ALL IN(VOLVED)

27 • 28 • 29 JUNE 2025

Rome (Italy)

SCIENTIFIC COMMITTEE:
Ana Mingorance, Massimiliano Bianchi, Michela Fagiolini

An event organized by **CDKL5 insieme verso la cura**
In collaboration with **CDKL5 Middle East and North Africa**

CDKL5 INSIEME VERSO LA CURA

CDKL5 MIDDLE EAST & NORTH AFRICA
الشرق الأوسط وشمال أفريقيا

Friday 27th of June

From 10.00 **Welcome and registration** at the event reception desk located at the hotel entrance. Welcome bag delivery

13.00 **Buffet lunch for presidents** (with family) and pharma

15.00 - 16.30 **Meeting: "Different organizations, same objective"** - "Properzio" room
- Attendees: Presidents of the CDKL5 Foundations and Associations
- Coordinator: Antonino Caridi - CDKL5 UK President - IFCR President - CDKL5 Alliance President

16.30 - 17.00 **Light snack**

17.00 - 18.30 **Meeting with industry** - "Properzio" room
- Attendees: Presidents of the CDKL5 Foundations and Associations, pharmaceutical company representatives
- Coordinator: Antonino Caridi

18.30 **Meeting all participants** - "Olimpico" room

19.00 **All in 1 photo** - "Olimpico" room

19.30 **Dinner for children and cdkl5 guests**

20.00 **General dinner** for all participants

Saturday 28th of June

8:40 **ALL IN(FORMED)** - "Olimpico" room

8:50 - 9:00 **Welcome** - Antonino Caridi - "Olimpico" room

9:00 - 12:35 / 15:00 - 18:00 - "Catullo" room

1:1 meetings – Researchers, Pharma, Clinicians, Representatives of the associations

9:00 - 10:30 **ALL IN(FORMED) Part 1** - "Olimpico" room

Chair: Dr. Ana Mingorance

- **Intro: Progress in the last 12 months**
  Dr. Ana Mingorance (LouLou Foundation)
- **Where we are with understanding CDKL5 and CDD**
  Prof. Tim Benke (University of Colorado School of Medicine)
- **CANDID study update**
  Dr. Xavier Liogier (LouLou Foundation)
- **ELPIS Global Biomarker study update**
  Prof. Massimiliano Bianchi (Ulysses Neuroscience Ltd.)
- **Caregivers' voice in leveraging CDD burden**
  Carol-Anne Partridge (Co-Founder, Chairperson and Family Support Champion CDKL5 UK)
- **Q&A**

10:30 - 10:45 **Break**

10:45 - 12:15 **ALL IN(FORMED) Part 2** - "Olimpico" room

Chair: Prof. Massimiliano Bianchi

- **Spotlights on Enzyme Replacement Therapy**
  Prof. Maria Luisa Tutino (University of Naples Federico II)
  Prof. Elisabetta Ciani (University of Bologna)
- **Spotlight on Gene Therapy**
  Dr. Stuart Cobb (Neurogene Inc)
- **Spotlight on X reactivation**
  Dr. Kyle Fink (University of California, Davis)
- **Spotlight on the DEEp Ocean trial**
  Marina Trivisano (IRCCS Ospedale Pediatrico Bambino Gesù)
- **Q&A**

12:15 - 12:35 **ALL IN(FORMED) Part 3** - "Olimpico" room

• **Comprehensive Physical Therapy Intervention for children with CDKL5 deficiency**

Dr. Priscila Cunha Santos - Senior Pediatric Physical Therapist Neurology and Neuroscience in High Hopes Dubai Pediatric Therapy Center

Dr. Kunali Doshi - Senior Pediatric Therapist in High Hopes Dubai Pediatric Therapy Center

13.00 **Lunch for children and cdkl5 guests**

13.30 **General lunch** for all participants

13:30 - 15:00 **Poster Presentation Session** - Inside the hotel in the corridor that runs alongside the "Olimpico" room

GROUP A researchers with projects that want to pitch to pharma, and pharma

15.00-18.00 **ALL IN PARTNERING** - "Olimpico" room

Attendees: projects that want to pitch to Pharma, and Pharma representatives

15:00 - 16:00 **Research on new therapies**

Chair: Dr. Dan Lavery

• **X reactivation**

Dr. Kyle Fink (University of California, Davis)

• **Enzyme Replacement Therapy**

Prof. Maria Luisa Tutino (University of Naples Federico II)

Prof. Elisabetta Ciani (University of Bologna)

• **Small Molecules Targeting Microtubules**

Prof. Massimiliano Bianchi (Angel Neurotherapeutics Ltd.)

5 minute data blitz - Poster winner Presentation

16:00 - 17:00 **Assays to screen for new therapies**

Chair: Prof. Michela Fagiolini

• **Zebrafish Model in CDKL5**

Prof. Leonor Cancela (University of Algarve)

• **Drosophila Model in CDKL5**
Dr. Maria del Carmen Martín (Príncipe Felipe Research Center)
• **Preclinical Models and Biomarkers in CDKL5**
Dr. Enya Paschen (Ulysses Neuroscience Ltd.)
Dr. Connor Maltby (Ulysses Neuroscience Ltd.)

GROUP B **families, children and other guest**

15.00-18.00 **ALL IN 1 BIG FAMILY** - Outside the hotel, near the "Olimpico" room
• **Pet therapy**
Auriga Onlus
A.N.U.C.S.S. (ETS)

15.00-19.00 **Saliva samples & Elpis biocollection** - "Properzio" room

19.00 **Dinner for children and cdkl5 guests**

19.30 **General dinner for all participants**

21:15 **Poster winner award ceremony**

following
• **Feel Good With Music**
by Mauro D'Alessandro - Director of the BATTiTi New School of Music in collaboration with Ciro Paduano
• **Wishing tree decoration**

Sunday 29th of June

9:30 **ALL IN 1 COMUNITY** - "Olimpico" room
#1minuteofhope - Italy

9:40-9:50 **Introduction of the day** - Mais Kanan - CDKL5 MENA
#1minuteofhope - Perù

9:50 - 10:20 **Story of two parents** – Lynn and Majid Jafar - Loulou Foundation
#1minuteofhope - USA

10:20-10:50 **Sibling** - Alessandro Caridi - CDKL5 insieme verso la cura
#1minuteofhope - Canada

10:50-11:20 **A possible future: Perspective and Dreams** – Dott.ssa Michela Fagiolini
#1minuteofhope - Japan

11:20-11:50 **The Strength of the Community: From Isolation to Embrace**
Part 1: Sandra Pérez Berdugo, Jose A. Ortiz Miranda - AACDKL5 Spain
#1minuteofhope - Ukraine
Part 2: Manuel Vigara Zafra - AACDKL5 Spain
#1minuteofhope - Mena

11:50-11:55 **Collaboration and commitment** - Luca Cordero di Montezemolo - Fondazione Telethon President

11:55-12:15 **The Role of Patient Associations in the Research Pathway** - Laura Romano - Fondazione Telethon
#1minuteofhope - France

12:15-12:25 **Conclusion** - Barbara Verdirame - CDKL5 insieme verso la cura

12:25 -12:30 **Music video All in(volved)**

12.45 **Lunch for children and CDKL5 guests**

13.15 **General lunch for all participants**

Greetings until we'll meet again

Abstract - Poster

TITLE

Functional characterization of a cdkl5 zebrafish mutant reveals neurodevelopmental and sensory-motor deficits relevant to CDKL5 deficiency disorder

AUTHORS

Salamanca M.[2], Andriotto S.[4], Albanesi A. [2], D' Angelo D. [2], Franco L. [2], Raffaello A. [2],Bonaldo P., Braghetta P.[3], Miletto Petrazzini ME.[2], dal Maschio M.[1,2]. and Facchinello N. [4]

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ABSTRACT

Mutations in the CDKL5 gene are associated with CDKL5 Deficiency Disorder (CDD), a rare X-linked developmental encephalopathy marked by severe neurodevelopmental delay, microcephaly, autistic-like behaviors, epilepsy, muscle tone impairment, and sleep disturbances. In this study, we established a cdkl5 zebrafish mutant line using CRISPR-Cas9 technology to target the catalytic domain of the Cdkl5 protein. Morphological analysis of cdkl5 mutant zebrafish revealed significant developmental delays compared to wild-type controls, including reduced body length, decreased brain width and volume associated with a significant reduction in neuronal population. Regarding the locomotor behavior in response to light-dark stimulation, the mutant fish exhibited a significantly reduced free swimming distance with a peculiar pattern of initial hyper-activity and increased turning frequency. Treatment with the proconvulsant agent PTZ, showed an increase in both parameters, interestingly with a significantly reduced impact on the mutant than the control group. Evaluation of the relative population of gabaergic cells across the whole imaged brain, revealed a 10% reduction of the Gad1B-positive cells in the mutant fish. Whole brain analysis of spontaneous activity showed on average that the mutants have a larger number of coactive neurons with a reduction on the event duration for the retino-recipient regions and for the thalamic complex. Analysis of visually-induced activity in the Tectum and Cerebellum showed a compression in the retinotopic representation of the visual field and altered motion direction encoding. Lastly, when we assessed the oculomotor response in mutant fish to examine their basic visuomotor integration, we found that bout number and vigor, along with the tail beat frequency were significantly impaired. In conclusion, we present a functional characterization of a cdkl5 mutant line. This model provides a valuable tool for unraveling the complex mechanisms underlying CDD and advancing targeted therapeutic strategies.

TITLE

Targeting Microtubule Dynamics in CDKL5 Deficiency Disorder (CDD): Initial Validation of Novel Compounds and Behavioural Characterization in Cdkl5 Mutants

AUTHORS

Davide Selleri[1,2,] Enya Paschen[1], Connor Maltby[1], Cian Gavin[1], Jessica Pinto[1], Priya Jayabal[1], Massimiliano Bianchi[1,3]

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ABSTRACT

CDKL5 Deficiency Disorder (CDD) is a rare developmental and epileptic encephalopathy (DEE) caused by CDKL5 gene mutations. Patients show early-onset epilepsy, cognitive and motor impairments, and behavioural abnormalities. CDKL5 interacts with microtubule (MT)-associated proteins, and its deficiency alters dendritic arborization, reduces spine density, and impairs synaptic organization; processes linked to MT dysregulation.

Preclinical studies highlighting that Cdkl5 loss induce MT dysregulation suggest the cytoskeleton as a promising therapeutic target in CDD. In this context, we investigated the effects of novel synthetic neurosteroid derivatives targeting microtubules.

We characterized the behavioural phenotype of male Cdkl5-knockout (KO) and female Cdkl5- heterozygous (HET) mice and identified hyperactivity, decreased burrowing and nest building behaviour as well as increased anxiety as robust phenotypes in the male Cdkl5-KO. As expected the mosaic nature of the female Cdkl5-HET resulted in a mild behavioural phenotype. After the behavioural characterization, we conducted a pilot study involving the repetition of the behavioural tests after sub-chronic treatment with ULY-333 (10 mg/kg, s.c.; once a day for 12 days), the parent compound of our new class of neurosteroids. This regimen led to a partial rescue of some of the behavioural deficits observed in Cdkl5-deficient mice. Moreover, infrared Western blot analysis of brain region homogenates showed a trend toward recovery of a-tubulin post-translational modifications (PTMs), such as acetylation and tyrosination, which are markers of microtubules dynamics and were found dysregulated in both CDD patients and models.

These findings support MT-targeting neurosteroids as a potential therapeutic approach to restore behavioural and molecular functions in CDD.

TITLE

"Exploiting microRNAs-derived extracellular vesicles to disclose novel biomarkers and therapeutic approaches for CDKL5 deficiency disorder".

AUTHORS

V. Cardinale[1], G. Chiantia[1], D. Comai[1], C. Cicconetti[2], F. Anselmi[2], A. Marcantoni[3], S. Oliviero[2], A. Gurgone[1] & M. Giustetto[1].

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ABSTRACT

CDKL5 deficiency disorder (CDD) is a severe neurodevelopmental disease caused by mutations in the X-linked CDKL5 gene, leading to cognitive, motor, and autonomic dysfunctions. As our hope is that therapeutic strategies will soon emerge, the identification of objective, non-invasive, and manageable biomarkers is urgently needed.

Because mounting evidence show that by analysing the content of extracellular vesicles (EVs), membrane-bound nanoparticles released by cells, novel biomarkers and molecular causes of neurological conditions have been revealed, we thought to use the same approach for CDD. To this aim, we performed miRNA profiling of salivary EVs from over 20 CDD patients and neurotypical controls, we identified 17 differentially expressed miRNAs (DEmiRNAs), many are brain-enriched and linked to pathogenic processes such as autism and epilepsy. To strengthen the data obtained from the initial group, 15 out of 20 CDD patients underwent a one-year follow-up study. Current analyses are aimed at identifying best suitable DEmiRNAs candidates as biomarkers for CDD. In parallel, EVs were isolated from cultured cortical neurons (NDEVs) of both CDKL5-KO and WT mice. We observed that WT neurons treated for 48 hours with CDKL5-KO NDEVs exhibited severe alterations in both transmitter release and connectivity of excitatory synapses. Intriguingly, treating CDKL5-KO neurons with WT-NDEVs rescued the excitatory synaptic defects shown by these cells. Finally, miRNomic profiling of CDKL5-KO NDEVs has revealed several DEmiRNAs that are associated with neuronal organization, synaptic development and function pathways by GO enrichment analyses. Thus, these data disclosed that: (a) salivary EV-derived miRNAs hold promise as accessible, non-invasive, molecular biomarkers for CDD; (b) CDKL5 may play a role of in EV-mediated cell-to-cell communication; (c)miRNAs are potential therapeutic targets for the disease.

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TITLE

Functional impact of pathological CDKL5 mutations in CDKL5 deficiency disorder: generation of cellular and neuronal models to study microtubule-related functions

AUTHORS

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[2]Laboratory of Medical Cytogenetics and Molecular Genetics, Centro di Ricerche e Tecnologie Biomediche, IRCCS Istituto Auxologico Italiano, Milano, Italy.

ABSTRACT

Mutations in CDKL5 cause CDKL5 Deficiency Disorder (CDD), a rare neurodevelopmental condition. Most patients are heterozygous females who, due to random X-chromosome inactivation, are mosaics expressing either the wild-type or mutant allele. Based on mutation type, patients can be grouped into those with nonsense or frameshift mutations (leading to complete loss of CDKL5) and those with missense mutations (resulting in catalytically inactive CDKL5). It is well established that CDKL5 regulates microtubule (MT) functions through its interaction with MT-binding proteins, including the plus-end tracking protein CLIP170. CDKL5 loss impairs CLIP170's ability to bind MTs and interact with partners such as dynactin, leading to defects in neuronal morphology and MT-dependent transport. Pharmacological targeting of CLIP170 has been shown to improve structural and cognitive deficits in Cdkl5 knockdown models, highlighting its therapeutic potential. However, the impact of hypomorphic CDKL5 variants on MT dynamics and CLIP170 function remains poorly understood. To address this point, we generated human iPSC-derived neurons from peripheral blood of a CDD patient carrying the CDKL5-N71D missense mutation. This variant disrupts CDKL5's kinase activity without affecting its stability. N71D neurons exhibit abnormal morphology, including shortened axons, reduced dendritic arborization, and enlarged growth cones, along with mislocalization of CLIP170 and dynactin at the growth cone. To further dissect the impact of hypofunctional CDKL5, we are generating CRISPR-Cas9-edited cell lines expressing pathogenic missense variants. These models will allow direct comparison between CDKL5 loss and hypofunctionality on MT-dependent processes, contributing to establish a genotype–phenotype correlation, which remains to be fully explored in CDD.

TITLE

Gut-Brain Axis and Circadian Dysregulation in a Mouse Model of CDKL5 Deficiency Disorder

AUTHORS

M.G. Giuliano[1*], A. Tognozzi[2*], F. Damiani[3], K.C. Ashtiani[4], G. Vecchieschi[3], S. Cornuti[3], A. Miniati[1], E. Putignano[5], V. Suckow[6], V.M. Kalscheuer[6], P. Baldi[4], T. Pizzorusso[3], R. Mazziotti[7], P. Tognini[1]

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ABSTRACT

CDKL5 deficiency disorder (CDD) is a rare neurodevelopmental condition characterized by intellectual disability, seizures, and comorbidities such as gastrointestinal dysfunction and sleep disturbances. Despite their clinical relevance, the mechanisms underlying these symptoms remain poorly understood. Our research aims to uncover the underlying pathophysiology of CDD and identify novel biomarkers by focusing on these comorbid aspects.

We recently demonstrated that gut microbiota composition in a CDD mouse model differs from that of wild-type (WT) mice. Notably, antibiotic treatment ameliorated dysbiosis and improved both behavior and neuronal function. Moreover, fecal transplantation could transfer the phenotype of CDKL5 KO mice to WT recipients, suggesting a key role for the microbiome in modulating neurodevelopmental outcomes. To further explore CDD pathophysiology, we focused on sleep disturbances and explored the role of circadian rhythms. We conducted a detailed chronobiological analysis. Thermographic recordings revealed increased locomotor activity and elevated body temperature in Cdkl5 KO mice, particularly at light-phase transitions. Sleep analysis showed reduced total sleep time and shorter sleep bouts. Transcriptomic profiling of suprachiasmatic nucleus (SCN) and hippocampus across six time points revealed an expanded set of oscillating genes in KO mice, with altered phase distribution. Notably, GO enrichment of SCN-specific oscillating genes indicated immune- and inflammatory-related processes. Metabolic cage data identified disruptions in feeding, drinking, and respiratory exchange ratio daily rhythms. Together, these findings suggest that CDKL5 loss disrupts circadian regulation, with potential downstream effects on sleep, metabolism, and brain immune function. Combined with our microbiome data, these results support a multifactorial model of CDD and may inform future therapeutic strategies.

TITLE

Early detection of motor alterations in mouse models of Cdkl5 deficiency disorder and Rett Syndrome through automated analysis

AUTHORS

Livia Cosentino, Chiara Urbinati, Lisa Scansalegna, Bianca De Filippis
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ABSTRACT

CDKL5 deficiency disorder (CDD) and Rett syndrome (RTT) are rare neurological disorders characterized by cognitive, social, motor, and physiological impairments that emerge in infancy and predominantly affect females. Both conditions are caused by de novo mutations in X-linked genes. Their low prevalence and sporadic nature make diagnosis particularly challenging, often requiring experienced clinicians. Consequently, the path to clinical recognition is frequently long and often occurs after the closure of critical periods of brain development, when interventions become less effective. Emerging evidence revealed mild motor alterations during early postnatal life in both patients and mouse models, supporting the potential use of computer vision tools for automated action-based identification of at-risk newborns. Exploiting the standardization provided by animal models, we aimed at providing proof that the automated analysis of motor patterns can help recognizing mouse pups carrying CDD- and RTT-causing mutations before the onset of overt symptoms. To this end, we collected videos of spontaneously moving mouse pups during the first postnatal weeks of life, and trained action recognition models to distinguish mutant from wild type (wt) mouse pups based on their estimated poses. When evaluated on independent data, the model successfully differentiated between mutant and wt pups across postnatal ages, and stratifying the training data by age significantly improved prediction accuracy. Our findings highlight the potential of automated detection of CDD and RTT in animal models by leveraging early spontaneous movement alterations that precede full symptoms development and support the future application of this methodology in clinical settings to benefit patients.

Special thanks

with the patronage

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il CAAmaleonte

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