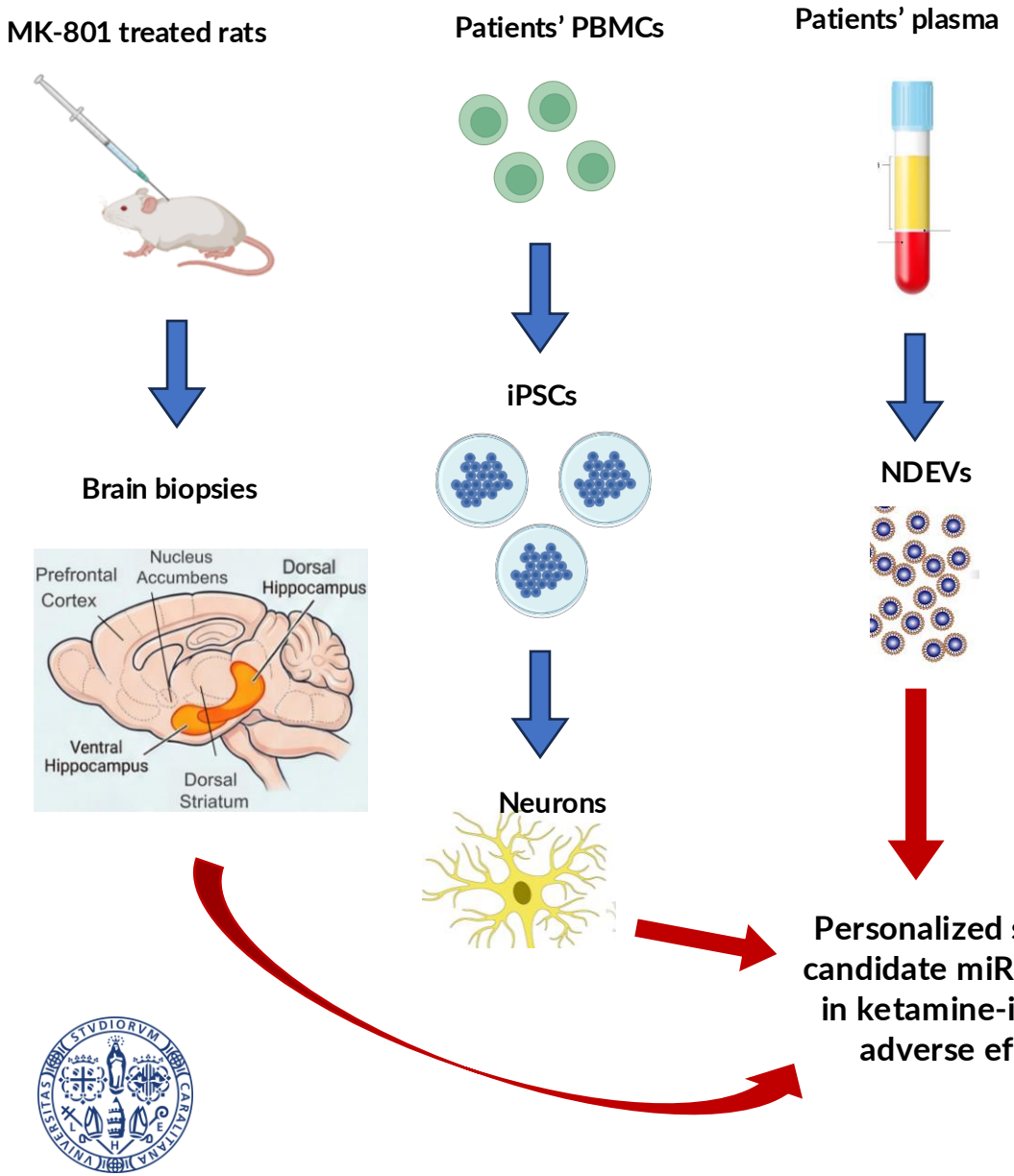
Study of the pharmacoepigenomics of ketamine

AIM OF THE PROJECT

To investigate the functional role of **neuron-derived extracellular vesicles (NDEVs) candidate miRNAs** to provide insights into the molecular mechanisms underlying **ketamine-induced recovery agitation and vomiting** by using **patient-derived iPSCs**.
Investigation of **GRIN2A role** in ketamine-induced side effects.

ANALYSES

- RNA extraction from a schizophrenic rat model biopsies;
- iPSCs generation and differentiation into excitatory neurons;
- Neuron-derived extracellular vesicles (NDEVs) isolation and characterization;
- Assessment of candidate miRNAs expression levels.



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Precision therapy of innovative drugs for pediatric Aicardi-Goutières (AGS) syndrome

AGS is a rare autosomal recessive type-I interferonopathy (ORPHA number 51, www.orpha.net)
1-5 cases every 10.000 people

Disease definition:

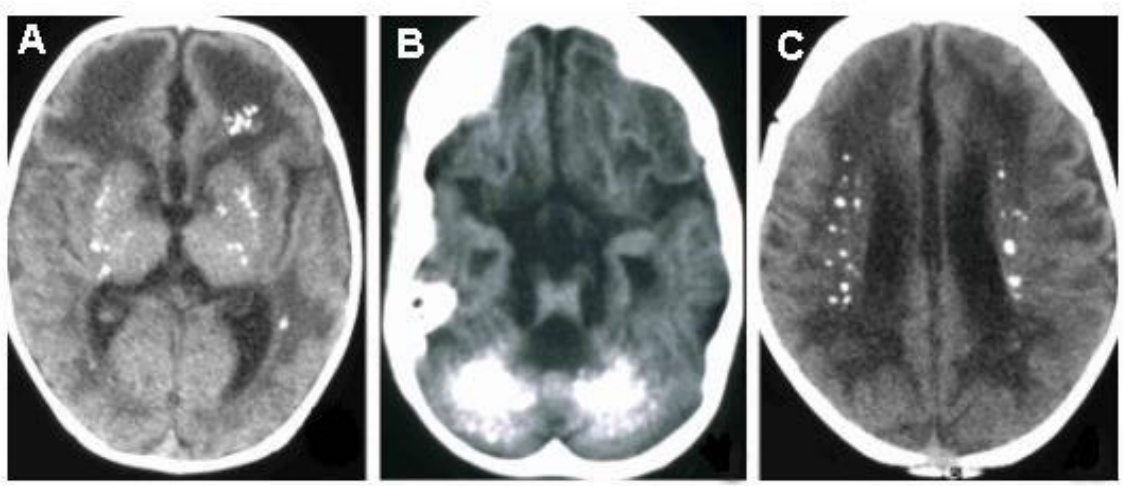
subacute encephalopathy characterized by basal ganglia calcification, leukodystrophy, cerebrospinal fluid (CSF) lymphocytosis

Clinical features of the disease:

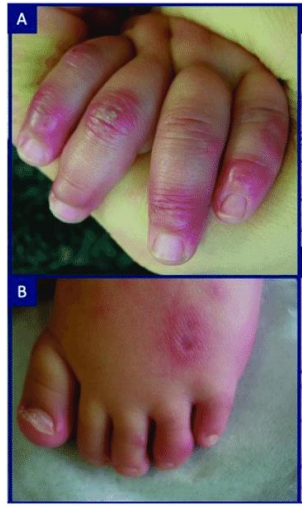
- Neurodevelopmental degeneration
- Microcephaly
- Mental delay and dystonia
- Tetraparesis
- Skin lesions
- Immune manifestations
- **Enhanced type I interferon (INF-I) signaling** in blood and CSF

- Poor life expectation

Around 10% of patients die within the first 5 years of life



Intracranial calcification on CT scan in individuals with AGS. Calcification is seen in the basal ganglia (A), in the dentate nuclei of the cerebellum (B) and in a periventricular distribution (C). Rice et al., 2007



Rice et al., 2007

Precision therapy of innovative drugs for pediatric Aicardi-Goutières (AGS) syndrome

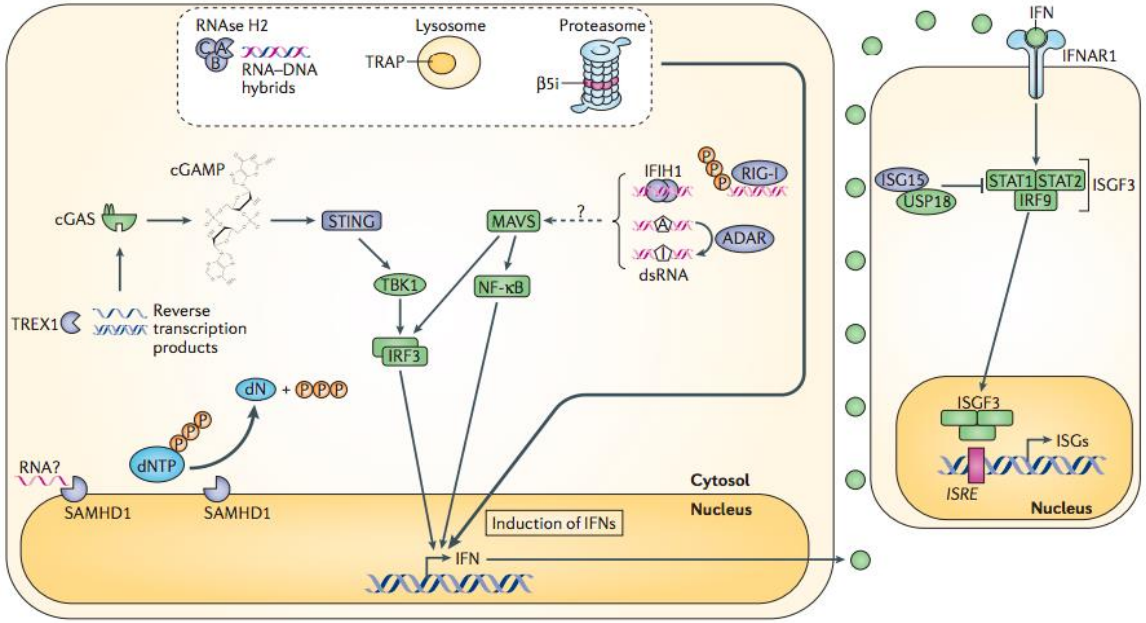
AGS is classified in **9 sub-types** based on the causative mutation

AGS SUBTYPE	MUTATED GENE	CYTOGENETIC LOCATION	FUNCTION
AGS1	*TREX1*	3p21.31	DNA 3' to 5' exonuclease, prevents autoimmunity caused by endogenous retroelements.
AGS2	*RNASEH2B*	13q14.3	Beta subunit of the human ribonuclease H2 enzyme complex which cleaves ribonucleotides from RNA:DNA duplexes.
AGS3	*RNASEH2C*	11q13.1	Subunit C of the human ribonuclease H2 enzyme complex which cleaves ribonucleotides from RNA:DNA duplexes.
AGS4	*RNASEH2A*	19p13.13	Subunit A of the human ribonuclease H2 enzyme complex which cleaves ribonucleotides from RNA:DNA duplexes.
AGS5	*SAMHD1*	20q11.23	Converts deoxynucleoside triphosphates to constituent deoxynucleoside and inorganic triphosphate.
AGS6	*ADAR1*	1q21.3	Converts adenosine to inosine in double strand RNA.
AGS7	*IFIH1*	2q24.2	Encodes for a cytoplasmic receptor that senses dsRNA viral products to activate type I interferon signaling through the MAVS adaptor molecule.
AGS8	*LSM11*	5q33.3	Part of the U7 small nuclear ribonucleoprotein (snRNP) complex involved in the processing of RDH pre-mRNAs.
AGS9	*RNU7-1*	12p13.31	Role in processing the 3-prime stem-loop structure of replication-dependent histone pre-mRNAs.

Table 1. AGS subtypes and their genetic alterations (OMIM-Online Mendelian Inheritance in Man database)

Mutations occur in genes involved in **nucleic acid metabolism**:

Accumulation of cytosolic nucleic acids, that trigger the type-I interferon production

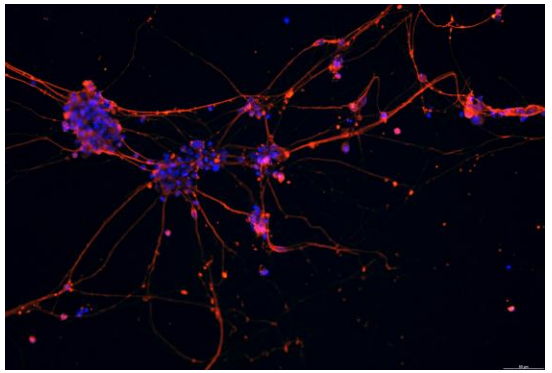


Crow et al, 2015.Nat Rev Immunol.

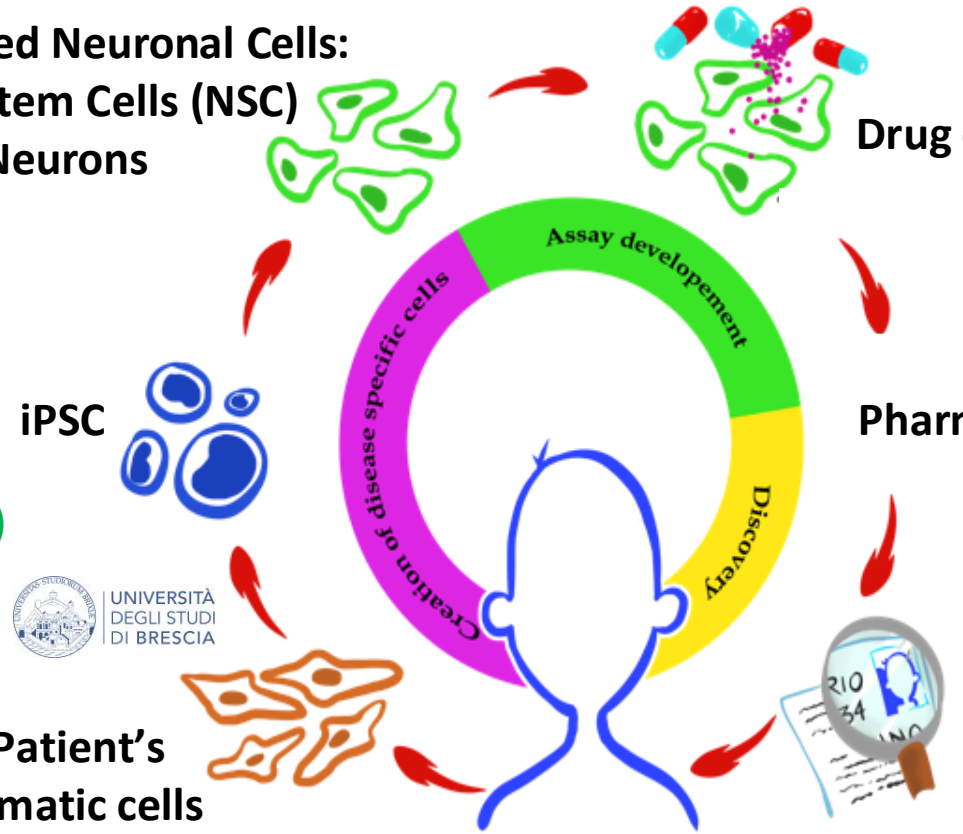
Precision therapy of innovative drugs for pediatric Aicardi-Goutières (AGS) syndrome

AIM OF THE PROJECT

Evaluate **safety and efficacy of drugs** on **AGS patient-specific *in vitro* model of patient-specific neural stem cells and differentiated neurons**



Differentiated Neuronal Cells:
-Neural Stem Cells (NSC)
-Neurons



- Glucocorticoids
- Thiopurines
- JAK inhibitors
- reverse transcriptase inhibitors
- STING inhibitors

-cells deriving from AGS patients
-cells deriving from a healthy control (BJ)

✓ **DRUG SAFETY**
❖ **DRUG EFFICACY**

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