FRRB: Regional Foundation for Biomedical Research (Lombardy)

CALL “Unmet Medical Needs”

PROJECT: “DROP BY DROP”
Deciphering the molecular signature in Kleefstra syndrome: proof of principle working model for chromatinopathies

OFFICIAL START: May 15th 2023
3 MAJOR AIMS:

✓ Classification of KS patients based on genotype and phenotype
  Italian Registry

✓ Testing drugs counteracting the detrimental effects of mutations in the patients' LCLs

✓ Modeling selected patient-specific mutations with 3D brain organoids for assessing ameliorative effects of drugs selected in aim 2
6 WORKPAKAGES:

**Policlinico Hospital - Milan**

**WP1**: Setting up a Registry of the Italian patients with Kleefstra syndrome

**WP2**: Biobanking of immortalized lymphoblastoid cell lines (LCLs)

**Papa Giovanni XXIII Hospital - Bergamo**

**WP3**: Precise characterization of genetic imbalances causing Kleefstra syndrome in each patient, in the attempt to establish a genotype/phenotype correlation

**WP4**: Quantification of the mutated gene product to classify the patients on the basis of pathophysiological mechanisms

**University of Milan**

**WP5**: Testing drugs counteracting the detrimental effects of causative mutations in the immortalized lymphoblastoid cell lines

**WP6**: Modeling selected patients-specific mutations with 3D cerebellar organoids for assessing possible ameliorative effects of drugs selected in the WP5
6 WORKPAKAGES:

Policlinico Hospital - Milan

**WP1**: Setting up a Registry of the Italian patients with Kleefstra syndrome

**WP2**: Biobanking of immortalized lymphoblastoid cell lines (LCLs)

Papa Giovanni XXIII Hospital - Bergamo

**WP3**: Precise characterization of genetic imbalances causing Kleefstra syndrome in each patient, in the attempt to establish a genotype/phenotype correlation

**WP4**: Quantification of the mutated gene product to classify the patients on the basis of pathophysiological mechanisms

University of Milan

**WP5**: Testing drugs counteracting the detrimental effects of causative mutations in the immortalized lymphoblastoid cell lines

**WP6**: Modeling selected patients-specific mutations with 3D cerebellar organoids for assessing possible ameliorative effects of drugs selected in the WP5
6 WORKPAKAGES:

Policlinico Hospital - Milan

WP1: Setting up a Registry of the Italian patients with Kleefstra syndrome

WP2: Biobanking of immortalized lymphoblastoid cell lines (LCLs)
WP1: KS REGISTRY

PATHOLOGY REGISTRY

- CENTRALIZED SYSTEM
- HOMOGENEOUS DATA

Three main aims:

- DIAGNOSTIC CRITERIA
- GENOTYPE-PROGNOSIS CORRELATION
- WELL ESTABLISHED SANITARY SERVICES

CLINICAL DATA

- NEURODEVELOPMENTAL ASPECTS
  - SLEEP
  - BEHAVIOURAL
  - REGRESSION
- MALFORMATIONS AND DYSMORPHISMS
- ADULT AGE

Epidemiological study

- SYNDROME INCIDENCE
- TERRITORY DISTRIBUTION

Biobanking

- WP2: Biobanking of immortalized lymphoblastoid cell lines (LCLs)

Clinical Research

- ADEQUATE COHORT
- DIAGNOSTIC CRITERIA
- G/P CORRELATIONS
WP1: KS REGISTRY

CLINICAL ACTIVITY

QUESTIONNAIRE
- ANAGRAPHIC
- PRENATAL
- NEURODEVELOPMENTAL DISEASES
- FUNCTIONAL MULTISYSTEM DISEASES

MEDICAL EXAMINATION
- FACIAL FEATURES
- SKIN/ADNEXA FEATURES
- SKELETAL DISORDERS
- GENITOURINARY MALFORMATIONS
WP1: KS REGISTRY

- **Web-based**
- **Four thematic areas**
  - General information
  - Clinical data
  - Instrumental data
  - Genetical data
- **Modular cards**
  - ADD NEW FEATURES (VERTICALLY)
  - UPDATED FEATURES (HORIZONTALLY)
- **Universal language (english, HPO vocabulary)**

**PATHOLOGY REGISTRY**

- CENTRALIZED SYSTEM
- HOMOGENEOUS DATA

**Three main aims:**

- DIAGNOSTIC CRITERIA
- GENOTYPE-PROGNOSIS CORRELATION
- WELL ESTABLISHED SANITARY SERVICES
WP1: KS REGISTRY

EPIDEMIOLOGICAL STUDY

- SYNDROME INCIDENCE
- TERRITORY DISTRIBUTION

IN ITALY 50-60 KNOWN CASES

HEALTHCARE SYSTEM IMPLEMENTATION
WP2: BIOBANKING

CHROMATINOPATHIES CORRELATIONS

KS CLINICAL FEATURES

CHROMATINOPATHIES CLINICAL FEATURES

BIOBANKING

WP2: Biobanking of immortalized lymphoblastoid cell lines (LCLs)
WP2: Biobanking of immortalized lymphoblastoid cell lines (LCLs)

Papa Giovanni XXIII Hospital - Bergamo

WP3
- Confirmation of missense mutations
- Precise characterization of genomic imbalances (breakpoints)

WP4
- Quantification of the mutated gene product

WP5
- *In vitro* drugs testing

WP6
- 3D cerebellar organoids

Selection of patients-specific mutations
Epigenetic disorders: Lessons from the animals–animal models in chromatinopathies
Rubinstein-Taybi and Cornelia De Lange Syndromes


Lithium as a possible therapeutic strategy for Cornelia de Lange syndrome. Grazioli et al., Cell Death Discovery 2021.
drop by drop…

… proof of principle of approaching workflow for rare disease
THANKS!

Bergamo Hospital
Papa Giovanni XXIII
Maria Iascone
Laura Pezzoli

University of Milan
Cristina Gervasini
Valentina Massa

Milan Hospital Policlinico
Donatella Milani
Camilla Meossi
Federica Gaudioso

lpezzoli@asst-pg23.it