EPTRI
European Paediatric Translational Research Infrastructure

EPTRI SCIENTIFIC MEETING

BOOK OF ABSTRACTS

BOLOGNA, ITALY

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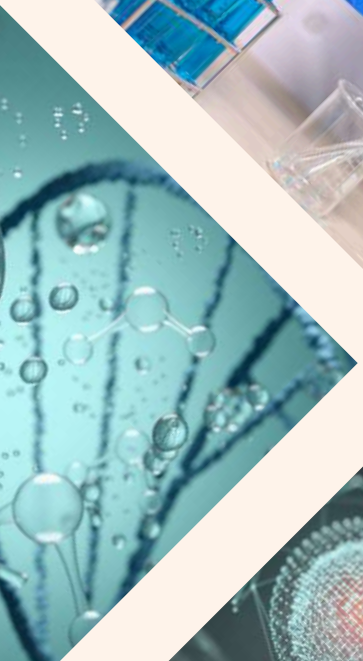

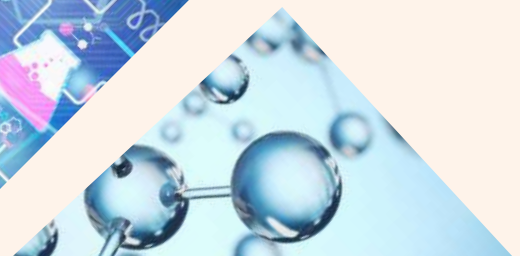

“The Challenge of Paediatric Research”

SPEAKER SECTION

SPEAKER: VIVIANA GIANNUZZI

Challenges and opportunities for paediatric research from the new proposed EU rules

Viviana Giannuzzi[1]

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In the paediatric field, non-profit research has always played a key role in advancing knowledge and evidence-based resources.
Over the past twenty years, the EU Paediatric Regulation (EC) 1901/2006 has established a system of obligations, incentives and rewards to stimulate the Research and Development (R&D) of medicines for children.
Currently, the Paediatric Regulation is being revised as part of the ongoing revision of the General EU Pharmaceutical legislation aimed at improving the availability and access to effective and affordable medicines, including those for children and rare disease patients. In this context, the European Commission has proposed a regulation and a directive that are in the hands of the European Council.
Among the proposed rules, the ones that would more greatly impact on the paediatric no-profit research deal with: unmet medical needs identification, repurposing, mechanism of action criteria for Paediatric Investigation Plans (PIPs), possible simplification of the PIP procedure, hospital exemptions for advanced therapies, participation in EMA activities.
As an example, multi-stakeholder actions have been proposed to identify unmet medical needs, even if no paediatric-specific provisions have been proposed, in contrast with the current applicable provisions of the Paediatric Regulation. Moreover, the opportunity for non-profit entities to present data for authorising therapeutic indications will demand researchers to liaise with regulatory authorities and possibly turn off-label to approved uses. Academia will also expect to contribute to identifying paediatric conditions potentially targetable by a drug based on its mechanism of action.
In conclusion, the proposal to revise the EU pharmaceutical legislation is promising for EU citizens and for special populations, like children. The proposed changes in the regulatory pharmaceutical landscape will affect paediatric research and academia will be demanded to strengthen its regulatory expertise to participate in the R&D of paediatric medicines.

SPEAKER: RICCARDO MASETTI

The gut microbiome in paediatric stem cell transplantation: challenges and perspectives

Davide Leardini[1], Merli Pietro[2], Muratore Edoardo[1], Venturelli Francesco[1], Marasco Giovanni[3], Leardini Davide[1], Baccelli Francesco[1], Bossu' Gianluca[1], Belotti Tamara[1], Marangoni Antonella[4], Djusse Marielle Ezekielle[4], Lazzarotto Tiziana[4], Prete Arcangelo[1], Faraci Maura[5], Cefalo Maria Giuseppina[2], Angelino G[2], Quagliarella F[2], Brigidi Patrizia[6], Gabelli Maria[7], Barbara Giovanni[3], Locatelli Franco[2], Masetti Riccardo[1]

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Background: FMT has become the standard of care for Clostridium difficile resistant infections and has been explored for other indications in the field of hematopoietic stem cell transplantation (HSCT). Indeed, in this setting it has been used to treat steroid refractory (sr)-GvHD (Malard F, 2023) as well as to decolonize patients carrying a MDRO (Battipaglia G, 2019). Additionally, microbiota diversity before HSCT has been associated with transplant outcome both in adults (Peled J, 2020) and children (Masetti R, 2024). Despite increasing use, FMT has been rarely performed in pediatric hematologic patients; here, we report the experience of 3 Italian centers.

Methods: we collect data of all pediatric patients receiving a FMT in 3 pediatric Italian centers (Roma, Bologna and Padova) for one of the 2 indication: i) sr-GvHD or ii) decolonization of MDRO (in this case, as additional inclusion criteria, the patient had to be scheduled or had already received an allogeneic HSCT).

Results: 28 patients were included, with a median age at FMT of 4,0 years (range 0.8-18.6), 16, 9 and 3 from Rome, Bologna, and Padova, respectively. The indication for allo-HSCT was oncologic disease in 20 and non-oncologic in 8. The donor was HLA-identical sibling in 6, haploidentical family member in 11, matched unrelated donors in 9 and cord blood in 2 cases. Stem cell source was Bone Marrow in 50%. Eighteen patients received FMT for eradication of MDR germs, 5 for treatment of intestinal SR-GvHD, and 5 for both indications. A total of 45 infusions of FMT were performed (median of 1/patient, range 1-4), via upper digestive tract, using endoscopy in 17 patients, a naso-jeujenal tube in 9 and percutaneous endoscopic jejunostomy in 2. In all cases, an unrelated fecal donor was selected, with frozen material employed in 93% of patients. No severe adverse events were observed following the procedure, 5 patients reported grade I-II adverse events (abdominal pain, nausea, SIRS) (Table 1). Regarding eradication of MDR bacteria, 14 received FMT pre allo-HSCT, while 9 a median of 263 days post-transplantation (range 55-487). The decolonization rate was 74% and 50% at 1- and 6-weeks post FMT, respectively. Ten patients received FMT for the treatment of intestinal SR-GvHD, after a median of 4,5 lines of treatment (range 3-7). The overall response rate and Complete response rate at 14 days after FMT were 80% and 50%, respectively, while at 28 days after FMT they were 78% and 67% (Figure 1). Metagenomic analysis in a subset of patients undergoing FMT for intestinal SR-GvHD showed a progressive increase in alpha diversity, with reduction in pathobionts and increase in commensals after the fecal infusion.

Conclusions: FMT was found to be a safe and well-tolerated procedure in children undergoing allo-HSCT with an encouraging rate of decolonization from MDR and remission of SR-GvHD.

SPEAKER: TIMOTHY CHOU

Paediatric Moonshot – Accelerating Global Paediatric Translational AI Research

Many don't realize that 60% of rural U.S. counties lack pediatric expertise. Three states have no pediatric emergency physicians. While the U.S. has 3,000 pediatric cardiologists, none serve rural counties; globally, there are only 300 in India and just one in Rwanda. Yet, we have the technology to build AI applications for cardiology, orthopedics, oncology, radiology, and emergency medicine—bringing expert-level diagnostics and treatment to underserved communities.

All childhood diseases are rare diseases. Take focal cortical dysplasia (FCD), a rare brain lesion that, if untreated, causes epileptic seizures. A teenage boy has suffered 2-3 seizures per night for over a decade. His early MRI scans showed nothing, leading to years of ineffective drug treatments. Recently, a new MRI scan suggested he has FCD—an operable condition that could cure him for life. The challenge? While 25,000 FCD cases occur annually in the U.S., no pediatric neuro-radiologist sees enough cases to become an expert. But AI could change that. By accessing MRI images worldwide, we can train an AI model to diagnose FCD in real-time on any MRI machine, offering hope for a future with improved diagnosis processes.

Trustworthy, privacy-preserving, real-time AI applications deployed at the point of care are the only systemic way to reduce healthcare inequity, lower cost and improve patient outcomes across the world.

While centralized infrastructure has driven the rise of consumer AI applications (e.g., ChatGPT), **centralized infrastructure will not work for AI in healthcare and life sciences**. The data sizes are much larger, the demands for privacy much higher and the need for real-time results much greater.

Advancing AI in healthcare requires data. Unlike other software, reliable, accurate non-biased AI applications cannot be built without large quantities of diverse data. That data is in the building of hospitals, clinics and research labs across the world. Real-time data is in the clinical machines (ultrasound, EKG, bedside monitor). Real time data is in the research machines (sequencers, mass spectrometers) and offline data is available in the PACS and EMRs.

Launched out of Stanford University, BevelCloud has engineered **a secure, privacy-preserving distributed AI cloud infrastructure**. Rather than move the data to the AI application move the AI application to the data in the building. This infrastructure enables moving AI research work from the bench to the bedside.

We are building a Distributed AI Lab for Healthcare and Life Sciences to provide authorized applications with access to real-time data from all imaging machines, as well as offline data from PACS and EMRs. The Lab when completed will encompass 32 sites, over 3000 distributed servers as well as access to over 2,000 TB of real-time imaging data (CT, MRI, Ultrasound, Xray, PET) as well as all PACS and EMR data. We will use distributed, federated, swarm learning technology to **translate 100+ deep learn research applications from the bench to the bedside**. See appcommons.bevelcloud.ai for examples.

While we've primarily focused on machine-generated data—especially imaging data—but there's also valuable text data within PACS and EMRs. By engineering digital twins for PACS and EMRs, we've enabled seamless data access. Now, with the ability to deploy an in-the-building LLM (e.g., DeepSeek, LLaMA3…), we're opening doors to an entirely new class of applications.

Here are three groundbreaking projects we're working on all focused on text data.

Total Recall: A Patient Agent

A local LLM trained on medical records offers "total recall." Andy Guinigundo, Director of Precision Oncology at Cincinnati Cancer Advisors, says, "It's like a patient with perfect recall." Queries work via text or voice in any language. We're scaling this tech across hospitals to boost productivity, especially for infusion nurses and pre-visit summaries. Deployed on BevelCloud's distributed AI infrastructure.

Distributed AI Clinical Trial Matching

The goal: Answer, "What trials is Jane Smith eligible for?" Matching patients to trials requires analyzing massive data—EMR records (up to 3,500 pages) and drug protocols (300+ pages). Our multi-AI system enables an EMR-based agent to interact with a protocol agent to determine eligibility. The EMR stays in-hospital, and drug protocols remain secure within biopharma firewalls.

Zero-Cost Labeling: AI for Medical Imaging

Deep learning in medical imaging needs labeled data, but specialists lack time, and interns lack expertise. We're automating labeling using PACS digital twins—leveraging expert-authored PACS reports as the primary data source. This approach cuts costs and speeds up high-quality medical image labeling.

We're excited about the future of AI in healthcare. If you're interested in collaborating or learning more, reach out!

SPEAKER: MAREK MIGDAL

The Birthday of EPTRI AISBL

Marek Migdal[1,2]

1 – EPTRI; 2 - Children's Memorial Health Institute, Warsaw, Poland

The European Paediatric Translational Research Infrastructure (EPTRI) started as a European funded initiative, coordinated by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) arising from the need to find answers to the serious lack of medicines for children. As of March 4th, 2024, it has been established as a non-profit research organization incorporated in the form of an Association Internationale Sans But Lucrative (AISBL) governed by Belgian law, based at Leuven University. EPTRI AISBL consists of 18 members representing 9 different countries, bringing together a diverse range of expertise and institutions dedicated to paediatric research and innovation. It promotes various initiatives, including the publication of The EPTRI Manifesto on Paediatric Research, EPTRI surveys, and a toolkit. Additionally, a one-year online educational program has been developed to support paediatric research.

EPTRI AISBL is organized as a distributed Research Infrastructure according to a Hub and Spoke model, composed of several research units grouped within Thematic Research Platforms - TRPs (according to their area of expertise) and National Nodes (according to their location), and is governed through well-defined statutes and internal procedures, where the General Assembly and the Board of Directors oversee strategic decisions, while the CMO is responsible for implementing these decisions and managing the daily operations of EPTRI AISBL.

It provides paediatric research services in five technical and scientific domains focusing on paediatric medicines discovery, biomarkers and biosamples, developmental pharmacology,

paediatric medicines formulations, paediatric medical devices. Additionally, upcoming TRPs will focus on advanced therapy medicinal products and digital health technology. These TRPs offer integrated, cutting-edge services to advance paediatric research in the development of medicines, devices, and technologies. A transversal platform delivers centralized services to support all stages of paediatric research in the basic, pre-clinical, and translational settings. EPTRI AISBL fosters an open science environment, removing geographical, institutional, and financial barriers to innovation in paediatric research.

EPTRI AISBL is a member of several key partnerships, including Enpr-EMA (Category 3), supporting paediatric drug development and clinical trials; the European Open Science Cloud (EOSC), enhancing collaboration, data sharing, and digital innovation; the EU Health Coalition, advocating for paediatric research in health policies; and the European Alliance for Transformative Therapies (TRANSFORM), contributing to regulatory improvements.

EPTR AISBL has been involved in a European funded project, Orphadev4kids with the aim to implement a complex innovation ecosystem in the orphan and paediatric medical devices field by supporting academy, research centres and SMEs that invest on paediatric devices development. With specific objectives are to provide access to a paediatric MDs Platform for users needing dedicated research and development services, establish a comprehensive ecosystem that includes tools, facilities, and support services, and develop three case studies focusing on osteogenesis imperfecta and cyanotic congenital cardiac diseases.

EPTRI AISBL's future directions included its application for the European Strategy Forum on Research Infrastructures (ESFRI) 2026 Roadmap, with the goal of being recognized as a European Research Infrastructure. The application focused on advancing ATMPs, expanding the use of MDs beyond diagnostics to include other paediatric applications, emphasizing digital health applications, and developing an innovative clinical research platform to support cutting-edge methodological approaches.

EPTRI AISBL continuously maps paediatric expertise and competencies across EU and non-EU countries through online surveys to identify potential service providers and invites organizations to join EPTRI AISBL by completing and submitting the Association Form to coordinator@eptri.eu, with the aim of advancing knowledge on human development and ontogeny and supporting the discovery of new therapies and devices for children.

“EPTRI Paediatric Medicines Discovery TRP”

SPEAKER SECTION

SPEAKER: FEDERICA D’AMICO

Alterations of the microbiota in lactating Göttingen Minipig sows treated with metformin.

Federica D'Amico[1] Silvia Bencivenni[1], Augusta Zannoni[1], Domenico Ventrella[1], Alberto Elmi[2], Maria Laura Bacci[1], Mikael Niku[3], Patrizia Brigidi[1], Monica Forni[1], Silvia Turroni[1]

1 – University of Bologna; 2 – University of Pisa; 3 – University of Helsinki

Background: Early gut microbiota dysbiosis can affect child’s health and has been linked to the onset and progression of several diseases later in life (e.g., asthma, allergies, obesity, type 2 diabetes). Breast milk is recognized as a major driver of the structure and dynamics of the gut microbial community from the earliest moments of infant life. In addition to nutritious and prebiotic compounds, milk is associated with a specific microbiota that is shaped by several maternal factors, including gut microorganisms and medications (e.g., metformin, an antidiabetic drug). However, the impact of the latter on the milk microbiota is still largely unknown. In this context, the Göttingen Minipig has been proposed as the most appropriate animal model to study the safety of drug use during pregnancy and lactation due to its physiological and metabolic similarities to humans, milk volume and ethical factors. Furthermore, this animal model seems promising for microbiota studies due to its genetic stability and microbiological control, and has been used to study gut microbiota modifications in other contexts. In this study, we investigated the gut and milk microbiota composition of Göttingen Minipig sows receiving prolonged metformin administration, and followed the dynamics of the gut microbiota of the corresponding piglets.

Methods: One week after farrowing, four sows received oral metformin (500 mg/day) for 2 weeks, followed by 850 mg/day during the third week. Stool and milk samples were collected from each sow 5-6 days after farrowing and at the end of each weekly metformin treatment. In addition, rectal swabs were collected from piglets before treatment and weekly during the metformin administration. Characterization of all microbial ecosystems was performed by Illumina 16S rRNA amplicon sequencing.

Results: The milk microbiota of Göttingen Minipig sows after metformin administration showed an increase of biodiversity that correlated with higher drug doses. Increased levels of Prevotella and Ruminococcus, and reduced relative abundance of Fusobacterium and Porphyromonas were observed after the last week of treatment. As expected, the gut microbiota of sows was strongly affected by metformin use, with a significant reduction in health-associated Oscillospiraceae members over time. Analysis of piglet gut microbial communities is ongoing.

Preliminary conclusions: In addition to demonstrating the relevance of the Göttingen Minipig as a valid model for studying the impact of medications on maternal microbiota, our results suggest that both milk and gut microbiota of sows may be affected by metformin intake and thus have an impact on piglet gut microbial development in a critical timeframe.

SPEAKER: SULEMAN KHAN ZADRAM

Innovative Targeting of GD2-positive Childhood Neuroblastoma tumors with Photooncolytic phage nanovector platforms.

Suleman Khan Zadran[1], Giovanni Perini[1]

1 – University of Bologna, Department of Pharmacy and Biotechnology

Background: Disialoganglioside-GD2 is a key molecular target for neuroblastoma (NB) immunotherapy which is based on the employment of GD2-targeting antibodies. However, about 50% of treated patients can experience tumor relapse due to limited immune-mediated cytotoxicity and poor antibody penetration into tumors.

Aim: To address this problem, we developed a penetrating photooncolytic phage nanovector platform that selectively targets GD2-expressing NB cells.

Results: The phage bioconjugates, functionalized with photosensitizers, result in specific oncolysis of GD2-positive NB cells upon light irradiation, without

affecting GD2-negative ones. Notably, the bioconjugates penetrate deep into GD2-positive tumor spheroids to induce breakdown and cell death. Additionally, to overcome resistance from GD2 loss, often linked to poor prognosis, we introduced a CRISPRa strategy to reactivate GD2 expression in GD2-negative cells.

Conclusion: The approach offers a minimally invasive and highly effective strategy to target NB and addresses critical aspects of anti-GD2 resistance.

POSTER SECTION

Advances in pediatric nephrology: AI-based repurposing studies to identify new promising vasopressin V2 receptor ligands.

Grazia Tamma[1], Daniela Trisciuzzi[1], Ines Angelini[1], Mariangela Centrone[1], Annarita Di Mise[2], Marianna Ranieri[1], Giovanna Valenti[1], Cosimo Damiano Altomare[1], Susanna Cotecchia[1], Orazio Nicolotti[1]

1 – University of Bari Aldo Moro; 2 – University of Milano-Bicocca;

Summary of purpose: Abnormal vasopressin functioning is associated with different disorders including diabetes insipidus (DI), the inappropriate secretion of antidiuretic hormone (SIADH) that are characterized by hypo- and hypernatremia in children and require timely recognition and treatment.

Autosomal recessive polycystic kidney disease (ARPKD) is also associated with altered vasopressin V2 receptor (V2R) responses. ARPKD is a rare genetic disorder highly significant in pediatric nephrology. Hepatorenal fibrocystic syndrome and renal cysts are observed in ARPKD pediatric patients. Importantly, clinical manifestations may occur in utero or at birth. ARPKD shares many

similarities with Autosomal dominant polycystic kidney disease (ADPKD) including increased cyclic adenosine monophosphate (cAMP). The vasopressin V2 receptor (V2R) antagonist, tolvaptan, has been recently approved for the treatment of progressive disease in adult ADPKD patients. Conversely, there is no current cure for ARPKD. Activation of V2R not only regulates renal water reabsorption but is also involved in controlling cell proliferation, cancer, and the enlargement of cysts in PKD patients. Based on these findings, the major aim of this study is to identify new molecules modulating V2R-dependent signaling. To this purpose, an inverse screening of a large collection of known drugs was performed to identify novel V2R ligands that might modulate different receptor-mediated effects.

Methodology: The inverse screening campaign was run by using PLATO, a homemade target fishing platform. Structure-based studies were also carried out. Renal collecting duct MCD4 cells, stably expressing human V2R and aquaporin-2 (AQP2), were used as an experimental model to test the effects of drugs. Confocal analysis and Western Blotting studies were carried out to show the expression and the localization of the V2R. Fluorescence Resonance Energy Transfer (FRET), and calcein fluorescence quenching (CFQ) were applied to evaluate changes in intracellular cAMP and DDAVP-induced water flux.

Results: The initial screening yielded 185 candidate V2R modulators, having predicted IC50 values against V2R better than 0.1 μM. Among these, five molecules with predicted IC50 towards V2R below 50 nM were prioritized for further analysis. Confocal analysis and Western Blotting studies confirmed the expression of V2R in MCD4 cells, used as an experimental in vitro model.

Therefore, FRET studies were carried out to test whether these compounds affect the DDAVP-induced cAMP responses. Interestingly, we found that one of these, known to be a selective antagonist of the purinergic receptor P2Y12-R, potentiates the effect of DDAVP by increasing the intracellular level of cAMP. More importantly, another drug, coded as F2544, at 1 nM concentration significantly reduced the DDAVP-dependent cAMP production. Functional CFQ studies revealed that this drug reduced the DDAVP-induced water reabsorption, with effects comparable to tolvaptan, which is a well-established V2R antagonist used as a positive control. In this respect, an in-depth computational investigation showed a nice overlap of the molecular interaction fields generated from the binding sites of V2R and F2544. Finally, molecular docking simulations returned a promising posing and scoring of F2544 in the V2R binding site.

Conclusions: Our studies identified for the first time new V2R ligands by applying an AI-based approach. Combining in-depth computational investigations and functional studies, F2544 was prioritized for being repurposed for treating diseases associated with abnormal V2R signaling, such as ARPKD in pediatric nephrology.

“EPTRI Developmental Pharmacology TRP”

SPEAKER SECTION

SPEAKER: KAREL ALLEGAERT

EPTRI Developmental Pharmacology TRP

Karel Allegaert[1]

1 – European Paediatric Translational Research Infrastructure (EPTRI), Leuven, Belgium

Developmental pharmacology plays a vital role in addressing the unique pharmacological needs of paediatric patients, incorporating growth, maturation, and disease-specific considerations. Collaboration across disciplines is crucial for advancing this field, ensuring that pharmacology services and clinical methods are interconnected and foster innovative solutions.

A significant challenge in paediatric pharmacology is the development of age-appropriate formulations and addressing the specific needs of children, including taste preferences and rare diseases. In recent years, regulatory frameworks have started evolving, with the ongoing revision of the European paediatric drug regulation. The focus is shifting from traditional indication-based approaches to molecular target-based drug development, a strategy successfully employed in paediatric oncology. This evolution promises greater precision but introduces challenges, particularly the feasibility of conducting multiple clinical trials and the risk of generating insufficient data to guide treatment decisions effectively. Likely relevant for paediatrics is the revision of the European Regulation, considering the mode of action concept for paediatric drug development.

Furthermore, the acceptance of extrapolation methodologies (latest ICH decision) is a positive development, enabling the application of data from adults or related diseases to paediatric populations. Advances in pharmacokinetic modelling, particularly physiologically based pharmacokinetic (PBPK) models, allow for predictions of drug behaviour in children, even in the absence of specific clinical data. These models, integrating in vitro data, animal models, and physiological data, help address scenarios where limited data exist, such as in very young or critically ill children.

In summary, developmental pharmacology is an interdisciplinary field that balances innovation with practical feasibility. It requires careful integration of regulatory, clinical, and pharmacological knowledge to ensure drugs are safe and effective for paediatric patients. By leveraging data-driven approaches, collaboration, and advanced modelling techniques, the field can overcome existing challenges and optimize drug development for children, ultimately improving therapeutic outcomes.

SPEAKER: PIER GIORGIO COJUTTI

Pharmacometrics for better dosing in children

Traditionally, dosing in children has been based on allometric scaling, which consists of predicting pharmacokinetic parameters such as clearance or distribution volume for pediatrics from normal-weight adult values. However, a single, universal allometric exponent is unlikely to exist and is instead expected to vary based on many factors such as drug properties and physiological

characteristics such as age and weight. Pharmacometrics is a new pharmacological science that, by using pharmaco-statistical models of drug pharmacokinetics and/or pharmacodynamics based on real-world observed data, enables to estimate the entity of pharmacological parameters and the clinical factors that may affect them, thuis allowing a more personalized therapy. In children, such models have been successfully applied to optimize dosing of the antimicrobials linezolid and meropenem in hospitalized patients with multi-drug resistance infections, as well as to predict the adequate dosage of FXIII in patients with FXIII congenital deficiency.

SPEAKER: CATERINA DERUVO

DOACs in pediatric thromboembolic disorders: Translating science from the lab to the clinic.

Caterina Deruvo[1], Francesco Samarelli[1], Rosa Purgatorio[1], Marco Catto[1], Modesto de Candia[1], Cosimo D. Altomare[1]

1 – Department of Pharmacy – Pharmaceutical Sciences, University of Bari Aldo Moro

Approximately 95% of venous thromboembolic events (VTE) in the pediatric population are associated with severe conditions, including cancer, nephrotic syndrome, congenital heart disease, systemic lupus erythematosus, and the use of central venous catheters (CVC) for intensive or long-term therapies. In this context, Direct Oral Anticoagulants (DOACs) such as rivaroxaban, dabigatran, apixaban, and edoxaban, already used in adults, represent promising alternatives to traditional anticoagulant therapy, based on heparins and vitamin K antagonists (VKAs). DOACs are characterized by more predictable pharmacokinetics, which reduce the need for frequent monitoring and improving treatment adherence.

Rivaroxaban and dabigatran have been approved for pediatric VTE, but concerns remain regarding their safety and efficacy. A large meta-analysis of seven randomized clinical trials (RCTs) published up to 2021 on DOACs in children with VTE suggests that they may represent a valid alternative to standard therapy. The results oof a study on 1,139 cases indicate that DOACs reduce the risk of VTE recurrence, with mortality and major bleeding rates similar to those of standard therapy, but with a higher incidence of non-major bleeding. Dabigatran and rivaroxaban showed similar effects, although rivaroxaban was associated with a higher risk of non-major bleeding. Recent studies, such as EINSTEIN Junior and DIVERSITY, confirm the efficacy of DOACs in children with VTE, with outcomes comparable to standard therapy.

One of the key aspects in the development of pediatric drugs is related to age-dependent pharmacokinetics and pharmacodynamics. Hepatic metabolism and renal function in children are not fully developed, affecting the absorption, distribution, metabolism, and excretion of drugs (ADMET). Renal clearance in neonates and infants is immature, thereby significantly affecting the elimination of drugs such as dabigatran, which is 85% dependent on renal function. Moreover, cytochrome P450 enzymes and efflux transporters, such as P-glycoprotein (P-gp), progressively mature with age, altering the bioavailability and metabolism of DOACs like apixaban and rivaroxaban, which are strong inhibitors of CYP3A4 and substrates of P-gp. Dabigatran etexilate prodrug requires metabolic activation before exerting its anticoagulant effect. Rivaroxaban and edoxaban, administered once daily (OD), may improve adherence compared to apixaban and dabigatran, which require a twice-daily (BID) administration. However, rivaroxaban's bioavailability depends on food intake, a factor that could impact its effectiveness in children, particularly in

younger patients with feeding difficulties. To develop effective and safe pediatric anticoagulant therapies, it is crucial to combine clinical studies with advanced predictive models, supported by chemoinformatic tools and in-vitro evaluations of ADMET parameters. These approaches allow for dose optimization and reduce the risk of side effects, ensuring that DOACs can be used in pediatrics with adequate safety profile. Our contribution in this field deals with in-vitro permeability assays, assessment of the potential interaction with P-gp and affinity to plasma proteins, in order to assess possible interactions with other drugs or foods and how they can affect the drug bioavailability.

POSTER SECTION

Dexmedetomidine as a Promising Neuroprotective Sedoanalgesic in Neonatal Therapeutic Hypothermia: A Systematic Review and Meta-Analysis.

Enrico Cocchi[1], Juleda Shabani[2], Arianna Aceti[1], Gina Ancora[3], Luigi Corvaglia[1], Federico Marchetti[1]

1 – Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum - University of Bologna, Bologna, Italy; 2 – Department of Medicine and Surgery, Alma Mater Studiorum - University of Bologna, Bologna, Italy; 3 – Neonatal Intensive Care Unit, AUSL Romagna, Infermi Hospital, Rimini, Italy

Background: Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and neurodevelopmental disabilities. Therapeutic hypothermia (TH) is the standard of care, but optimized sedoanalgesic strategies remain critical. Dexmedetomidine shows promise as an alternative to traditional sedatives, but its role in this context remains systematically underexplored.

Objective: This meta-analysis evaluates the safety and efficacy of dexmedetomidine in neonates undergoing TH for HIE.

Methods: A systematic search of Medline, Scopus, EMBASE, WOS, ClinicalTrials, and Cochrane Library identified studies published from January 2014 to October 2024. Studies focusing on dexmedetomidine in neonatal TH with relevant outcomes were included. Selection followed PRISMA guidelines, with independent quality assessments. The protocol was registered in PROSPERO (CRD42024605817). Results are presented as meta-analyses or evidence-based discussions when pooling was unfeasible.

Results: Seven studies involving 609 neonates were included: four cohort studies (n = 486) and three case series (n = 123). Dexmedetomidine provided comparable sedation to traditional agents (MD = -0.01 [-0.68 - 0.66], p = 0.99) and significantly reduced seizure risk (OR 0.31 [0.10 - 0.98], $p < 0.05$) with a non-inferior safety profile. Trends suggested shorter duration of mechanical ventilation and time to full enteral feeding. Substantial heterogeneity in dosing protocols highlights the need for standardization.

Conclusions: Dexmedetomidine appears to be a safe and promising sedative in neonatal TH for HIE, with potential neuroprotective, respiratory, and gastrointestinal benefits. Despite limited evidence and the absence of randomized clinical trials, its non-inferior efficacy and safety warrant further exploration and urges the development of standardized dosing protocols.

Alterations of the microbiota in lactating Göttingen Minipig sows treated with metformin.

Federica D'Amico[1] Silvia Bencivenni[1], Augusta Zannoni[1], Domenico Ventrella[1], Alberto Elmi[2], Maria Laura Bacci[1], Mikael Niku[3], Patrizia Brigidi[1], Monica Forni[1], Silvia Turroni[1]

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Background: Early gut microbiota dysbiosis can affect child's health and has been linked to the onset and progression of several diseases later in life (e.g., asthma, allergies, obesity, type 2 diabetes). Breast milk is recognized as a major driver of the structure and dynamics of the gut microbial community from the earliest moments of infant life. In addition to nutritious and prebiotic compounds, milk is associated with a specific microbiota that is shaped by several maternal factors, including gut microorganisms and medications (e.g., metformin, an antidiabetic drug). However, the impact of the latter on the milk microbiota is still largely unknown. In this context, the Göttingen Minipig has been proposed as the most appropriate animal model to study the safety of drug use during pregnancy and lactation due to its physiological and metabolic similarities to humans, milk volume and ethical factors. Furthermore, this animal model seems promising for microbiota studies due to its genetic stability and microbiological control, and has been used to study gut microbiota modifications in other contexts. In this study, we investigated the gut and milk microbiota composition of Göttingen Minipig sows receiving prolonged metformin administration, and followed the dynamics of the gut microbiota of the corresponding piglets.

Methods: One week after farrowing, four sows received oral metformin (500 mg/day) for 2 weeks, followed by 850 mg/day during the third week. Stool and milk samples were collected from each sow 5-6 days after farrowing and at the end of each weekly metformin treatment. In addition, rectal swabs were collected from piglets before treatment and weekly during the metformin administration. Characterization of all microbial ecosystems was performed by Illumina 16S rRNA amplicon sequencing.

Results: The milk microbiota of Göttingen Minipig sows after metformin administration showed an increase of biodiversity that correlated with higher drug doses. Increased levels of Prevotella and Ruminococcus, and reduced relative abundance of Fusobacterium and Porphyromonas were observed after the last week of treatment. As expected, the gut microbiota of sows was strongly affected by metformin use, with a significant reduction in health-associated Oscillospiraceae members over time. Analysis of piglet gut microbial communities is ongoing.

Preliminary conclusions: In addition to demonstrating the relevance of the Göttingen Minipig as a valid model for studying the impact of medications on maternal microbiota, our results suggest that both milk and gut microbiota of sows may be affected by metformin intake and thus have an impact on piglet gut microbial development in a critical timeframe.

“EPTRI Paediatric Biomarkers & Biosamples TRP”

SPEAKER SECTION

SPEAKER: GIOVANNI CAZZANIGA

Genetic Characterization at Diagnosis of Patients with Acute Lymphoblastic Leukemia Enrolled in Italy in the AIEOP-BFM ALL 2017 Protocol.

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The genetic characterization of pediatric patients with acute lymphoblastic leukemia (ALL) enrolled in AIEOP protocols is conducted in Monza, and it includes a combined analysis of fusion transcripts (whole transcriptome, RNA-seq), identification of gene copy number alterations (digital MLPA), and minimal residual disease (MRD) assessment through IG/TR rearrangement monitoring (NGS and RQ-PCR).

Transcriptomic analysis using NGS (RNA-seq) has led to significant advancements in the genetic characterization of acute lymphoblastic leukemia (ALL). Children newly diagnosed with ALL and enrolled in Italy in the AIEOP-BFM ALL2017 protocol are prospectively analyzed by RNA-seq, with the primary goal of identifying fusion genes.

During the first 28 months of enrollment, transcriptomic analysis was evaluable in 599 out of 613 consecutive B-cell precursor ALL (BCP-ALL) cases (97.7%). At least one fusion gene associated with BCP-ALL was identified in 49.6% (297/599) of cases and validated by RT-PCR or FISH. Among these fusion genes, 116 (39% of identified fusions and 19.4% of the total cases) would not have been detected using conventional multiplex RT-PCR screening performed in parallel. Seven patients presented tyrosine kinase-involving fusions associated with the BCR::ABL1-like subgroup, classified as ABL-class (1.2%), making them eligible for specific therapy and enrollment in the EsPhALL2017/COGAALL1631 protocol. The PAX5 gene was identified as a fusion partner in 23 patients (3.8%), while CRLF2 rearrangement was observed in 23 patients (3.8%). Fifteen patients tested positive for the IGH::DUX4 fusion (2.7%), and eight patients showed other IGH rearrangements (1.3%) with different gene partners, including CEBP (n=4), MYC (n=2), BCL2 (n=1), and EPOR (n=1). Thirteen patients had rearrangements involving ZNF384 (2.2%), and eight involved MEF2D (1.3%). Fusion genes involving ETV6 (n=5, 0.8%), RUNX1 (n=3, 0.5%), and KMT2A (n=3, 0.5%) with non-canonical partners were also identified. Seven patients (1.2%) presented fusion genes classified as "others."

Regarding T-cell precursor ALL (T-ALL), during the first 28 months of enrollment, transcriptomic analysis was evaluable in 137 out of 144 consecutive cases (95.1%). At least one fusion gene associated with T-ALL was identified in 46/137 (33.5%) cases and validated by RT-PCR. Eleven patients carried the STIL::TAL1 fusion gene (8.0%), while nine were classified as KMT2A-rearranged (KMT2Ar, 6.5%), eight as MLLT10-class (5.8%), eight as ABL-class (5.8%), three as ETV6-class (2.1%),

and two as CDK6-class. Additionally, two patients carried the NPM1::ALK fusion, one SET::NUP214, one HOXA10::TRB, and one STMN1::SPI1. Among the KMT2Ar patients, two carried KMT2A::MLLT1, two KMT2A::MLLT4, two KMT2A::ELL, two KMT2A::AFDN, and one KMT2A::CBL. Among MLLT10-class patients, seven had PICALM::MLLT10 rearrangements and one DDX3X::MLLT10. Among ABL-class patients, five carried NUP214::ABL1, one ETV6::ABL1, one TNRCSB::ABL1, and one SEPT9::ABL1. Among ETV6-class patients, two had ETV6::NCOA2 and one ETV6::BCL2L14, while the CDK6-class patients carried CDK6::EVX1 (one case) and CDK6::HOXA11 (one case).

The incidence of fusion genes in the T-ALL cohort was surprisingly high (33.5%), enabling the identification of potential targets for precision therapies, such as tyrosine kinase inhibitors (TKIs) in ABL-class patients, currently being evaluated in an international study.

In the near future, correlation analyses between identified fusions, clinical characteristics at diagnosis, and treatment response will be necessary.

SPEAKER: SHAMIMA RAHMAN

Advancing Mitochondrial Medicine: An Integrative Genomics Approach to Gene Discovery and Therapeutic Innovation

Primary mitochondrial disease are a group of more than 400 monogenic disorders characterised by mitochondrial dysfunction presenting with a bewildering array of clinical features, ranging from brain malformations and congenital lactic acidosis to late onset progressive external ophthalmoplegia, myopathy, parkinsonism and cognitive decline. These disorders share difficulties in clinical recognition and establishing a definitive genetic diagnosis, and intractability to therapeutic interventions. In this talk, I will review my group's work in identifying and curating mitochondrial disease genes, developing computational resources to aid diagnosis, and exploratory work in gene therapy. I will also highlight the importance of global collaboration to achieve optimal outcomes for this group of rare, frequently multisystem and often devastating disorders.

POSTER SECTION

Preliminary Results of Humoral Response Targeting Specific Epitopes of Human Endogenous Retroviruses in Kawasaki Disease and MIS-C.

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Background: Human endogenous retroviruses (HERVs) are relics of ancestral germline infections by exogenous retroviruses, resulting in proviruses transmitted to offspring and integrated in the DNA. HERVs trigger the expression of inflammatory effectors, like cytokines and inflammatory effectors could, in turn, increase HERVs activation. Aberrant expression of two different families of HERVs (i.e. HERV-W and HERV-K) in blood of KD and MIS -C patients vs healthy controls has been demonstrated. The immune response against HERVs in MIS-C and KD have not previously been evaluated.

Objectives: To evaluate the prevalence and magnitude of the immune humoral response against HERV-W and HERV-K epitopes and interferon regulatory factor 5 (IRF5) in patients with KD and MIS-C. To determine associations of clinical features, presentation, laboratory values and coronary involvement (CALs) with humoral response to HERVs and IRF5.

Methods: Study period: October 2020 to June 2021. Population: contemporaneous KD, MIS-C and COVID-19 patients from 2 sites. KD defined by AHA guidelines and MIS-C by CDC criteria. Demographic, laboratory and echocardiograpic data were performed to all KD and MIS-C patients. The reactivity (IgG) against envelope epitopes of HERV-H, HERV-K, HERV-W and IRF5 was tested by indirect ELISA and mesured as Ab optical density (OD) in patients serum blood samples before treatment and compared to healthy controls (HCs). Correlations between clinical and lab data AND Ab against HERVs and IRF5 were investigated. The study was approved by IRB.

Results: 8 KD, 16 MIS-C and 7 COVID-19 (COV) patients and 41 age- and sex-matched healthy controls (HC) were enrolled. Ab anti Hervs W were significantly different in KD vs COVID (p=0.43) and KD vs HCs (p=0.012), Ab antiHervs H were different KD vs HCs (p=0.008), MIS-C vs HCs (p=0.009), Ab anti Hervs K were different in KD vs HCs (p=0.006) , KD vs HCs (p=0.006), MIS-C vs HCs (p=<0.001), COVID vs HCs (p=0.014), MIS-C vs HCs (p=<0.001) and COVID vs HCs (p=0.014); Ab anti IRF-5 were different among grousps as follows: KD vs COVID (p=0.039), KD vs HCs (p=0.014), MIS-C vs HCs (p=<0.001) and MIS-C vs COVID (p=0.012).

Conclusions: In KD and MIS-C the humoral response targeting specific epitopes of HERVs seems to partially contribute to immune response. We found higher humoral response against HERV-W in KD vs COVID and controls, while lower against HERV-K and IRF5 in controls vs KD and MIS-C. Ab against IRF5 are associated with % of lymphocytes, total days of fever and days before treatment. The elevation of IgG response to HERVs and IRF5 might suggest that exposition to these factors causes a secondary antigenic driven immune response in KD. Larger cohorts are needed to further investigate the associations with inflammation to shed a light into the pathogenesis of KD, and to define whether they can represent biomarkers for diagnosis and prognosis.

Metabolomics by liquid chromatography - mass spectrometry for the study of newborn and paediatric diseases.

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Metabolomics refers to the quali-quantitative study of small molecules, i.e. metabolites or hormones, contained in a defined biological sample or system. It is a valuable tool for understanding metabolic changes associated with physiological and pathological conditions, leading to the identification and quantitation of specific biomarkers. Metabolomics also allows the characterization of metabolic alterations induced by treatments, which can provide a more tailored and individualized treatment plan.

Modern liquid chromatography – mass spectrometry (LC-MS) technologies allow for comprehensive metabolomic studies by means of targeted or untargeted approaches. The Center for Applied Biomedical Research of the University of Bologna has more than 15 years' experience in developing and validating LC-MS methods and standard operative procedure for sample collection, storage and processing. Targeted applications are available on the API 4000 Q-Trap (Sciex) triple quadrupole platform for the sensitive and accurate quantitation of panels of steroid hormones, amino acids, biogenic amines, tricarboxylic acids, acylcarnitines, sphingomyelins, glycerophospholipids, endocannabinoids, arachidonic acid derivatives, indoles, nucleotides, endocrine disruptors and antiepileptic drugs in several biological fluids such as serum, plasma, saliva and dried blood spots (DBS). Untargeted metabolomics is available on the Orbitrap Exploris 240 high resolution platform (Thermo Scientific). Methods for expanded metabolite profiling in plasma, serum and urine were developed, operating in polarity switching and data-dependent acquisition mode for achieving larger possible information. A workstation for raw data processing is also available, equipped with Compound Discoverer 3.3 software, referencing to m/z Cloud and ChemSpider spectral libraries for metabolite identification. The untargeted workflow enables the accurate identification and relative quantification of hundreds of metabolites from biofluids, both of human and microbiome origin as well as exogenous chemicals from environmental exposure. All methods are provided with optimized and validated sample extraction procedures including protein precipitation, liquid-liquid extraction, on-line and off-line solid phase extraction. Our LC-MS methods overall demonstrate high throughput and robustness, making them suitable for large-scale clinical metabolomic studies.

First applications of our LC-MS metabolomic facility will focus on the host-microbiome interactions in the frame of bronchiolitis, complications of premature birth, hematologic diseases of childhood and stem cell transplantation, as well as in the longitudinal evolution of endocrinological diseases from paediatric to adult age, including obesity, type 1 and 2 diabetes, adrenal diseases and deficits of steroidogenesis, Turner syndrome and others. Biobanks for these purposes are currently under development. Most of the mentioned studies will benefit from the possibility to use micro-sampling, such as DBS, or non-invasive fluids, such as saliva or urine, which are particularly suited for paediatric populations. Methods dedicated to faecal matter analyses are also under development.

In conclusion, we created a workflow encompassing LC-MS analytics, microbiome characterization, and specialistic clinical experience, allowing to design and conduct studies purposely addressing the study of metabolic derangement caused by several diseases and the influence of microbiome in their evolution.

High-throughput drug screening as drug repurposing strategy for poor outcome BCP-ALL subgroups.

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Background: 15% of pediatric ALL patients are unresponsive to conventional chemotherapy and relapse, raising the need for novel therapeutic schemes. Preclinical high-through put (HTP) drug screening enables monitoring of personalized responses to a collection of clinically approved and novel agents. This approach effectively suggests drug repurposing opportunities concerning single and drug combinations both specific to patient subgroups and across multiple groups.

Aim: Purpose of this study is to apply HTP drug screening to identify effective drugs (as a single agent or in combination) for three subgroups of poor prognosis pediatric BCP-ALL: CRLF2r Down Syndrome (DS), PAX5r, KMT2Ar.

Methods: Primary cells from 34 BCP-ALL patients of three distinct ALL subgroups (9 CRLF2r DS, 15 PAX5r, 10 KMT2Ar) expanded as Patient-derived Xenografts (PDX), leukemic cell lines and healthy controls were seeded in plates pre-coated with a library of 174 compounds under a 6-point concentration range (8nM-25uM) and CellTiter-Glo assay evaluated viability upon a 3-day culture. Additionally, the CRLF2-r BCP-ALL cell line MHH-CALL-4 was pre-treated for 6 hours with vehicle or Givinostat, an HDAC inhibitor with proven high efficacy against CRLF2r ALL to dissect compounds standing as synergistic partner for combination targeting in CRLF2r cases with or without DS. In either case, a quantitative drug sensitivity score (DSS) for each drug was computed and selected efficient compounds statistically identified by Mann Whitney U-test were further interrogated for their apoptotic potential using Annexin/7AAD cytofluorometric approach.

Results: With this approach, we were able to identify 9 compounds with a statistically significant profound anti-leukemic action for all ALL subgroups tested (DSS>50, p-value<0.05), accompanied by a minimum effect on healthy cells (DSS<10). These consist of the Bcl-2 inhibitor ABT-199 (Venetoclax), the HSP90 inhibitors AUY922 (Luminespib), EC144, PF-04929113, NVP-HSP990, the BET bromodomain inhibitor JQ1, the microtubule polymer stabilizer Paclitaxel, as well as two agents of the classical chemotherapy for BCP-ALL, the glucocorticoid Dexamethasone and the antimitotic Vincristine. ABT-199 (Venetoclax) was revealed as the most promising among them, not affecting healthy hematopoietic stem cells and already approved for clinical use for other haematological settings. Further in vitro validation in our ALL samples confirmed its potency in nanomolar concentrations. Interestingly, we observed an NF-kB inhibitor to selectively target DS-ALL cases irrespective of additional leukemia characteristics (mean rank difference 13.26, p-value<0.0001). In the combination setting, we managed to couple Givinostat, our previously established compound active for CRLF2r ALL cases, with Trametinib (ZIP synergy 7.04 and 16.83 for MUTZ-5 and MHH-CALL-4 respectively) or Venetoclax (ZIP synergy 9.23 and 5.03), thus providing a successful synergistic targeting further confirmed in CRLF2r ALL blasts, whose synergistic mechanism of action is currently investigated.

Genetic subgroup-specific candidate drugs were further explored based on stringent efficacy and toxicity cutoffs, and selected for further validation in vitro and in PDX in vivo models. Whilst two multi-target receptor tyrosine kinases (RTKs) inhibitors (Dovitinib and Foretinib) were identified as novel therapeutic candidates for KMT2Ar ALL, gilteritinib, a second-generation FLT3 inhibitor, demonstrated promising efficacy and toxicity profile in PAX5r PDX blasts.

Conclusion: This study has highlighted the emerging benefit of HTP drug screening applications guiding the early design of therapies for multiple or specific patient subgroups in an approach of repurposing drugs available in the pharmacological landscape. Further studies are needed to confirm drugs efficacy in high risk ALL subgroup, when combined to standard chemotherapy.

Urinary miRNA signatures as potential biomarkers of patent ductus arteriosus and therapeutic response to ibuprofen in preterm infants.

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BACKGROUND: Patent ductus arteriosus (PDA) is one of the most common complications in preterm infants (1). The decision to treat PDA is usually based on the echocardiographic diagnosis of a hemodynamically significant PDA (hsPDA) that is associated with higher rates of mortality and multiorgan comorbidities. Ibuprofen is the first line therapy; however, it is ineffective in approximately 30% of patients (2) and may cause side effects. Biomarkers are increasingly recognized as key tools in the identification of patient sub-populations most likely to benefit from treatment, and the development of well-characterized, validated biomarkers for neonatal care has been recently advocated (3). Unfortunately, to date, there are no biomarkers useful to identify infants at high risk of developing hsPDA and/or not responders to pharmacological treatment. In recent years, microRNA (miRNAs) profiling was applied to several pediatric conditions (4) to investigate potential biomarkers of disease, for early diagnosis and/or therapeutic management. However, their potential as predictive tools for the pharmacological management of PDA is still an unexplored path.

AIM: The aim of this study is to assess potential associations between urinary miRNAs signatures and the risk of developing hsPDA and it is refractory to pharmacological treatment in preterm infants.

METHODS: 50 infants with 23+0-29+0 weeks of gestational age or with a birth weight less than 1500 g will be consecutively enrolled at the Neonatal Intensive Care Unit of Careggi Hospital of Florence. Urine samples will be collected on the first 24 h of life and after 3 days of ibuprofen/paracetamol treatment, for the measurement of the entire miRNome. Echocardiography for hsPDA diagnosis will be performed between 24 and 72 h of life to diagnose hsPDA and its response to the first cycle of ibuprofen (10-5-5 mg/kg/day). The entire miRnome will be analysed by the Agilent SurePrint human miRNA microarray.

PRELIMINARY RESULTS: An exploratory miRNome analysis has been conducted in pooled samples from 3 neonates without PDA, 3 neonates whose PDA successfully closed after ibuprofen and 3 neonates whose hsPDA failed to close. Real time validation showed that mir-6089 and miR-137 expression increased upon physiological closure in controls and in neonates who were successfully treated with ibuprofen but not in those who did not achieve pharmacological PDA closure.

CONCLUSIONS: This preliminary analysis suggests that miR-137 and miR-6089 may be potential biomarkers of hsPDA and treatment response that deserve validation in extended cohort of patients. Moreover, functional studies into their role may also disclose new mechanisms underlying PDA development and therapeutic targets.

Vaginal miR-210-3p as a potential biomarker for early fetal growth restriction: a proof-of-concept case-control study.

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Fetal growth restriction (FGR) is a condition in which biometric and functional parameters of the fetus pathologically deviates from the expected growth trajectory, resulting in low birth weight and impaired organ function. FGR globally affects 10–15% of all pregnancies, reaching 30% in low-income countries, and it is associated with increased risk for both acute and long-term multi-organ adverse consequences. Furthermore, this condition is the second leading cause of perinatal morbidity and mortality, behind preterm delivery. Unfortunately, up to 50% of FGR are undetected until the third trimester or at birth and undiagnosed FGR have 2–9 times higher risk of perinatal death and complications to those diagnosed prenatally. The identification of FGR markers could improve the monitoring and surveillance of pregnancies, support in the identification of patients eligible for prophylactic pharmacotherapy and offer mechanistic insights into the pathophysiology and into new pharmacological targets and treatments.

MicroRNAs (miRNAs) play an important role in regulating utero-placental vascular function, placental and fetal development and a series of differentially expressed miRNAs were reported in the placentas from pregnancies complicated by preeclampsia (PE) and FGR. Among those, miR-210 is a well-known hypoxia-inducible miRNA expressed in the villous and extra villous trophoblasts of the placenta and several in vitro evidence pointed out for its prominent role in modulating trophoblasts invasion and migration and mitochondrial activity. miR-210 up-regulation is also crucial for endothelial cell proliferation, migration and angiogenic response to hypoxia. In this proof-of-concept study, we hypothesized that defective placentation might lead to altered miRNA release from gestational tissues into vaginal fluid (VF). In this study we explored the ability of 210-3p measured in VF samples to identify early cases of FGR and its correlations with neonatal outcomes.

Twenty-nine women with pregnancies complicated by early FGR diagnosis and 25 controls matched for gestational age were enrolled and their VF and plasma were collected. MiR-210-3p was measured by RT-qPCR and their targets were identified by in-silico analysis.

VF miR-210-3p levels were significantly lower in early FGR cases compared to controls ($p<0.05$), particularly in more severe cases and in women who later developed preeclampsia ($p<0.05$). Furthermore, VF miR-210-3p levels were correlated with lower birth weight, preterm birth and severe birth complications ($p<0.05$). miR-210-3p was not detectable in plasma samples.

In silico analyses identified HIF-1α, HIF-3α, BDNF, IGFBP3, RAD52 and TWIST-1 as experimentally validated targets of miR-210-3p. Among the predicted biological pathways controlled by miR-210-3p, we found hypoxia-responsive signaling such as autophagy, oxidative stress and metabolic pathways.

Although validation is needed, these results suggest that measuring miR-210-3p levels in vaginal fluid can identify early FGR; future mechanistic studies will investigate whether pharmacological strategies based on miR-210-3p or its targets may be useful for controlling FGR.

Rare premature aging diseases in children: how to face diagnostic challenges through specific biomarkers.

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1 – CNR Institute of Molecular Genetics "LLCS" Unit of Bologna; 2 – CNR Institute of Molecular Genetics "LLCS" Pavia

Premature aging syndromes are congenital or ealy onset diseases featuring one ore more aging phenotypes. Among these pathologies, Werner syndrome, Bloom syndrome and Rothmund-Thomson syndrome, but play also a role in Ataxia-telangiectasia, Cockayne syndrome, Nijmegen breakage syndrome, Seckel syndrome and xeroderma pigmentosum, are associated with mutations in DNA repair enzymes, while Hutchinson-Gilford Progeria, atypical Werner syndrome and Mandibuloacral dysplasia are due to mutations in genes of the nuclear envelope. Although genetic screening allows precise diagnosis of those diseases, the diagnostic path is often complicated by lack of biomarkers allowing a pre-screening. We are proposing molecular markers of disease for some of the above-mentioned premature aging syndromes, namely nuclear envelope linked progeroid forms and xeroderma pigmentosum.

Epigenetic Rerogramming by Decitabine in Retinoblastoma.

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1 – Consiglio Nazionale delle Ricerche; 2 – Institute for Organic Synthesis and Photoreactivity; 3 – Instituto di Fisiologia Clinica

Background: Retinoblastoma (Rb) is a rare cancer, yet it is the most common eye tumor in children. It can occur as either a familial or sporadic form, with the sporadic variant being more prevalent, though its downstream effects on epigenetic markers remain largely unclear. Treatment for retinoblastoma typically involves aggressive chemotherapy and surgical resection. The identification of specific epigenetic characteristics of non-hereditary (sporadic) Rb has led to the development of advanced, high-throughput methods to explore its epigenetic profile. Our previous research showed that treatment with the demethylating agent 5-Aza-2'-deoxycytidine (decitabine; DAC) induced cell cycle arrest and apoptosis in retinoblastoma in a well characterized Retinoblastoma model (WERI-Rb1). Our analysis of time-dependent gene expression in WERI-Rb1 cells following DAC exposure led to the development of testable hypotheses for further investigating the epigenetic impact on the initiation and progression of retinoblastoma tumors.

Methods: Gene expression analysis of publicly available patients' primary tumors and normal retina datasets have been compared with those found in WERI-Rb-1 cells to assess the relevancy of DAC-driven genes as markers of primary retinoblastoma tumors. The effect of DAC treatment has been evaluated in vivo, both in subcutaneous xenografts, and in orthotopic models. qPCR analysis of gene expression, and Methylation-Specific PCR (MSP) has been performed.

Results: Our network maps' analysis of differentially expressed genes in primary tumors compared with DAC-driven genes identified 15 hub/driver genes that could have a pivotal role in the genesis and progression of retinoblastoma. DAC treatment induced significant tumor growth arrest in vivo in both subcutaneous and orthotopic xenograft retinoblastoma models. This was associated with gene expression changes either by direct switching-on of epigenetically locked genes, or by an indirect regulation of linked genes, suggesting the possible use of DAC as an epigenetic anti-cancer drug for the treatment of retinoblastoma patients.

Conclusion: There is a pressing need to develop innovative treatments for retinoblastoma. Our research revealed that DAC can effectively suppress the growth and progression of retinoblastoma in in vivo models, offering a potential new therapeutic approach to battle this destructive disease. This discovery highlights the impact of this epigenetic modifying therapy in reprogramming tumor dynamics, and thus its potential to preserve both the vision, and lives, of affected children.

SPEAKER SECTION

SPEAKER: ANTONIO LOPALCO

Development of Midazolam/γ-Cyclodextrin Pediatric Orodispersible Films Using Direct Powder Extrusion 3D Printing

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Midazolam (MDZ) is a benzodiazepine administered via oral or sublingual routes in cases of antiepileptic treatment and surgical anesthesia but with limited bioavailability, low stability and an unpleasant taste. To overcome these limits 0.2% (w/v) MDZ oral solution containing γ-cyclodextrin (γ-CD)[1] have been developed for pediatric patients. However, solid forms adhering to the buccal mucosa and rapidly releasing MDZ would be beneficial. Orodispersible films (ODFs) are a potential solution, typically containing hydrophilic polymers that quickly dissolve in the buccal cavity, leading to rapid dissolution and drug delivery[2]. Direct printing of pharmaceutical powders allows the creation of personalized paediatric dosage forms, such as orodispersible films (ODFs)[3]. In this study, we present an optimized protocol to prepare midazolam (MDZ)/γ-cyclodextrin (γ-CD) inclusion complex-loaded ODFs using the innovative direct powder extrusion 3D printing technique (DPE). ODFs were formulated with a polymer blend consisting of polyethylene oxide and hydroxypropyl methylcellulose, in the presence or without γ-CD. An in-depth analytical investigation using NMR and LC-MS spectrometry demonstrated that MDZ/γ-CD inclusion complex could form in situ during the printing process. ODFs with the preformed inclusion complex and MDZ alone were also prepared and characterized in terms of drug loading, morphology, disintegration, drug release, and mucoadhesion. ODFs containing either the in situ-formed or preformed inclusion complex were equivalent and exhibited superior performance compared to films without γ-CD. The use of γ-CD was particularly advantageous in enhancing the film disintegration and MDZ dissolution. MDZ-loaded ODFs were successfully developed using DPE to produce thin, fast-dissolving films that are particularly suitable for paediatric populations. This approach facilitated the production of personalized dosage forms and enabled the creation of beneficial molecular interactions that would typically require additional pharmaceutical processes.

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SPEAKER: SERENA BERTONI

Development of a new oral drug formulation for the treatment of Infantile Hemangioma in newborns.

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The infantile hemangioma (IH) is the most common benign vascular tumor in the pediatric population. The first-line therapy for its treatment is oral propranolol, currently formulated as oral solution prepared extemporaneously in hospital pharmacy or available as concentrated solution (Hemangiol®). Recent studies have shown that a combination of oral propranolol and corticosteroids gives a faster response and significantly reduces the tumor volume in IH patients. However, there is currently no child-appropriate formulation available for administering a drug combination for IH treatment. In this study, solid lipid microparticles (MPs) were developed as a controlled and age-appropriate drug delivery system for the oral administration of a fixed-dose combination of propranolol hydrochloride and a corticosteroid, either prednisolone (combination I) or prednisolone acetate (combination II). The MPs were produced using spray congealing, a solvent-free technology that generates highly spherical and free-flowing particles. MPs were composed of an orally-approved lipid excipient (Compritol® 888 ATO), used alone as matrix-forming material (m-MPs) or combined with a hydrophilic polymer (polyethylenglycol, PEG) to obtain hybrid MPs (h-MPs). The produced formulations were characterized regarding drug loading amount, size, morphology and solid-state properties. Dissolution studies were conducted through an in vitro model specifically designed to simulates the gastrointestinal physiology (e.g. fluids volume and composition, digestion processes, etc.) of newborns. The obtained release profiles were compared considering the different fixed-dose combinations (I or II), type of MPs (matrix or hybrid) and administration vehicles (milk or apple juice). Spray congealed-MPs were successfully loaded with the two combinations with optimum production yields (about 70-80%) and satisfactory loading efficiencies (up to 90% considering a 1% w/w loading of each drug), indicating that this delivery system is suitable for administering two drugs, even with very different hydrophilic/hydrophobic properties, in the same dosage form. The morphological characterization showed spherical and non-aggregated particles with the crystalline drugs homogeneously distributed throughout the particle volume. Scanning electron microscopy images showed a homogeneous structure in case of m-MPs and a biphasic structure consisting in multiple PEG cores embedded in a lipid matrix in case of h-MPs. The in vitro release studies indicated that both types of MPs were able to control the release of propranolol and the corticosteroid drug for an extended period of time (about 3 hours) compared to free drugs. However, h-MPs guaranteed more consistent release profiles with less differences when varying drug combination or administration drink compared to m-MPs.

Overall, the proposed microparticle-based formulation represents a suitable dosage form for newborns and addresses the limitations of oral solutions used for IH treatment: the amount of MPs to be administered can be easily adjusted based on the patient's weight, enabling precise dosing and MPs can be dispersed in both baby-milk or apple juice, as recommended by the EMA to enhance compliance in newborns and infants. Based on the release profiles obtained, the h-MPs should help maintaining stable drug levels in the patient’s bloodstream, thus better therapeutic effect, by providing a sustained release over an extended period, as well as fewer variations in the drug's absorption depending on the type of drink used for administration (milk or juice).

SPEAKER: SMITA SALUNKE

Accelerating Safer Administration of Medicines to Children in Low Resource Settings – Bridging Stakeholder Viewpoints.

Alka Mukne[1], Vandana Patravale[2], Pradeep Behera[3], K. Bangarurajan[4], Esmerald Hermans[5*], Jennifer Walsh[6*], Smita Salunke[7*]

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*On behalf of European Paediatric Formulation Initiative (EuPFI)

Background: Medication use in paediatric population is prone to dosing error as small dose volumes are required to be administered. Using safe and effective administration devices to prevent over-dosing and under-dosing is a key approach to secure paediatric medication safety. It is especially important to understand the pharmacotherapy needs of children living in resource-limited conditions and find solutions that accelerate the de-velopment and adoption of user-friendly administration devices. Hence, a workshop was held to understand the uptake of the already existing administration devices for oral and respiratory medicines in low- and middle-income countries, and to assess the level of awareness of issues associated with use of administration devices as well as the need of innovative devices.

Method: The workshop featured a panel where researchers shared findings on paediatric medicine administration devices, followed by presentations on clinical and industry challenges. Participants then discussed procedural and operational issues and proposed solutions.

Results: The panel highlighted country-dependent use of devices for paediatric oral and inhaled medicines. Indian HCPs prioritize access, availability, and affordability, while European developers adhere to strict regulations on accuracy, dose markings, and labelling. In India, innovation is limited by lower regulatory reliance, with a focus on simplifying administration. The top-rated solutions, supported by all stakeholders, are device innovation and regulatory harmonization.

Conclusions: Discussions and knowledge shared during this event showed the effectiveness of the workshop in fostering a deeper understanding of the issues regarding use and development of administration devices in low resource settings.

POSTER SECTION

A case report of a young patient with Beta Thalassaemia Major.

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Background: Haemoglobinopathies are very serious clinical conditions caused by genetic mutations, monogenic diseases. Among them, Beta Thalassaemia Major and Intermedia are very frequent diseases in Albania, with a high prevalence in our population. People with Beta Thalassaemia nowadays live longer and have a quite quality of life due to the quality of blood transfusions and a good iron chelation therapy compliance. From time to time there are a few side effects of general treatment and for this reason strict monitoring is needed. There is still more to do, in terms of permanent cure.

Aim: To report a difficult case of a 4 years old boy, suffering from Beta Thalasaemia Major who presented with abdominal discomfort and hematemesis.

Results: This patient was in treatment with blood transfusion (pure red blood cell) since the first year of life, once in three weeks. After 20 transfusions (when Ferritin level was above 1000 ng/ml) it was administered oral iron chelation therapy (Deferasirox) with a moderate dose per day (20 mg/kg/day). He was compliant and the ferritin level started to go down. 6 months after treatment he started to present with pale skin and complained from abdominal pain. It was excluded every abdominal pathology through ultrasound and laboratory examinations. Pain medications were administered from time to time.

One night he was admitted to Emergency Pediatric Ward with severe pain and hematemesis three times during the night. His Complete Blood Count showed severe anemia (nethertheless he was transfused two days ago) After some fast examinations and an urgent fibrogastroscopy, the boy was diagnosed with duodenal ulcer perforation (a very rare or uncommon in this age group, probably due to use of iron chelation therapy) and a surgery was underwent successfully.

Firstly, the patient was stabilized with blood transfusion and rehydration. In our opinion it was the effect of oral iron chelator drug, which causes this complication, unreported till now.

Discussion: A better understanding and awareness, a strictly monitoring of patients suffering from Thalassaemia and other haemoglobinopathies could help health professionals to act in the proper way and to save patients' lives. Better treatments are on the way, and we need to be optimistic.

Design of bilayered buccal films for azithromycin administration in pediatric population.

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Currently, azithromycin (AZT) represents one of the most prescribed drugs in pediatric population. It is generally administered through the oral route and employed for the treatment of different infectious diseases, such as acute bacterial sinus, otitis media, pharyngitis, tonsillitis, pneumonia, bronchitis, urogenital tract and skin infections. However, several drawbacks of AZT, like its low aqueous solubility, poor oral bioavailability and bitter taste, can affect the therapy efficacy and the children compliance. For this reason, alternative strategies useful to improve AZT administration should be investigated. In this context, buccal films can be considered as child-friendly promising formulations thanks to their thinness, flexibility, ease applicability and ability to ensure accurate dosing. Therefore, in this study we firstly aimed to obtain a mucoadhesive primary layer capable of establishing a closed and prolonged contact with mucosa and controlling AZT release. Secondly, a further layer was evaluated to be applied on the primary one, to assure a unidirectional absorption through the buccal mucosa and limit the drug bitter taste in the mouth. Specifically, for the primary layer preparation, solutions based on different selected mucoadhesive polymers (hydroxypropylmethylcellulose HPMC, sodium hyaluronate HYA, sodium alginate ALG, xanthan gum XG, carrageenan CAR and chitosan CH) were mixed with excipients able to increase drug solubility (Soluplus SOL and polyvinylpyrrolidone PVP, K25 or K90). The obtained solutions, loaded with AZT, were finally cast in a silicon mold and oven-dried at 70 °C for 7 h. After this, an ethylcellulose solution was sprayed on the primary polymeric layer and immediately oven-dried at 70 °C for 5 min, in order to obtain the second layer. Films were characterized in terms of thickness, weight, drug content, water uptake (WU) ability and in vitro release. The preliminary selection allowed us to formulate loaded films (theoretical amount of AZT equal to 9.9 mg/cm2) composed of CS/PVP (K25 and K90), CS/SOL, HYA/SOL and ALG/SOL. The obtained films were uniform, slightly opalescent, thin (thickness lower than 0.3 mm), and presented a drug content equal to 20-25 % w/w, also confirmed by X-ray analysis. Finally, WU ability and in vitro release depended on the polymeric composition of the film. Particularly, films based on CS/PVP and CS/SOL reached the maximum ability to hydrate after 2 hours, tended to solubilize and determined a quick drug release. On the other hand, HYA/SOL and ALG/SOL showed a more gradual hydration ability and sustained release, due to the high viscosity of the polymeric network in the gelled state. Interestingly, bilayered films allowed the release of a lower amount of drug with respect to the primary polymeric layer, thus demonstrating that they could limit drug release inside the buccal cavity. This latter finding is extremely important considering the need for limiting the bitter taste of AZT and minimizing the extent to which the drug is swallowed. Further investigations will be carried out in order to investigate the mucoadhesion properties of films and their ability to promote drug diffusion through a mucosa. Films with the selected compositions will be prepared through 3D printing technology (3DP), as innovative tool able to meet the demands of personalized therapy.

Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia: Improving Biochemical Control and Treatment Outcomes.

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Background: Standard glucocorticoid therapy for congenital adrenal hyperplasia (CAH) often fails to adequately control androgen excess, leading to overtreatment with glucocorticoids and numerous adverse events. In Europe, two innovative modified-release hydrocortisone (MRHC) formulations are available: modified-release hydrocortisone tablets and capsules.

Modified-release tablets consist of an immediate-release outer layer and a prolonged-release core, allowing for once-daily dosing. However, this formulation does not replicate the physiological nocturnal cortisol rise, as cortisol levels increase only after the morning dose.

Modified-release capsules (MRHC, Efmody©, formerly Chronocort) provide delayed release and prolonged absorption, mimicking the natural circadian cortisol rhythm. MRHC is taken twice daily—two hours after dinner and one hour before breakfast—resulting in improved morning control of adrenal androgen markers in CAH patients and better disease management. Approved by AIFA (Determination 110/2021) for CAH patients ≥12 years, MRHC lacks clinical data in adolescents aged 12–18.

Objectives: We investigated whether modified-release hydrocortisone (MRHC), which mimics the circadian rhythm of cortisol, could improve disease control and evaluate its effectiveness, safety, and potential adverse effects

Methods: We conducted a 12-month prospective observational study on 18 CAH patients aged ≥12 who switched from conventional therapy to MRHC. Primary outcomes included reducing 17-hydroxyprogesterone (17OHP) levels below 1200 ng/dL, normalizing delta-4-androstenedione levels, reducing total hydrocortisone dose, and comparing adverse events and adrenal crises before and after the therapeutic switch. Secondary outcomes included ACTH, renin, testosterone levels, and metabolic profile parameters (BMI SDS, growth velocity SDS, and blood pressure).

Results: MRHC resulted in improved biochemical control, with a statistically significant morning 17OHP reduction observed after 3 months of MRHC therapy compared to conventional treatment ($p = 0.013$). However, at 6 months, the decrease was not statistically significant ($p = 0.116$). The percentage of patients with controlled 09:00h serum 17OHP (<1200 ng/dL) was 62.5% at 3 months and 45% at 6 months, compared to only 6% with standard therapy. The mean daily hydrocortisone dose was 15.4 mg/day at baseline and 15 mg/day at 6 months. No severe adverse events or adrenal crises were reported during MRHC therapy. Moreover, no laboratory, genetic, or clinical markers have been identified to predict which patients would benefit more from MRHC over standard treatment.

Conclusion: MRHC improved biochemical disease control in most patients, with a slight reduction in steroid dose over time and no severe adverse events or adrenal crises.

The Benefits of Glycosade and Maizena in the pediatric treatment of Glycogen Storage Diseases Type I, III, and IX: the experience of Emilia- Romagna.

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Background: Glycogen storage diseases (GSDs) are inherited metabolic disorders causing abnormal glycogen metabolism, leading to hypoglycemia and hepatomegaly. GSD I, III, and IX require dietary management to prevent metabolic decompensation. Traditional therapy with raw cornstarch (Maizena) provides sustained glucose release but requires frequent intake, particularly at night, imposing a burden on patients and caregivers. Glycoside, a modified waxy cornstarch, offers extended glucose release, reducing administration frequency and improving metabolic stability. This study evaluates Glycosade's benefits in pediatric GSD patients at the Emilia-Romagna Regional Reference Center for metabolic disease and newborn screening.

Materials and Methods: A retrospective study was conducted on 7 pediatric patients with GSD I, III, and IX. 5/7 patients switched from traditional cornstarch to Glycoside, and metabolic control was assessed over six months. Clinical evaluations included fasting glucose, lactate, triglycerides, liver enzyme levels, and growth parameters. Primary endpoints were glucose stability, nocturnal hypoglycemia reduction, and liver function improvement. Secondary endpoints included gastrointestinal tolerance, treatment adherence, and patient well-being. Dietary intake data were recorded, including macronutrient distribution and cornstarch administration.

Results: Most of the patients showed improved metabolic control with Glycosade. Glycemic stability increased, reducing nocturnal carbohydrate needs. 5/7 patients maintained stable fasting glucose at three months, compared to two before switching. 1/7 patients with glycogenosis IXa take neither of the two compositions. Growth parameters remained stable, with 3 patients experiencing significant weight gain. Treatment adherence improved, reducing nighttime feedings and enhancing sleep quality. Gastrointestinal tolerance varied, with some patients tolerating Glycosade better than Maizena.

Discussion: Glycoside provided prolonged glucose release, minimizing hypoglycemia risk and improving adherence. Stabilized liver enzymes suggest reduced hepatic glycogen accumulation, enhancing long-term prognosis. Weight changes varied despite the known possibility of weight gain associated with these formulations. Glycosade's higher cost may limit accessibility, necessitating further cost-effectiveness studies. Expanding the study to a larger cohort will help validate these findings and determine optimal dosing regimens tailored to individual metabolic needs.

Investigation into user perspectives of minitablets for paediatric treatments in LMICs.

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Background: Minitablets have been identified as a promising dosage form for the paediatric population. However, there is limited evidence-based data available on acceptability of minitablets, particularly handling aspects of minitablet. Additionally, there is insufficient information on whether there are differences in user opinions based on socio-economic status, health condition, or level of experience. Hence, this project aims to investigate user perspectives from LMICs on using minitablets versus conventional tablets for paediatric treatments.

Methods: A descriptive cross-sectional pan-India study was conducted with parents of children aged between 0 to 12 years using a paper-based survey. Parents were recruited from two main settings: schools and hospitals. Ethical approvals were obtained from these institutions. A pilot questionnaire was developed to assess various user aspects such as socioeconomic status, health condition, perceived swallowability wr.t to number and size, types of minitablets, administration methods, choice of packaging, ease/comfort of handling minitablets and willingness to use minitablets over conventional tablets.

Findings: 60 parents were recruited from schools and hospitals. 52% of the parents were classified as middle/upper middle class, while 48% fell into the lower middle-class category. 45% parents reported their children to be either healthy or experienced acute illnesses, while 55% reported their children had chronic conditions. Among all participants, 67% were willing to administer 1.5mm tablets (majority aged 2-8yrs), 26% were willing to administer 3mm tablets (majority aged 6-11yrs), and 7% were willing to administer 4mm tablets (majority aged 9-12yrs). The parents reported the ability of taking minitablets if fewer than 10 tablets were administered at a time, especially for 1.5mm. The willingness to administer number of minitablets varied for as per socioeconomic status particularly for 1.5mm size tablet. Majority (59%) parents of chronically ill children selected 3mm and 4mm sized minitablets while the parents (74%) with healthy children chose 1.5mm. With regards to ease of handling minitablets, 30% of parents reported difficulty with 1.5mm tablets, while all other sizes were described to be easy to handle. For the type of minitablet, overall, 55% of participants said they preferred a minitablet that melts on the tongue and 45% would prefer a tablet that dissolves in water. With regards to administration of minitablets with soft food, the majority (46%) of parents with children aged 1-8 years used chocolate, ice cream, milk, and jelly, 33% preferred juice or water for age 12 months- 5 years, and 21% reported using soup and rice for ages 5-12 years. More than 50% of parents from lower-income background employed manipulation strategies to encourage their children to take medicine, while more than 80% of parents from high income background said that their children eventually take tablets after some initial resistance. Regarding the packaging for minitablet 35% of parents selected a device dispensing one tablet at a time, while 65% choose a package containing multiple tablets they could count and administer.

Conclusion: This study underscores that the acceptability of dosage forms is multifaceted, influenced by socio-economic status, parental education, affordability, prior experience, perceived benefits, ease of use, cultural relevance, and the availability of support and training. This pilot phase identified significant gaps in survey methodology, particularly in effectively correlating tablet characteristics with tablet number and size, association with socioeconomic status. Moving forward, revisions to the questionnaire are essential to accurately capture these correlations. Future plans include expanding the study to encompass LMICs, conducting a comprehensive survey across India, other LMICs, and European nations.

“EPTRI Advances Therapy Medicinal Products TRP”

SPEAKER SECTION

SPEAKER: GIOVANNI MIGLIACCIO

Advancing paediatric care through ATMPs: challenges, opportunities, and the role of EPTRI

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Advanced Therapy Medicinal Products (ATMPs) are an emerging class of medicinal products harnessing gene, cell, and tissue-based therapies to treat severe and life-threatening conditions. These therapies provide personalized, regenerative solutions tailored to a patient’s genetic background, disease progression, and immune response. ATMPs are especially crucial for pediatric patients, as many rare monogenic disorders manifest during fetal or neonatal stages, where conventional treatments are either lacking or purely palliative.

Currently, 18 ATMPs have been licensed, with 10 specifically including or dedicated to pediatric patients.

Despite their potential, ATMPs face substantial challenges in development and accessibility. In paediatric medicine, the small patient population limits financial incentives, often resulting in market failures and reduced investment in research and commercialization. Additionally, the complex regulatory approval processes and the high development costs further hinder their broader adoption in clinical settings.

To overcome these barriers, initiatives such as the Pediatric Advanced Medicines Biotech proposal and the European Pediatric Translational Research Infrastructure (EPTRI) are working to enhance accessibility, foster collaborative research, and establish sustainable pricing and marketing strategies. Notably, the EPTRI Thematic Research Platform on ATMPs plays a critical role in driving innovation and ensuring these life-changing therapies reach the paediatric patients who need them most. Addressing financial, regulatory, and logistical barriers is essential for the successful integration of ATMPs into clinical practice, ultimately improving outcomes for children with rare and life-threatening diseases.

POSTER SECTION

Luspatercept, a novel therapeutic approach in patients affected from Beta Thalassaemia Major.

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It is always a challenge deeping insight in haemoglobinopathies concerns.

Haemoglobinopathies (hemoglobin disorders) caused by genetic mutations are autosomal recessive disorders and the most frequent genetic inherited diseases seen worldwide, specifically and above all among Mediterranean countries. Thalassaemia syndromes (Beta Thalassaemia Major/ Intermedia and Sickle Cell Disease) have been the first diagnosed diseases since in intrauterine life using recombinant DNA techniques. So, a better understanding of their pathophysiology has given a spectacular improvement and a considerable impact into these conditions management.

It is estimated annual births of more than 330 000 affected infants who are going to suffer from these disorders. The distribution of these diseases or disorders is historically linked to current or previously malaria endemic regions, however nowadays immigration has led to a worldwide distribution, making them a global health problem.

Till now we still cannot have a permanent resolve of these diseases, unless a successful bone marrow transplantation or Stem Cell Transplantation.

Crucial therapies like regular blood transfusions and an optimal compliance of iron chelation therapy seem to have a great importance for a successful treatment of these individuals promising a longer life expectancy.

During the last decade, new treatment approaches and novel therapies have been proposed, some of which have the potential to change the natural history of these disorders. Indeed, the first erythroid maturation agent, luspatercept and gene therapy have been approved for beta thalassaemia adult patients. A green light is given for use in children and this makes us confident and optimistic in offering a qualitative life to our children affected.

At EHA 2024, the investigators reported safety data from the first part of the two-part study, using Luspatercept, specifically regarding patients with transfusion dependent β-thalassemia who were younger than 18 but no younger than 12 years of age. These data were from 12 patients who had received at least four transfusions in the 24 weeks pre-enrollment. This novel treatment hopes to reduce anemia, to minimize chronic red blood cell transfusions, and mitigate secondary iron overload.

Conclusion: The advances of the understanding of hemoglobinopathies and the specificity in each type of them seem to help scientists to pave the way to develop several novel treatments and novel therapies.

It is now clear that efficacy and safety of many therapies in children and adults is still under study. In the future and upcoming years, the therapeutic approach to these disorders is going to become more

complex and will change the natural history and the real burden of these disorders which really impact individuals and societies.

Venetoclax and Azacitidine in Pediatric High-risk Myeloproliferative Neoplasms: the AIEOP Experience.

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Background: Refractory and/or relapsed acute myeloid leukemia (AML r/r), advanced myelodysplastic syndromes (MDS-EB), and therapy-related myelodysplastic syndromes/acute myeloid leukemia (t-MDS/AML) represent a significant therapeutic challenge for pediatric hemato-oncologists, as these diseases are often resistant to conventional cytotoxic therapies and have a high relapse rate.

Affected patients have often undergone intensive pretreatment and experienced considerable toxicity, making it crucial to adopt less toxic therapies to minimize further adverse effects.

Aim: In this retrospective, multicenter study, 31 pediatric patients (median age of 10 years, range 2-20) with high-risk myeloid malignancies were treated with a combination of venetoclax and azacitidine (ven-aza) (median number of cycles: 2, range 1-7) at centers affiliated with the Italian Association of Pediatric Hematology and Oncology (AIEOP). The patients were diagnosed with AML r/r (n=18), MDS-EB (n=6), and t-MDS/AML (n=7).

Results: The results showed a complete remission (CR) rate of 48.4%, with an overall response rate (ORR), defined as the sum of CR and PR, of 71%. A total of 58.1% of patients successfully proceeded to hematopoietic stem cell transplantation (HSCT). With a median follow-up of 216 days (32 – 1004) from the start of ven-aza, the one-year event-free survival (EFS) was 53.5% (95% CI: 35.8%-79.9%), significantly higher in patients who underwent HSCT ($p < 0.0001$). Ven-aza demonstrated excellent efficacy in the subgroup of patients with AML r/r harboring KMT2A rearrangement and in patients with MDS-EB with UBTF-TD.

Grade ≥3 adverse events included neutropenia (12 patients), febrile neutropenia (8 patients), fungal infections (2 patients), and hypertransaminasemia associated with diarrhea (1 patient). No treatment-related deaths were reported.

Conclusion: Our study demonstrates that ven-aza represents a safe and effective bridging strategy to HSCT in pediatric and young adult patients with high-risk myeloid malignancies.

Perinatal Cell-Derived Spheroids as a Dual Therapeutic Strategy for Type 1 Diabetes Mellitus.

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Background: Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by the selective destruction of pancreatic beta cells, leading to absolute insulin deficiency. Current therapies rely on exogenous insulin administration, which does not address the underlying immune dysregulation nor restore endogenous insulin production. Advanced cellular strategies leveraging the regenerative and immunomodulatory properties of stem cells may provide a more comprehensive therapeutic approach.

Aim: This study investigates the potential of perinatal cell-derived spheroids as a dual therapeutic strategy for T1DM, integrating both insulin secretion and immune modulation. We first characterized the immunomodulatory capacity of spheroids composed of Wharton's jelly mesenchymal stem cells (WJ-MSCs) combined with amniotic epithelial cells (AECs). These spheroids were co-cultured with activated peripheral blood mononuclear cells (PBMCs) from healthy donors to assess their effect on pro-inflammatory and regulatory immune populations. Subsequently, we induced endocrine differentiation in AECs to generate insulin-producing cells, confirming the expression of pancreatic markers via immunofluorescence. Differentiated AECs were then integrated with undifferentiated WJ-MSCs to form structured spheroids with both functional insulin secretion and immunomodulatory properties.

Results: Our findings indicate that undifferentiated perinatal spheroids exert significant immunomodulatory effects, attenuating pro-inflammatory responses while promoting anti-inflammatory pathways. Spheroids containing insulin-producing AECs formed cohesive three-dimensional structures and exhibited functional potential for insulin secretion. Further investigations will evaluate the therapeutic efficacy of these spheroids in preclinical models, with a focus on their dual role in immune regulation and metabolic restoration.

Conclusion: These results support the potential of perinatal cell-derived spheroids as a novel cell-based therapy for T1DM, addressing both beta-cell replacement and immune-mediated disease mechanisms. This strategy may pave the way for innovative treatments that surpass conventional insulin therapy, offering a more integrated and durable therapeutic approach for pediatric and adult T1DM patients.

Pioneering paediatric DMD therapies: precision gene editing in iPSC and preclinical mouse models.

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Duchenne muscular dystrophy (DMD) is a severe paediatric neuromuscular disorder caused by mutations in the dystrophin gene, leading to progressive muscle degeneration and early mortality. Despite recent advances, effective treatments remain elusive, highlighting the need for robust translational research models that faithfully represent the paediatric disease environment and inform therapeutic development.

Patient-derived induced pluripotent stem cells (iPSCs) serve as pivotal in vitro platforms to recapitulate the core features of DMD pathology while providing a patient-centric perspective crucial for paediatric research. In our laboratory, we combine these iPSC models with next-generation gene editing tools - specifically base and prime editing - to accurately correct pathogenic mutations responsible for DMD.

To further optimise and assess these approaches, we employ preclinical mouse models of DMD, thus establishing a comprehensive translational pipeline. By integrating the specificity of iPSC-based systems with the physiological complexity of in vivo studies, we can rigorously evaluate safety, efficacy, and delivery strategies, as well as potential off-target effects, prior to clinical translation.

Our research program aligns with the goals of the European Paediatric Translational Research Infrastructure by expediting the development of transformative therapies for children affected by DMD and other rare diseases. By harnessing cutting-edge iPSC technology, established mouse models, and precise gene editing, we aim to accelerate the path from bench to bedside, ultimately improving outcomes for paediatric patients and advancing the field of neuromuscular research.

Off-the-shelf non-viral CARCIK cells derived from Cord Blood: A GMP-compliant approach for the treatment of hematologic malignancies.

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Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment of hematologic malignancies. However, its widespread adoption is limited by the challenges associated with autologous manufacturing, including high costs, lengthy production times, and variability in T-cell quality. To overcome these limitations, over the past decade, we have developed a non-viral gene transfer platform utilizing the Sleeping Beauty transposon system and electroporation to engineer Cytokine-Induced Killer (CIK) Cells (PCT/EP2015/075980). With an AIFA-approved Good Manufacturing Practice (GMP) Cell Factory at our institution, we have been conducting academic early-phase clinical trials since 2017 to evaluate the CARCIK-19 product for the treatment of Acute Lymphoblastic Leukemia (NCT03389035, NCT05252403). These trials demonstrated that up to 85% of treated patients achieved complete remission, with a favorable safety profile. These groundbreaking results marked the first successful application of CARCIK therapy worldwide (PMID 32870895, Lussana ASH2022, Rambaldi ASH2022)). Furthermore, an ongoing phase I/II study is currently assessing the safety and efficacy of partially matched donor-derived CARCIK-CD19 cells for the treatment of B-cell non-Hodgkin lymphoma and B-cell chronic lymphocytic leukemia outside the transplant setting (NCT05869279).

To further advance our non-viral platform toward an efficient and cost-effective off-the-shelf CAR T-cell therapy, we explored the feasibility of generating allogeneic CAR-CIK cells derived from cord blood (CB). Cord blood has been widely used in hematopoietic stem cell transplantation due to its advantages, including reduced graft-versus-host disease (GvHD) risk and superior proliferative capacity.

In this study, we optimized a GMP-compliant method for generating CAR-expressing CIK (CARCIK) cells from cryopreserved CB units. CIK cells, which exhibit both T-cell receptor (TCR)-mediated and natural killer (NK)-like activity, provide an effective mechanism for targeting malignant cells while minimizing the risk of inducing GvHD (PMID: 17606446, 16953207, Gaipa ASH2018). The integration of the Sleeping Beauty transposon system enabled efficient CAR transgene delivery into CB-derived CIK cells, leading to robust expansion and stable CAR expression.

We conducted a comparative analysis of the metabolic and functional properties of CB-derived CARCIK cells versus their peripheral blood (PB)-derived counterparts. CB-derived CARCIK cells demonstrated reduced glycolysis, enhanced mitochondrial respiration, and a higher proportion of naïve and memory-like T cells, suggesting superior persistence and longevity. In vivo efficacy was evaluated using a DAUDI xenograft model, where CB-derived CARCIK-CD19 cells exhibited potent antitumor activity, effectively controlling disease progression and prolonging survival.

These findings support the integration of CB-derived CARCIK cells into future clinical applications, offering a readily available, off-the-shelf cellular therapy with a favorable safety profile. The unique immunobiology of CB T cells, combined with the scalability of CIK cell expansion and the efficiency of the Sleeping Beauty transposon system, provides a viable solution to the current limitations of autologous CAR T-cell therapy. Given the urgent need for accessible and cost-effective immunotherapies, CB-derived CARCIK cells represent a promising alternative for the treatment of hematologic malignancies. Ongoing and planned clinical trials will further define their therapeutic potential, paving the way for broader clinical implementation and improved patient outcomes.

Accessing the intrathecal space in a porcine paediatric model: description of

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The piglet has emerged as one of the most complete and accurate models for neonatal and paediatric translational medicine due to genetical, anatomical and physiological similarities with humans. The porcine brain resembles humans in terms of weight, volume, cortical surface area, myelination, composition and electrical activity, and its development extends from prenatal to early postnatal life. Moreover, due to their longer lifespan, pigs are a great model to study inherited/genetic conditions. All of the above have contributed to the interest toward piglets for gene therapy for neurological disorders. In such scenario, it became pivotal to validate reproducible techniques to access the intrathecal space allowing for cerebrospinal (CFS) sampling and local drug administration. This abstract describes two techniques developed for Cisterna magna (CM) puncture and lumbar spinal catheter placements, as well as some applications.

The CM study, divided into a cadaver phase and an in vivo one, was conducted on 2-30 days-old piglets: after hand palpation of the occipital protuberance, a line identifying the median spinal plane was marked; a second one was then traced between the cranial margins of the atlas wings. A 22G×75mm spinal needle was introduced along the median line to a depth of 4mm, 5mm posteriorly to the intersection of the two lines; the tip of the needle was directed cranioventrally using the cranial margin of the wings as an external landmark. The technique allowed the safe CSF collection in all animals [1].

The second study, once again divided into a cadaver and an in vivo phase, identified the L2-L3 intervertebral space as the best one for percutaneous insertion of spinal catheter, reaching the CM, in 30 days-old piglets. Again, the newly developed technique allowed for safe placement of the device in all subject. The proposed technique requires less skilled operators when compared to the other existing method, which involves surgical approach, and potentially leads to fewer complications [2].

The above-mentioned methodologies were then used in a trial aimed at creating a comprehensive map of Central Nervous System (CNS) transduction by eight recombinant adeno-associated virus (rAAV) serotypes upon cerebrospinal fluid administration in neonatal piglets. rAAV9 showed the highest transduction efficiency and the widest distribution capability, robustly transducing both glia and neurons, including the motor neurons of the spinal cord [3]. Alongside, pre-injection CSF samples from 5, 30 and 50 days-old subjects were used for a metabolomic quantitative profiling of their composition, that highlighted several differences between ages, potentially related to the tightening of the blood-brain barrier [4].

According to the author's experience, focussing on the set up and standardization of the methodologies to be used to deliver drugs intrathecally and to collect uncontaminated CSF samples,

is a mandatory preliminary step allowing for smoother, more refined trials, in full compliance with the 3Rs principle. Moreover, the in-depth quantification of the CSF composition represents a critical tool to better understand the physiology of such an important lab animal, especially prior to establishing and phenotyping disease models.

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“Enhancing Paediatric Medical Devices in Europe”

SPEAKER SECTION

SPEAKER: JANA RUSSO

Paediatric and orphan devices under MDR – manufacturers’ perspective

The European Medical devices regulation 2017/745 (MDR) does not provide specific pathways to the European market for orphan or paediatric devices. The MDCG 2024-10 is a step in the right direction, providing criteria on how to classify an orphan device and allowing specific considerations for applying the MDR concept of clinical evidence to orphan devices. However, orphan devices continue to face challenges in reaching the European patients. These are related to the overall inefficiencies of the current system, such as unpredictability of conformity assessment in terms of timelines and costs as well as high administrative burden created by the MDR. In that connection, recent MedTech Europe survey data<https://www.medtecheurope.org/resource-library/medtech-europe-2024-regulatory-survey-key-findings-and-insights/> shows that a significant number of orphan device manufacturers plan reductions to their orphan devices portfolio under MDR. In order to put in place a specific orphan devices’ pathway as well as to deliver on the overall goals of MDR and IVDR (EU 2017/746), the MedTech regulatory system needs a dedicated governance structure. In addition, orphan device manufacturers need support in terms of financial incentives to be able to re-invest into orphan devices’ production.

SPEAKER: ANNELIENE JONKER

DeCODe: Develop Child and Orphan Device Support

The journey of each baby, child or young person living with a rare disease or severe or complex condition depends on medical devices for their diagnosis, treatment, and care. The average patient in a hospital has 10-15 medical devices around their hospital bed, which increases exponentially with the severity or complexity of the disease. The development of these technologies, the so-called paediatric and orphan medical devices, is slowly gaining much-needed attention. The recent development of the first guidance for the development of orphan devices has, as such, been a significant step forward in the rare diseases landscape. However, while the importance of paediatric and orphan medical devices has been acknowledged, there is a significant unmet need for paediatric and orphan medical devices, specifically those for babies and small children, and there is a high need to stimulate the development of novel or adapted paediatric and orphan medical devices.

To support paediatric and orphan medical device developers, the DeCODe consortium, co-funded by the European Commission, represents a ground-breaking initiative aimed at catalysing device innovation. This collaborative group, comprising clinicians, researchers, industry experts, and regulatory authorities, develops a pivotal platform for developing safe and effective paediatric and orphan medical devices. It will do so to accelerate the development of novel, innovative paediatric and orphan medical device solutions at all stages of the product lifecycle towards implementation. It will map paediatric and orphan medical device stakeholders and initiatives and develop a critical pathway analysis for the optimal development of novel paediatric orphan medical technologies. In

spring 2025, an open call will be held for paediatric medical device stakeholders to apply for support for their use cases. Use cases are meticulously selected based on their medical significance, feasibility, and potential impact. Technical assistance is provided to use cases' applicants, including guidance on device design, engineering, and regulatory compliance tailored to the paediatric population.
By uniting the diverse expertise of the consortium, DeCODe aims to facilitate the innovation of developers and surmount regulatory challenges. Ultimately, DeCODe aims to accelerate the development of essential medical devices that enhance and transform the quality of care for our children living with rare diseases.

SPEAKER: SOFIA FERREIRA QUARTINO

i4KIDS 4RARE – From Challenge to Adoption: Acceleration of Paediatric Orphan Medical Devices

Background: Children represent 25% of the world's population, yet there is a significant gap in medical innovation between adult and paediatric care. Factors such as perceived risk, limited market size, regulatory complexity and diffusion of paediatric expertise have hindered investment in paediatric healthcare. Rare diseases, which affect approximately 8% of the world's children, often lack dedicated medical products due to these challenges. In particular, there are an estimated 7,000 to 8,000 rare diseases affecting approximately 400 million people worldwide, with only 5% receiving specific treatments.

Objective: The i4KIDS-4RARE initiative aims to bridge this gap by developing and implementing a specialized accelerator program. This program is dedicated to fostering the creation and advancement of innovative solutions tailored for paediatric patients with rare diseases, particularly in areas with unmet medical needs.

Methods: The accelerator program focuses on three critical domains:

1. **Paediatric Cardiology:** Accelerating the development of a device to monitor patients during complex surgeries for congenital heart disease.
2. **Paediatric Rehabilitation:** Developing a home rehabilitation platform for children with spinal muscular atrophy (SMA).
3. **Paediatric Neurology:** Launching a challenge-based program for rare paediatric epilepsy (Epicare).

The program provides a structured framework, essential resources, mentorship, and financial support to innovators, researchers, and healthcare professionals. By fostering a supportive ecosystem that encourages multidisciplinary collaboration, knowledge exchange, and cross-sector partnerships, i4KIDS-4RARE aims to transform breakthrough ideas into tangible solutions.

Expected Outcomes: Through strategic partnerships with the European Reference Network (ERN), healthcare organizations, and industry experts, i4KIDS-4RARE seeks to facilitate collaborative research, development, and validation of novel orphan medical devices. This initiative addresses the medical, research, and social needs of paediatric patients with rare diseases, ensuring they receive accurate diagnoses and appropriate treatments.

Conclusion: i4KIDS-4RARE represents a pioneering effort to accelerate the development of orphan medical devices for children with rare diseases, aiming to improve their quality of life and bridge the existing gap in paediatric healthcare innovation.

SPEAKER: SANDRA BRASIL

Medical Devices and Digital Health Solutions for Paediatric and Rare Diseases.

Authors: Sandra Brasil[1], Eleonora Sarracco[1], Donato Bonifazi[1], Anneliene Jonker[2]

1 – European Paediatric Translational Research Infrastructure (EPTRI), 2 – Health Technology and Services Research (HTSR) group, University of Twente.

Abstract: Background: The medical devices (MDs) field has expanded during the last years, leading to innovative medical solutions and significantly improving patient care, however, MDs are mainly developed for the adult population, while paediatric applications rely on MDs repurposing and/ or adaptation lacking consideration for changes in disease features, growth development and hormonal changes. There is a lack of approved MDs labelled specifically for paediatric use and designed and developed specifically for children and young adults. A large gap still exists between the conceptual idea and the final clinical application for paediatric devices, mostly due to the significant development costs and regulatory efforts required, hindering Europe's competitiveness in MD development particularly in small population areas. In the EU, medical devices are regulated by the new Regulation (EU) 2017/745, entered into force in May 2021. Fostering the development of MDs tailored to children's needs, is a multidisciplinary challenge and requires different expertise, competencies, methods and technologies. In almost all cases, MDs need to be available in various sizes and configurations due to variations in the patient's anthropometric dimensions. Depending on the paediatric age groups that are targeted by a given MD, research protocols should plan to recruit and enrol enough participants to ensure uniform distribution across the age spectrum. Many of the protocols will depend on the MD's intended use and whether it is being used to diagnose, manage a temporary or permanent disease state, treat an injury, or correct a condition. Hence, there is the need to maintain a constant collaborative approach with patients and families that represent the final users and the key actor of any paediatric research services including those on MDs.

Objectives: We propose to develop a platform linking different stakeholders, such as researchers, clinicians, patients's families and representatives and SMEs to promote the exchange of expertise needed to the swift development and market access to MDs specifically tailored to the paediatric population. This platform will provide expertise on: **i)** Design and development of MDs from the concept of the idea with the related analysis to the performance studies; **ii)** Prototype design and risks analysis including safety risks (mechanical, electrical, electronic or non-clinical toxicological testing); **iii)** Medical device validation to provide evidence that device specifications conform with user needs and their

intended use; **iv)** End-user/usability assessment to enable a medical device design team to improve the usability of their devices.

Conclusion: By combining expertise from different areas and providing a multi-disciplinary stakeholder network, our proposal will break down fragmentation between various disciplines of medicine and technological areas in order to conceive and develop tailored, patient-centred, safer and integrated MDs that can seamlessly be introduced in healthcare systems.

SPEAKER: GIOVANNI TRISOLINO

Virtual Surgical Planning and 3D-Printing of Personalized surgical devices for children with rare bone diseases.

Giovanni Trisolino[1], Grazia Chiara Menozzi[1], Giulia Alessandri[1]

1 – IRCCS ISTITUTO ORTOPEDICO RIZZOLI BOLOGNA

Background: Virtual reality and 3D printing are revolutionizing orthopedic surgery by enabling virtual surgical planning (VSP) and patient-specific instruments (PSIs) to enhance precision and reduce costs. Our hospital has established an in-office 3D printing Point of Care (3DP-PoC) using cost-effective Fused Deposition Modeling (FDM) with Polylactic Acid (PLA) to produce PSIs. This study presents preliminary results of the 3DP-PoC program for treating pediatric skeletal deformities.

Methods: We assessed the safety and efficacy of ann-HTPLA 3D-printed PSIs for pediatric limb deformity correction. Low-dose CT scans were used for imaging, followed by segmentation (Mimics, Materialise 26.0) and conversion into 3D models (STL format). These models improved tactile understanding, surgical planning, and communication with surgeons, residents, and families. Surgical simulation was performed in a non-immersive virtual environment, evaluating deformity correction, osteotomy planning, and fixation selection.

Results: Since 2018, 145 skeletal segments in 117 patients (including 15 oncology cases) have been treated with VSP. In 52 patients (75 segments), 3D-printed PSIs were used (158 total). These PSIs ranged from 3.8 cm^3 to 58.8 cm^3, with 95.2% demonstrating effective use.

Additionally, 47 bone grafts were shaped, including 39 homologous donor grafts—13 pre-shaped in a clean room and 26 shaped intraoperatively. PSI-assisted procedures were on average 45 minutes shorter and required fewer fluoroscopy shots. Optimal correction was achieved in 37% of cases, while 41% had under-corrections and 22% had over-corrections. Major complications occurred in 13.8% of patients, including 4.3% infections. Intraoperative use of 3D-printed PSIs did not increase infection rates or other complications.

Conclusions: In-office 3D printing is proving to be a valuable tool for pediatric limb deformity correction. Ann-HTPLA PSIs demonstrated high usability and safety, supporting their role in cost-effective surgical planning. Further research is needed to refine correction accuracy and optimize patient outcome.

SPEAKER: ILONA MERTELSEDER

Issues in paediatric fracture management

Ilona Mertelseder[1], Annelie-Martina Weinberg[1]

1 – Department of Orthopaedics and Traumatology, Medical University of Graz

Managing pediatric fractures is challenging, especially when the growth plate (physis) is involved. Implant selection must minimize interference with skeletal development. Preserving the physis is crucial to preventing limb length discrepancies and angular deformities, which may require correction. But also the composition need to be healthy to avoid long-term complications. Conventional fixation methods avoid transphyseal implantation of non-resorbable materials, such as stainless steel or titanium, to prevent premature closure, though this may compromise stabilization. The high stiffness of these materials (high Young's modulus relative to bone) can induce stress shielding, weakening adjacent bone and increasing refracture risk. Additionally, implant removal is necessary due to material precipitates, adding to the patient's burden.

Biodegradable materials, particularly magnesium (Mg)-based alloys, are promising alternatives. Mg alloys have a Young's modulus closer to bone, reducing stress shielding. Their controlled degradation in vivo allows temporary stabilization without removal, which is beneficial in pediatric applications where retained implants may disrupt skeletal growth. Additionally, degradation products support bone healing.

ZX00, a magnesium-based alloy containing <0.5 wt% zinc (Zn) and <0.5 wt% calcium (Ca), is a promising pediatric fracture fixation option. Magnesium promotes osteogenesis and mineralization, supporting bone formation. Calcium enhances osteoblast adhesion and proliferation, facilitating bone-implant integration. Zinc improves corrosion resistance, controlling degradation and maintaining mechanical integrity during early healing. Implant degrades over time, removing the need for hardware removal surgery.

In transphyseal applications, uncontrolled degradation may cause growth disturbances similar to those observed with conventional materials. Therefore, precise control over degradation kinetics is crucial to ensuring biomechanical support during healing.

We studied eight three-month-old female juvenile sheep, implanting monocortical ZX00 screws in the right tibial epiphysis. The left tibia received a titanium (Ti) screw or remained untreated as a control (Marek R et al., unpublished data). Computed tomography and histopathological assessments were conducted, with euthanasia at 180 weeks post-surgery. Between weeks 3–52, ZX00 screws fractured at the physis, with fragments migrating away from the growth plate. Physis defect size decreased after week 12, and no limb length discrepancies were detected at skeletal maturity. From week 104, Ti-implanted limbs were significantly shorter than ZX00-treated and control limbs. At the same time, Ti legs also exhibited axis deviation. Histological analysis showed no adverse effects on organ architecture or immune infiltration. Similar results were observed in another group study (Suljevic O et al., unpublished). Bone histology confirmed new bone formation without foreign body response or screw encapsulation. These findings align with other studies from our research group in recent years.

Most pediatric implants in use are screws or K-wires. While screws are already available on the market with CE certification, a K-wire made from magnesium has been developed for the first time. Based on this innovation, a clinical trial in children is planned for distal radius fractures. This research aims to advance the development of resorbable implants, fostering healthier solutions in pediatric orthopedic trauma care.

POSTER SECTION

Intraoperative Evaluation of Right Ventricular Mechanics in a Pressure-Overload Swine Model.

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Objectives: Assessment of right ventricular (RV) mechanical performance during open chest surgery is typically based on invasive methods and subjective evaluations. This study developed a porcine model of acute progressive RV pressure overload to evaluate hemodynamic changes and validate the 3D-video kinematic assessment of the Videocardiograph (VCG).

Methods: Seven healthy Landrace pigs were instrumented under fluoroscopic guidance with Swan-Ganz and RV conductance catheters. Following a median sternotomy, pulmonary artery banding (PB) was performed in two stages to induce minimal (PBmin) and maximal (PBmax) pressure overload. In a proof-of-concept experiment, different PB steps were performed to record both videos for the VCG and invasive pressure-volume assessments (PV-loop). Additionally, these videos were subjectively evaluated by five consultant surgeons, similar to clinical routine.

Results: PBmax significantly increased Pes from baseline (21.17±3.31mmHg vs 39.85±7.82mmHg, p=0.001) and led to RV dilation, reduced ejection fraction (52.80±10.36% vs 33.99±9.88%, p=0.012), and decreased myocardial efficiency. In the proof-of-concept experiment, visual evaluations were highly variable among the cardiac surgeons, resulting in only a moderate reliability of their assessments (ICC=0.59 for RV-function; ICC=0.60 for filling status). VCG-derived epicardial z-axis displacements, systolic timing, diastolic velocity and volume demonstrated excellent relationships with PV-loop data.

Conclusions: This study established a porcine model of progressive RV pressure overload with robust PV-loop assessment. VCG-derived epicardial kinematics reliably quantified RV mechanical activity and correlated with gold-standard hemodynamic measurements. This non-invasive, cost-effective method shows promise for early detection of acute RV dysfunction in the operating room and warrants further clinical investigation.

Paediatric Formulation Challenges for Enteral Feeding Tube Administration – Current Understanding and Future Directions.

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The complex interplay between drug formulation risk factors and inherent anatomical and physiological differences put paediatric population at higher risk for administration of medication via enteral feeding tubes (EFTS). Hence, understanding the critical attributes of dosage forms and the interplay between tube, administration, and formulation factors is crucial for developing and evaluating products intended for administration via EFTs in paediatric patients. By thoroughly examining these aspects, the industry can identify specific challenges and requirements, leading to more effective and tailored drug formulations that not only meet the unique needs of paediatric patients but also ensure optimal delivery and efficacy when administered through EFTs. Moreover, a comprehensive understanding of these factors can guide regulatory evaluations and quality assurance processes. However, current literature reveals significant gaps in knowledge regarding some of these factors. There are several neglected areas that require further exploration and deeper understanding. This systematic review provides current understanding of these factors and highlights the areas of more targeted research needed to address the gaps, optimize formulation strategies, and ensure that products are both effective and safe for paediatric use via EFTs.

Knowledge Translation in Pediatric Rehabilitation Technology: From Research to Practice.

Patrice L. (Tamar) Weiss[1,2], Naomi Gefem[2], Barbara Maser[3], Tal Krasovsky[1]

1 – University of Haifa; 2 – ALYN Hospital; 3 – McGill University

Knowledge Translation (KT) is the process of applying research evidence to clinical practice to improve healthcare accessibility, effectiveness, and accountability. In pediatric rehabilitation, KT is essential for integrating novel technologies that enhance function, participation, and quality of life for children with disabilities. Despite technological advancements, many rehabilitation innovations face barriers to clinical implementation. This presentation will explore KT using three successful examples: powered mobility, head support systems, and telerehabilitation. Technological solutions, from hardware to software-based interventions, hold promise for improving rehabilitation outcomes. However, traditional research methodologies (e.g., randomized clinical trials) may not be suitable for evaluating assistive technologies due to rapid innovation cycles and the need for personalized adaptation. As a result, many promising technologies struggle to reach widespread clinical adoption.

Examples of successful knowledge translation in pediatric rehabilitation include: (1) Powered Mobility for Young Children, (2) Head Support Systems for Improved Function and Comfort and (3) Telerehabilitation for Remote Therapy Access.

(1) Historically, powered wheelchairs were not funded for children under six, based on the belief that young children could not safely operate them. Occupational therapists used global research evidence to advocate for early powered mobility, demonstrating that even toddlers could learn safe wheelchair use. Through policy change and simulator-based training, powered mobility became more accessible, improving independence, participation, and self-confidence.

(2) Proper head support is essential for children with severe disabilities, aiding posture, breathing, swallowing, and communication. A startup company, Headovations, partnered with clinicians to develop an innovative headrest (Headaloft). Through clinical trials and user feedback, the design was refined for better adaptability and comfort. The success of this project illustrates how collaborative development and real-world testing drive adoption.

(3) Telerehabilitation, using videoconferencing for therapy, was rapidly adopted during COVID-19. It addressed geographic and accessibility barriers, particularly for children unable to attend in-person sessions. The success of telerehabilitation led to ongoing hybrid models, expanding healthcare access. Challenges included technology literacy, regulatory concerns, and therapist training, highlighting the need for structured implementation strategies.

In contrast, some technologies remain in the research phase due to cost, feasibility, or technological maturity: Brain-Computer Interfaces (BCI): Despite decades of research, BCI remains impractical for clinical use due to high costs, complexity, and inconsistent performance. Robotic Feeding Devices: While robotic arms have potential for independent feeding, they are expensive and lack funding support, leading to limited adoption.

Factors influencing the success of knowledge translation include early stakeholder involvement, user-centered design, funding availability, and real-world testing. Barriers to success include high costs, regulatory hurdles, lack of clinician training, and slow policy changes. Technologies that succeed in clinical adoption often follow a structured KT approach, integrating research, user feedback, and iterative design.

In summary, effective knowledge translation bridges the gap between research and clinical practice, ensuring that children with disabilities benefit from emerging technologies. Future efforts should enhance research-to-practice pathways, focus on early design partnerships, and optimize the timing of clinical adoption. By overcoming KT barriers, rehabilitation professionals can work with families to maximize participation and quality of life for children in need.

SensiVR: an Extended Reality (XR)-based Digital Therapeutic solution (DTx) for the hybrid care of children with fine motor function disorders, using Virtual Reality (VR) and hand tracking technology.

Katarzyna Koba[1]

1 – RoboKoba

Background: The problem of limited availability and accessibility for traditional hand therapy for children is significant at both European and global levels. The dyspraxia condition, which causes a child to perform less well than expected in daily activities for their age and appear to move clumsily, affects 5-6% of the paediatric population. To address this issue, there is an urgent need to shift from paternalistic and expensive hospital-based treatment to individualized, hybrid outpatient intervention in pediatric care understanding patients' requirements. SensiVR is a unique, innovative VR-based and AI-driven serious game in the form of a Sensory Virtual Room (SVR) that provides monitoring with a personalized and digital therapeutic (DTx) approach to patients in both clinical and community settings. SensiVR reduces health inequalities in children's fine motor function skills, focusing mainly on prevention of mental health and improvement of movement skills with neurodevelopmental disorders such as Developmental Coordination Disorder (DCD), also known as dyspraxia syndrome related to the Sensory Processing Disorders (SPDs).

Methodology: Patients with diagnosis of various motor impairments and healthy volunteers will be included in the study. The structure of the study involves validation of AI models and ML models allowing us to observe the physical effects of muscle tone on the other motor skills through real-time biofeedback data analytics, while hand immersive training aims to mimic natural gesture sequences. The intended application is to improve fine motor function skills using VR and hand tracking technology in a sensory feedback and gamified Virtual Environment (VE). We chose a comparison group in which 50% have a diagnosis of various motor impairments and 50% have no disorders.

Results: The results obtained will highlight how SensiVR could improve children's school performance, such as writing, reading or speech as well as social interaction and emotional balance. Additionally, planned clinical trials in different countries might be a crucial step in the more patient-oriented and effective diagnosis of neurodevelopmental disorders among children.

Conclusion: The project aims to show that SensiVR has enormous potential in paediatric somatosensory and neuromuscular rehabilitation approaches and underline the importance of as well as early intervention for a variety of neurodiverse disorders affecting children.

Quantitative motor developmental trajectory for preterm infants based on unobtrusive technology.

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Preterm birth leads to an increased risk of long-term consequences, with over 50% of children born <30 weeks facing motor, cognitive, and behavioural impairments [1]. Motor development is closely linked to neurodevelopmental outcomes, so early, longitudinal monitoring of motor development is key to timely identifying neurodevelopmental disorders [1]. Current identification of potential motor impairments is based on motor-milestones achievement and clinical examinations. The first have demonstrated poor specificity, the latter are long and expensive, require trained personnel, limiting assessments only to the high-risk children [2].

Recently, technology-based approaches have been proposed for the assessment of motor performance in preterm infants, toddlers and children, with the final aim of early identifying motor impairments through usable tests for a widespread application [3,4]. Typically, these solutions rely on 2D/3D video capture or wearable inertial sensors and resulted promising, highlighting quantitatively measurable differences between preterm and full-term peer motor performance [3-5]. However, these studies remain predominantly explorative and descriptive: the analysed quantitative variables are focused exclusively on motor aspects during specific tasks and at a specific age, lacking a longitudinal perspective and a unified clinical interpretable meaning, fundamental to understand how motor difficulties prime and evolve and for an effective use in the clinical context.

This work aims at monitoring and interpreting the motor developmental trajectory of preterm infants, by using a unified quantitative technology-based approach, with the final aim of understanding causal pathways and identifying early biomarkers of motor impairments.

Very preterm infants (< 32 weeks gestational age) have been recruited and evaluated from birth to 24 months corrected age. Times of assessment match the timing of clinical follow ups (term equivalent age, 3, 6, 12, 18, 24 months, T0, T3, T6, T12, T18, and T24); a convenient control group of full-term infants with no apparent risk of neurodevelopmental disorder was also included.

Participants were assessed on the following specific milestone motor functions:

- Newborn quantitative motor assessment: video-based recordings of spontaneous movements (T0 and T3).
- Infant (>4 months) quantitative motor assessment: sensor-based [5] assessment of motor performance (sitting posture, independent posture, independent gait) from T6 to T24, when present.

Chosen technologies guarantee usability and acceptance in clinical context. Kinematic data are extracted from videos at T0 and T3 using open pose estimation technology (DeepLabCut [6]) and directly from sensors from T6 to T24. Quantitative interpretable metrics of motor control performance were extracted from the kinematic data of each analyzed task (e.g., phase time durations and variability, multiscale entropy for motor complexity, recurrence quantification analysis for motor regularity, harmonic ratio for smoothness, Poincarè plots for short and long term variability [5]).

Preliminary results presented here are specific to the analysis of independent gait at T18 and T24 (n=51). Very preterm children exhibited less mature motor performance compared to peers born at term, characterized by lower stability (i.e., longer stance and double support phases) and higher variability, independently from the analysed age and walking experience. This variability did not indicate a structured exploration of more complex movements, as evidenced by lower smoothness and complexity in the frontal plane. The ongoing longitudinal data collection for both preterm and full-term participants will increase the sample size, the tasks analysed, and will provide a longitudinal analysis of preterm motor trajectory.

[1] A.J. Spittle, et al. 2016; [2] K. Cahill-Rowley, J. Rose, 2016; [3] C.C.T. Clark, et al 2021; [4] K. Raghuram, et al. 2021; [5] M.C. Bisi, M. et al. 2022; [6] A. Mathis, P. et al. 2018

“Advancing Clinical Research in the Paediatric Population”

SPEAKER SECTION

SPEAKER: CLAUDIA PANSIERI

Application of a new methodological approach to overcome paediatric clinical trial challenges: GAPP study

Bayesian adaptive trial design for children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic, nociplastic or mixed pain.

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Gabapentin, although widely used in pediatric patients (3 months to <18 years old) diagnosed with chronic neuropathic, nociplastic or mixed pain in children does not have an approved indication and the efficacy and safety have not yet been well characterized. During the Gabapentin in Paediatric Pain (GAPP) project, funded by the European Commission (GA no. 602962) in 2013, we tried to solve this gap, however, generating evidence based on randomized clinical trials in this population has been extremely challenging due to two main barriers encountered that significantly impacting recruitment potential: a) the required one week wash-out period that was considered not acceptable by many patients/parents, b) the choice of an opioid, as active comparator that still today cannot be considered as a recognised standard of care.

It is in this context that we are currently working to a new GAPP study design aiming to evaluate the efficacy, pharmacokinetics, and safety of gabapentin in paediatric patients with chronic neuropathic, nociplastic and mixed pain, in which, instead of a traditional superiority study we will apply an adaptive study design, and a bayesian methodology, fully in line with the new openings from the European Commission regulations**.** The Bayesian trial design utilizes Bayes theory to generate probabilities based on prior observed data.

This shift to adaptive design should overcome the cited barriers since offers some key benefits:

a) Avoiding the Selection of a Comparator since the adaptive design helps to sidestep this issue by allowing the study to focus on the drug's effectiveness without necessarily comparing it against

a fixed alternative. This flexibility means that decisions can be made during the study, such as modifying dosing, sample size or patient groups based on interim results.

b) Reducing the Sample Size: The Bayesian methodology allows for more flexibility in statistical modeling, which can lead to a reduced number of patients enrolled in the study. This is because Bayesian methods use prior information (like data from previous studies or expert opinion) combined with current study data to draw conclusions, which can achieve sufficient statistical power with fewer participants. The use of the Bayesian adaptive approach in this study design results in the need for a smaller overall number of patients. We computed, for fixed sample size including 32 patients in the naïve cohort, 36 patients in the non-naïve cohort and significance levels $\alpha=0.05$, the power of detecting a positive effect for gabapentin.

c) Reduction of patient burden and increase in ethical compliance: as baseline measurements between two or more treatment groups are not required, there is not the need for a wash-out period. In this way the design enhances ethical compliance, making the trial more patient-centric and reducing risks and discomfort during the trial.

d) Enhancement of patient safety and treatment efficacy: an adaptive design improves patient safety by minimizing unnecessary treatment exposure. Indeed, this approach enables real-time adjustments based on interim analysis of acquired data. It also allows for the early termination of ineffective or unsafe treatments, optimizes dosing, and increases the likelihood that young patients receive therapies with the greatest potential for effectiveness.

A team of dedicated professionals of a no profit research consortium along with six excellence clinical centers with highly skilled investigators across Europe, is currently actively participating in the discussion and is committed to carrying out the new research-driven GAPP study. The goal is to acquire the clinical evidence necessary for obtaining marketing authorization based on the GAPP Paediatric Investigation Plan fulfilment.

SPEAKER: MICHELA STARACE

Paronychia in Selumetinib-treated patients

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In recent years, the management of neurofibromatosis type 1 (NF1), especially for pediatric patients with inoperable plexiform neurofibromas, has been revolutionized using targeted therapies. Selumetinib, a MEK1/2 kinase inhibitor, has been shown to significantly reduce tumor volume, with a positive impact on patients' symptoms and quality of life. However, treatment is often associated with dermatological adverse events that may affect patients' adherence to therapy. Careful preventive and therapeutic management of side effects is key to ensuring the continuity of selumetinib therapy and maximizing its benefits in pediatric patients with NF1.

The most frequent skin reactions include xerosis, acneiform rash, paronychia, periungual pyogenic granulomas, and hair changes such as thinning and pigmentation changes. Xerosis is particularly common in younger children, while acneiform rash and paronychia tend to occur more frequently in adolescents. The latter, appears to show a similar incidence among female and male patients. Mucositis is also a common effect, with an impact on nutrition and the patient's overall well-being. A significant side effect is paronychia with subsequent possible development of periungual pyogenic granulomas, which may cause pain and functional limitations, impairing the patient's daily activities. Clobetasol propionate in occlusion associated with mupurocin, a combination of betamethasone/fusidic acid, and topical beta-blockers represent the main

therapeutic choices for this condition. In severe cases, surgery with chemical matricectomy may be necessary. If these therapies do not show efficacy, dose adjustment or discontinuation of selumetinib may be required.
We conducted a retrospective study, including 23 patients evaluated at our Centre, 8 of whom developed paronychia, arising after the introduction of selumetinib. The clinical and, if applicable, dermoscopic presentation, therapy set and outcome, and any other comorbidities or selumetinib toxicities developed in this cohort of patients were evaluated, as well as the time from the initiation of treatment to the first occurrence of symptoms. A secondary objective is to formulate treatment recommendations that may improve quality of life, during a psychologically and physically demanding course for children and adolescents and enable continuation of ongoing therapy.
To assess paronychia severity, we adopted the MASCC skin toxicity study group's classification, which considers the extent of nail fold involvement, associated symptoms, and required interventions to grade drug-induced paronychia. According to this classification, Grade 1 entails no significant impact on daily activities, including mild findings such as nail fold edema, erythema, or disruption of the cuticle. Grade 2 involves more pronounced inflammation (e.g., edema or erythema with pain), possibly accompanied by discharge or partial nail plate separation. Conversely, Grade 3 indicates severe infection with potential abscess formation or extensive tissue involvement, often necessitating surgical intervention or intravenous antibiotics.

SPEAKER: GIULIO MALTONI

Efficacy of automated Insulin Delivery Systems in children and adolescents with type 1 diabetes: data from a real-world observational study

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Background: Most subjects with Type 1 Diabetes (T1D) do not reach the glucometabolic control targets recommended by the main international societies, expressed as Glycosilate Hemoglobin (HbA1c) and Continuous Glucose Monitoring (CGM) metrics: HbA1c <7% (53 mmol/mol), Time spent In the Range 70-180 mg/dl (TIR) >70%, Time spent Below the Range of 70 mg/dl (TBR) <4% , Time spent Above Range (TAR) >180 mg/dl <25%, TAR >250 mg/dl < 5% and Coefficient of Variations (CV) less than 36%.

The advent of automated insulin delivery systems (AID), although not still fully closed loop systems requiring the intervention of the patient/caregiver for the administration of the prandial bolus, have allowed for improving metabolic control. This is a longitudinal observational study to evaluate the efficacy of AID systems on glycemic control in a population of children and adolescents with T1D in real world.

Patients and Methods: We evaluated HbA1c (the last value and the last 6-month mean value) and CGM metrics of 240 subjects (age 2-18) with T1D (disease duration at least 1 year, on the same treatment for more than 6 months). They were subdivided into 3 groups based on insulin delivery system: Group 1 was AID systems users, Group 2 Sensor Augmented Pump therapy (SAP) users and Group 3 MultiDaily Injections (MDI) + CGM.

Results: Group 1 was composed of 112 subjects (mean age 14,00 +/-2,7 yrs), group 2 27 subjects (mean age 15,1 +/-5,2 yrs) and group 3 101 subjects (mean age 13,7 +/-3,1 yrs). The results are summarized in the table (data expressed as Group: 1 AID; 2 SAP; 3 MDI+CGM, Mean value +/- Std. Deviation)

HbA1c last value % (mmol/mol)	group 1:	6.8*(49) +/-0.7
HbA1c last value % (mmol/mol)	group 2:	7.4 (57) +/-1.0
HbA1c last value % (mmol/mol)	group 3:	7.7 (61) +/-1.1
HbA1c 6 months % (mmol/mol)	group 1:	6.8* (49) +/-0.6
HbA1c 6 months % (mmol/mol)	group 2:	7.5 (58) +/-1.0
HbA1c 6 months % (mmol/mol)	group 3:	7.7 (61) +/-1.3
TIR (%)	group 1:	67.2* +/-12.2
TIR (%)	group 2:	46.3 +/-18.3
TIR (%)	group 3:	50.2 +/-18.8
CV (%)	group 1:	35.7* +/-5.3
CV (%)	group 2:	40.4 +/-11.0
CV (%)	group 3:	38.7 +/-6.1
TAR >180 (%)	group 1:	20.9* +/-6.1
TAR >180 (%)	group 2:	27.8 +/-10.6
TAR >180 (%)	group 3:	27.5 +/-13.1
TAR >250 (%)	group 1:	9.4* +/-8.0
TAR >250 (%)	group 2:	24.0 +/-17.3
TAR >250 (%)	group 3:	21.9 +/-18.3
TBR (%)	group 1:	1.7* +/-1.5
TBR (%)	group 2:	2.7 +/-3.7
TBR (%)	group 3:	3.1 +/-3.4

We found a significant reduction in the mean HbA1c in Group 1 compared to both Group 2 and 3 (p=0,01 and <0,001 respectively). NO difference between group 2 vs 3. As for CGM metrics: the differences between Group 1 vs Group 2 and 3 in TIR, TAR>180, TAR>250 and CV were significant (p<0,001). A significant difference in TBR between Group 1 vs 3, non-difference between Group 1 vs 2.

Discussion and Conclusions: According to the emerging literature, we observed an improved metabolic control with AID systems compared to other insulin treatment strategies with HbA1c mean values in according to the recommended target. Mean values of Time in Range (TIR) increased by 21% and 17% (5 and 4 more hours spent every day in the optimal glycemic range) compared to SAP and MDI treatment respectively, and mean values of Time Above the higher Range of 250 mg/dl (TAR>250) reduced by 15 and 12%, in the absence of significant increases in Time spent in hypoglycemia range (TBR). TAR>180 mg/dl, TBR and CV comply with the international recommendations. In conclusion, AID systems are statistically associated with improved glycemic control compared to other insulin treatment strategies in real life conditions.

SPEAKER: SIFAN HU

Accelerating Safer Administration of Medicines to Children in Low Resource Settings – Bridging Stakeholder Viewpoints.

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*On behalf of European Paediatric Formulation Initiative (EuPFI)

Background: Medication use in paediatric population is prone to dosing error as small dose volumes are required to be administered. Using safe and effective administration devices to prevent over-dosing and under-dosing is a key approach to secure paediatric medication safety. It is especially important to understand the pharmacotherapy needs of children living in resource-limited conditions and find solutions that accelerate the de-velopment and adoption of user-friendly administration devices. Hence, a workshop was held to understand the uptake of the already existing administration devices for oral and respiratory medicines in low- and middle-income countries, and to assess the level of awareness of issues associated with use of administration devices as well as the need of innovative devices.

Method: The workshop featured a panel where researchers shared findings on paediatric medicine administration devices, followed by presentations on clinical and industry challenges. Participants then discussed procedural and operational issues and proposed solutions.

Results: The panel highlighted country-dependent use of devices for paediatric oral and inhaled medicines. Indian HCPs prioritize access, availability, and affordability, while European developers adhere to strict regulations on accuracy, dose markings, and labelling. In India, innovation is limited by lower regulatory reliance, with a focus on simplifying administration. The top-rated solutions, supported by all stakeholders, are device innovation and regulatory harmonization.

Conclusions: Discussions and knowledge shared during this event showed the effectiveness of the workshop in fostering a deeper understanding of the issues regarding use and development of administration devices in low resource settings.

SPEAKER: ROSTYSLAV MARYSHKO

Research and care for children with orphan diseases: experience of Ukraine during the war

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Orphan diseases represent a significant medical and social challenge both globally and in Ukraine. These diseases are characterized by low prevalence and are generally of genetic origin, requiring a

specialized approach to diagnosis and treatment. According to the European Organization for Rare Diseases (EURORDIS), there are approximately 7,000 such diseases worldwide, collectively affecting around 300 million people, which accounts for about 5% of the global population.

In recent decades, there has been a noticeable increase in interest in orphan diseases from both the medical community and the pharmaceutical industry. This is due to several factors. The introduction of innovative genetic and molecular research methods has significantly improved diagnostics, enabling more accurate and timely identification of rare (orphan) diseases.

The adoption of the «Orphan Drug Act» in the United States in 1983 marked a significant breakthrough in scientific research on previously overlooked and underestimated rare diseases. This law has improved the quality of life for patients and stimulated further advancements. Similar legislative measures have also been introduced in the European Union to support the development of medicines for orphan patients. In recent years, leading pharmaceutical companies worldwide have developed a substantial number of treatments, with more than 600 such drugs currently registered.

Ministries of Health Care in many countries are developing national action plans for rare diseases, participating in international initiatives, and sharing experiences to enhance the effectiveness of orphan disease management. Specialized medical institutions or reference centers are being established, where patients can receive comprehensive, highly specialized medical care. Public and private foundations allocate significant funds for research and the development of new diagnostic and treatment methods for orphan diseases. Support for scientific research in this field encourages the development of innovative therapies.

Patient organizations and public initiatives play a crucial role in raising awareness about the challenges faced by individuals with rare diseases. Despite positive developments, many patients continue to encounter difficulties in obtaining timely diagnoses and accessing appropriate treatments. Therefore, ongoing efforts to enhance healthcare systems, support scientific research in diagnostics, and develop accessible therapeutic strategies for those with orphan diseases remain a pressing concern for the global medical community.

Since the onset of the full-scale armed aggression on Ukrainian territory after February 24, 2022, numerous violations of the fundamental rights of children with severe orphan diseases have been observed. These include rights to safety, life, timely medical assistance, health and personal development, personal and family life, inviolability of the home, and state care and protection.

During the full-scale invasion, nearly 70% of Ukrainian children were forced to leave their homes, relocating within the country or abroad. The war has separated children from parents who have joined the defense efforts or were unable to leave Ukraine with their children due to martial law. Children remaining in Ukraine are continually exposed to dangers from mass shelling by Russian forces, damage to energy systems, water supplies, heating infrastructure, destruction of schools and hospitals, and the use of explosive devices against civilians.

The military aggression and escalating threats to children's safety have resulted in many remaining in their permanent residences, residing in temporarily occupied territories, being displaced within Ukraine, evacuated abroad, or relocated to non-government-controlled areas.

One of the most pressing issues under martial law is maintaining and supporting the health of children with orphan diseases who require regular medical supervision. Not all children can receive adequate medical care in their current locations due to ongoing shelling and systematic destruction of critical infrastructure. Parents and children are compelled to seek appropriate medical treatment and rehabilitation abroad.

Ensuring the availability of high-cost pharmaceutical treatments for children with rare (orphan) diseases presents a significant challenge. Currently, it is impossible to obtain accurate information regarding the fulfillment of needs for medications and therapeutic nutrition for these children.

Amid ongoing military actions, Ukraine's healthcare system faces unprecedented challenges. Despite these difficulties, providing medical care to children with rare diseases remains a priority.

Efforts are being made to ensure the continuity of diagnosis, treatment, and rehabilitation even under extreme conditions, as emphasized by the Ministry of Health of Ukraine.

Coordinated efforts by government bodies, the medical community, and public organizations have led to the development of a legislative framework aimed at the prevention and treatment of rare (orphan) diseases. Key regulatory acts include:

1. Law of Ukraine "On Amendments to the Fundamentals of Ukrainian Health Legislation to Ensure the Prevention and Treatment of Rare (Orphan) Diseases" No. 1213-VII, 2014 in which it is stated that a rare (orphan) disease is one that threatens human life or is chronically progressive, leading to reduced life expectancy or disability, with a prevalence of no more than 1:2000 among the population. The state is responsible for organizing appropriate medical care for citizens with orphan diseases, ensuring uninterrupted and free provision of necessary medications and specialized dietary products. To achieve this, a state registry of citizens suffering from such diseases is established.
2. Resolution of the Cabinet of Ministers of Ukraine No. 160 dated March 31, 2015 that approves the procedure for providing citizens with rare diseases with medications and specialized dietary products, defines mechanisms and procedures for delivering necessary assistance to such patients, ensuring continuous and free supply of required treatments.
3. Order of the Ministry of Health of Ukraine No. 778 dated October 27, 2014 that approves the list of rare (orphan) diseases, facilitating standardized approaches to their diagnosis and treatment.
4. Law Adopted by the Parliament of Ukraine in 2021 (Draft Law No. 4662) that regulates state procurement of innovative medicines for treating rare diseases through managed entry agreements that accelerates the process of providing patients with modern and effective medications.

These legislative acts and initiatives have laid the foundation for an effective system of support and treatment for citizens suffering from rare diseases in Ukraine, even amidst ongoing military actions.

Work continues creating a national registry of citizens with rare diseases and integrating it into the electronic health system (eHealth), which will improve the tracking and provision of medical care for such patients.

Despite challenging circumstances, reference and expert centers are being established and maintained, utilizing innovative genetic and molecular diagnostic methods for early disease detection.

Ukraine is actively collaborating with international partners, NGOs, and pharmaceutical companies to ensure the supply of necessary medications and equipment, as well as to exchange experiences in managing patients with orphan diseases.

Given limited resources, standards and clinical guidelines are being reviewed and optimized to ensure maximum treatment and rehabilitation efficiency at minimal cost.

Public organizations play a significant role in organizing assistance for patients with orphan diseases in our country. They actively work to improve the quality of life for patients with rare diseases, providing them with necessary support and resources. These organizations hold conferences, seminars, and events aimed at raising awareness of the issues faced by orphan patients and the need to develop a national strategy for their support.

The Public Union "Orphan Diseases of Ukraine," founded in 2016 through the efforts of approximately 10 public organizations united by the goal of implementing assistance for patients with rare diseases in Ukraine.

In addition to this organization, other public associations in Ukraine support patients with orphan diseases:

1. Charitable Foundation "Orphaned Tits": provides assistance to patients with rare diseases by supplying medical equipment, medications, and specialized nutrition, as well as offering informational and psychological support.

2. Public Organization "Patients of Ukraine": focuses on protecting patients' rights, including those suffering from rare diseases, and promotes improved access to treatment.
3. All-Ukrainian Organization "Joy of Movement": brings together parents facing the challenging chronic childhood disease, juvenile rheumatoid arthritis.
4. All-Ukrainian Association of Disabled Persons with Gaucher Disease: specializes in supporting patients with Gaucher disease by providing information, legal assistance, and facilitating access to necessary treatment.
5. All-Ukrainian Association for Assistance to Patients with Cystic Fibrosis: supports patients with cystic fibrosis by ensuring access to essential medical services and medications.

Efforts to improve medical care for patients with rare (orphan) diseases in Ukraine have yielded positive results. In recent years, there have been notable advancements in the diagnosis and treatment of orphan diseases:

1. Expansion of Neonatal Screening: Since October 2022, Ukraine has implemented an expanded neonatal screening program, testing newborns for 21 hereditary diseases. This initiative enables early detection of rare pathologies and timely initiation of treatment. Regional neonatal screening centers operate in Kyiv, Lviv, Kryvyi Rih, and Kharkiv, facilitating early diagnosis and intervention for rare conditions.
2. Increased Funding: In 2023, the state budget of Ukraine allocated nearly 763 million hryvnias for the procurement of medications to treat orphan diseases, significantly surpassing previous years' figures.
3. Support of Humanitarian Programs: International pharmaceutical companies continue to provide humanitarian aid, supplying patients with essential medications until state funding commences.

The medical infrastructure of Ukraine, providing assistance to patients with orphan diseases, includes specialized centers and programs aimed at early diagnosis, effective treatment, and support for such patients, significantly improving their quality of life. However, the number of such centers remains insufficient, and many patients face difficulties in obtaining the necessary assistance.

In this context, the establishment of reference centers within specialized scientific and practical institutions plays a key role in ensuring quality medical care. These centers help address the shortage of specialized institutions, expanding patients' access to timely diagnosis and modern treatment methods.

As of today, there are 18 such centers operating in Ukraine; however, further expansion of the specialized care network is required to fully meet patient needs.

One such center, established in 2023 at the State Institution "All-Ukrainian Center for Maternity and Childhood of the National Academy of Medical Sciences of Ukraine," is the "Reference Center for Rare (Orphan) Diseases in the areas of systemic, rheumatologic diseases of childhood" (ORPHA 280342).

The Reference Center provides diagnostic and treatment services for children up to 18 years old with rare systemic rheumatologic diseases: juvenile rheumatoid arthritis, systemic lupus erythematosus, juvenile dermatomyositis, and systemic sclerosis.

The center utilizes the resources of a multidisciplinary children's clinic and is one of the few medical institutions addressing orphan rheumatic diseases in Ukraine. A highly specialized multidisciplinary medical team ensures the diagnosis and treatment of the most severe patients from various regions of Ukraine, as well as continuous monitoring of autoimmune process characteristics. The center houses an expert commission for conducting biological therapy for patients with rheumatologic diseases, maintains a patient registry corresponding to the center's profile, and sustains ongoing contacts with patient organizations.

Despite the positive changes achieved in recent years regarding orphan diseases, patients continue to face difficulties accessing timely diagnosis and necessary treatment. The ongoing war has led to a brain drain among medical professionals, complicating the organization of specialized centers.
In conclusion, Ukraine's experience during the war demonstrates the healthcare system's high adaptability and determination in providing assistance to children with rare diseases. Despite significant challenges, government structures, medical institutions, and the international community are working together to improve diagnosis, treatment, and rehabilitation for this vulnerable group of patients.
Efforts must continue to support scientific research, develop modern diagnostic methods, ensure timely detection of orphan diseases, and create and promote medications that will be accessible to patients.
Our experience underscores the importance of prompt response, coordinated actions, and the continuous improvement of medical care standards under extreme conditions. The creation of a national registry and the provision of stable funding for patients with rare diseases remain pressing issues.

POSTER SECTION

Venetoclax and Azacitidine in Pediatric High-risk Myeloproliferative Neoplasms: the AIEOP Experience.

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Background: Refractory and/or relapsed acute myeloid leukemia (AML r/r), advanced myelodysplastic syndromes (MDS-EB), and therapy-related myelodysplastic syndromes/acute myeloid leukemia (t-MDS/AML) represent a significant therapeutic challenge for pediatric hemato-oncologists, as these diseases are often resistant to conventional cytotoxic therapies and have a high relapse rate.
Affected patients have often undergone intensive pretreatment and experienced considerable toxicity, making it crucial to adopt less toxic therapies to minimize further adverse effects.
Aim: In this retrospective, multicenter study, 31 pediatric patients (median age of 10 years, range 2-20) with high-risk myeloid malignancies were treated with a combination of venetoclax and azacitidine (ven-aza) (median number of cycles: 2, range 1-7) at centers affiliated with the Italian Association of Pediatric Hematology and Oncology (AIEOP). The patients were diagnosed with AML r/r (n=18), MDS-EB (n=6), and t-MDS/AML (n=7).
Results: The results showed a complete remission (CR) rate of 48.4%, with an overall response rate (ORR), defined as the sum of CR and PR, of 71%. A total of 58.1% of patients successfully proceeded to hematopoietic stem cell transplantation (HSCT). With a median follow-up of 216 days (32 – 1004)

from the start of ven-aza, the one-year event-free survival (EFS) was 53.5% (95% CI: 35.8%-79.9%), significantly higher in patients who underwent HSCT (p < 0.0001). Ven-aza demonstrated excellent efficacy in the subgroup of patients with AML r/r harboring KMT2A rearrangement and in patients with MDS-EB with UBTF-TD.
Grade ≥3 adverse events included neutropenia (12 patients), febrile neutropenia (8 patients), fungal infections (2 patients), and hypertransaminasemia associated with diarrhea (1 patient). No treatment-related deaths were reported.
Conclusion: Our study demonstrates that ven-aza represents a safe and effective bridging strategy to HSCT in pediatric and young adult patients with high-risk myeloid malignancies.

Preliminary Results of Humoral Response Targeting Specific Epitopes of Human Endogenous Retroviruses in Kawasaki Disease and MIS-C.

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Human endogenous retroviruses (HERVs) are relics of ancestral germline infections by exogenous retroviruses, resulting in proviruses transmitted to offspring and integrated in the DNA. HERVs trigger the expression of inflammatory effectors, like cytokines and inflammatory effectors could, in turn, increase HERVs activation. Aberrant expression of two different families of HERVs (i.e. HERV-W and HERV-K) in blood of KD and MIS -C patients vs healthy controls has been demonstrated. The immune response against HERVs in MIS-C and KD have not previously been evaluated.
Objectives: To evaluate the prevalence and magnitude of the immune humoral response against HERV-W and HERV-K epitopes and interferon regulatory factor 5 (IRF5) in patients with KD and MIS-C. To determine associations of clinical features, presentation, laboratory values and coronary involvement (CALs) with humoral response to HERVs and IRF5.
Methods: Study period: October 2020 to June 2021. Population: contemporaneous KD, MIS-C and COVID-19 patients from 2 sites. KD defined by AHA guidelines and MIS-C by CDC criteria. Demographic, laboratory and echocardiograpic data were performed to all KD and MIS-C patients. The reactivity (IgG) against envelope epitopes of HERV-H, HERV-K, HERV-W and IRF5 was tested by indirect ELISA and mesured as Ab optical density (OD) in patients serum blood samples before treatment and compared to healthy controls (HCs). Correlations between clinical and lab data AND Ab against HERVs and IRF5 were investigated. The study was approved by IRB.
Results: 8 KD, 16 MIS-C and 7 COVID-19 (COV) patients and 41 age- and sex-matched healthy controls (HC) were enrolled. Ab anti Hervs W were significantly different in KD vs COVID (p=0.43) and KD vs HCs (p=0.012), Ab antiHervs H were different KD vs HCs (p=0.008), MIS-C vs HCs (p=0.009), Ab anti Hervs K were different in KD vs HCs (p=0.006) , KD vs HCs (p=0.006), MIS-C vs HCs (p=<0.001), COVID vs HCs (p=0.014), MIS-C vs HCs (p=<0.001) and COVID vs HCs (p=0.014); Ab anti IRF-5 were different among grousps as follows: KD vs COVID (p=0.039), KD vs HCs (p=0.014), MIS-C vs HCs (p=<0.001) and MIS-C vs COVID (p=0.012).
Conclusions: In KD and MIS-C the humoral response targeting specific epitopes of HERVs seems to partially contribute to immune response. We found higher humoral response against HERV-W in KD vs COVID and controls, while lower against HERV-K and IRF5 in controls vs KD and MIS-C. Ab against IRF5 are associated with % of lymphocytes, total days of fever and days before treatment. The elevation of IgG response to HERVs and IRF5 might suggest that exposition to these factors causes a secondary antigenic driven immune response in KD. Larger cohorts are needed to further

investigate the associations with inflammation to shed a light into the pathogenesis of KD, and to define whether they can represent biomarkers for diagnosis and prognosis.

Diagnosis of Iron Deficiency Anemia in Children Using Conjunctival Photography: A Color Intensity Analysis Approach.

Ozan Emre EYUPOGLU[1]

1 – Istanbul Medipol University

Objective: This study aims to diagnose iron deficiency anemia in prepubescent children by using photographs of their conjunctiva. This method targets diagnosing iron deficiency anemia without the need for blood samples or kits. Early diagnosis aims to prevent problems related to iron deficiency in children and support healthy growth and development processes.
Method: The study included 100 girls and 100 boys aged 3-10 years. High-resolution photographs of the conjunctiva were taken using a smartphone or digital camera. These photographs were transferred to the Image J program, and the intensities of the red (R), green (G), and blue (B) color components were analyzed. The obtained color intensity data were compared with ferritin values to create calibration graphs. From the created calibration graphs, when the mean value of the color intensity of the conjunctival photograph of any child whose anemia status is unknown was placed, the ferritin value and thus the anemia status were determined. Statistical significance between control and healthy groups was given using the Student's t-test. Children with multiple medication use and those with diseases other than iron deficiency anemia were not included in the study.
Results: This method provides a sustainable and inexpensive approach to diagnosing iron deficiency anemia. The color intensity analysis of conjunctival photographs yielded results consistent with hemogram data. The study was successful in diagnosing iron deficiency anemia with an accuracy rate of 82.37%. Thus, early diagnosis of iron deficiency anemia was made possible, and the healthy growth and development processes of children were supported.

Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia: Improving Biochemical Control and Treatment Outcomes.

Federico Baronio[1], Michele Zagariello[1], Rita Ortolano[1], Daniele Zama[1,2], Marcello Lanari[1,2], Egidio Candela[1,2]

1 – Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna; 2 – Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna;

Background: Standard glucocorticoid therapy for congenital adrenal hyperplasia (CAH) often fails to adequately control androgen excess, leading to overtreatment with glucocorticoids and numerous adverse events. In Europe, two innovative modified-release hydrocortisone (MRHC) formulations are available: modified-release hydrocortisone tablets and capsules.
Modified-release tablets consist of an immediate-release outer layer and a prolonged-release core, allowing for once-daily dosing. However, this formulation does not replicate the physiological nocturnal cortisol rise, as cortisol levels increase only after the morning dose.
Modified-release capsules (MRHC, Efmody©, formerly Chronocort) provide delayed release and prolonged absorption, mimicking the natural circadian cortisol rhythm. MRHC is taken twice daily—two hours after dinner and one hour before breakfast—resulting in improved morning control of adrenal androgen markers in CAH patients and better disease management. Approved by AIFA (Determination 110/2021) for CAH patients ≥12 years, MRHC lacks clinical data in adolescents aged 12–18.

Objectives: We investigated whether modified-release hydrocortisone (MRHC), which mimics the circadian rhythm of cortisol, could improve disease control and evaluate its effectiveness, safety, and potential adverse effects

Methods: We conducted a 12-month prospective observational study on 18 CAH patients aged ≥12 who switched from conventional therapy to MRHC. Primary outcomes included reducing 17-hydroxyprogesterone (17OHP) levels below 1200 ng/dL, normalizing delta-4-androstenedione levels, reducing total hydrocortisone dose, and comparing adverse events and adrenal crises before and after the therapeutic switch. Secondary outcomes included ACTH, renin, testosterone levels, and metabolic profile parameters (BMI SDS, growth velocity SDS, and blood pressure).

Results: MRHC resulted in improved biochemical control, with a statistically significant morning 17OHP reduction observed after 3 months of MRHC therapy compared to conventional treatment ($p = 0.013$). However, at 6 months, the decrease was not statistically significant ($p = 0.116$). The percentage of patients with controlled 09:00h serum 17OHP (<1200 ng/dL) was 62.5% at 3 months and 45% at 6 months, compared to only 6% with standard therapy. The mean daily hydrocortisone dose was 15.4 mg/day at baseline and 15 mg/day at 6 months. No severe adverse events or adrenal crises were reported during MRHC therapy. Moreover, no laboratory, genetic, or clinical markers have been identified to predict which patients would benefit more from MRHC over standard treatment.

Conclusion: MRHC improved biochemical disease control in most patients, with a slight reduction in steroid dose over time and no severe adverse events or adrenal crises.

“Digital Health Technologies in Paediatric Research in the Framework of Strategic Collaboration ELIXIR–EPTRI”

SPEAKER SECTION

SPEAKER: CLAUDIO CARTA

Health Data Management and FAIRification in ELIXIR: the experience of the Italian Rare Diseases Community

Claudio Carta[1,2]

1 - Istituto Superiore di Sanità, Rome, Italy; 2 - ELIXIR-Italy Local Technical Coordinator and co-lead community Rare Diseases

In the European Union, a disease is classified as rare if it affects fewer than 5 in 10.000 people, but there are more than 7.000 Rare Diseases (RDs). As a result, it is estimated that 6-8% of the world's population is affected by a RD. Due to this scenario, the diagnosis and treatment of RDs are challenging and costly and the patients' journey to reach a diagnosis is an “odyssey”.

Data on RDs, among other things, are sensitive, scarce, highly distributed across institutes and countries, gathered in different formats and, in general, with low interoperability.

We should therefore need an infrastructure to efficiently analyse data across resources and countries for more than 7.000 diseases.

There is an absolute need to combine data.

Considering also that the Vision of the International Rare DIseases Research Consortium (IRDiRC) is to “Enable all people living with a RD to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention.”

In 2016, the "FAIR guiding principles for humans and machines", were published.

The FAIR guiding principles are an IRDiRC-recognised resource and FAIR data allows us to link data from several resources in compliance with the access restrictions of the data itself.

One of the EU strategic objectives for RDs is to “enhance making rare diseases registries and data FAIR”.

As reported in the ELIXIR EU Scientific programme and priorities 2024-2028, ELIXIR EU as well as ELIXIR IT and the European and Italian RD Community of ELIXIR support Health Data Management and FAIRification of data.

Looking at the Italian RD Community, it supports FAIR priniciples and thier implementations organizing for example Bring Your Own Data hackathon and Workshops on specific topics related to Health data and FAIRification.

For example, the Rome BYOD at ISS has evolved over the years thanks to the fruitful collaboration between international experts, among whom there were, as speakers/trainers, the authors of the paper on FAIR Data guiding principles.

The Rome BYODs have been supported over the years by ELIXIR nodes, European projects and institutions and have contributed significantly to defining general steps to make a data resource FAIR.

Activities in Health Data Management and data FAIRification in the RD field were also supported by internal projects of ELIXIR: ELIXIR Commissioned Service.

In these projects funded through ELIXIR's own budget, partners of the Italian Node of ELIXIR have led or Co-Led WPs. The results of these activities and projects were presented at international conferences.

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SPEAKER: MARCO VICECONTI

Digital twins in paediatric healthcare: some examples

Marco Viceconti[1]

1 – Università di Bologna

A Digital Twin in Healthcare (DTH) is a computer model that, when fed with a specific set of information relative to a particular patient, can predict a quantity of interest that is difficult or impossible to measure but necessary to inform a clinical decision on that patient. We present two clinical applications of digital twin technologies in paediatric musculoskeletal pathologies. The first makes it possible to minimise the risk of bone fracture during rehabilitation after massive skeletal reconstruction in children due to osteosarcomas. The second uses post-mortem CT scans to create a reference database to identify abuse bone fractures in infants.

Bone tumours are prevalent in children and adolescents. They all require the surgical resection of the tumour and a large segment of a skeleton with it; being growing subjects, the skeletal gap cannot be bridged with a prosthetic device. Surgeons at the Rizzoli Orthopaedic Institute developed a biological reconstruction technique where the massive defect is bridged with a massive bone bank graft within which an autologous vascularised transplant of the proximal fibula is inserted. Plates and screws are used to ensure primary stability. The bone graft is rapidly osseo-integrated with bone stumps; the vascularised fibula eventually re-populate the dead bone with living cells, causing a complete osteointegration of the graft. After long post-operative chemotherapy, these children need to undergo aggressive physical rehabilitation; however, it is important not to overload the reconstructed bone to avoid fractures. We developed a digital twin informed by a lower body CT scan and a short gait analysis that predicts the forces transmitted to the reconstructed bone during the rehabilitation exercises. We then used the CT scan to develop a patient-specific digital twin of the reconstructed bone segment and of the contralateral health one to predict if those loads would have been sufficient to cause bone fracture (Taddei, 2003).

In a second instance, we report how a collection of post-mortem whole-body CT scans of infants was used in combination with our bone biomechanics digital twin to create a normative table for the

loading in bending and torsion required to fracture an infant long bone as a function of age or body weight (Altai, 2018). This normative information is used to decide if an infant bone fracture is consistent with the incident narrative provided by the carers or if it might be caused by abuse. In particular, with these normative data, we were able to show that self-inflicted arm fractures during rolling movements in infants were physically impossible (Altai, 2020).

Digital Twins in healthcare are a powerful medical technology in some clinical contexts. Musculoskeletal and cardiovascular diseases are an ideal target because much of pathophysiology can be explained with the laws of physics. DTHs are particularly relevant in paediatric medicine due to the extreme intersubject variability and the limitations on the type of examinations that can be ethically performed.

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SPEAKER: RITA STAGNI

A technology-based solution for monitoring the neuro-motor developmental trajectory in high-risk infants and children from birth to adulthood.

Rita Stagni[1], Maria Cristina Bisi[1], Arianna Aceti[2], Duccio Maria Cordelli[2]

1 – DEI, University of Bologna; 2 – DIMEC, University of Bologna

Neurodevelopmental disorders (NDDs) encompass a group of heterogeneous clinical conditions with onset in early life, associated with abnormalities of development. In western countries, more than 1 in 10 children are thought to be affected by NDDs of different severity (Halfon et al. 2012). NDDs have multifactorial etiology, involving both genetic and environmental factors (De Felice et al, 2015), and affecting multiple domains of development (Cioni et al, 2016).

Despite the advances in understanding the etiology, pathogenetic pathways, and biological underpinnings of NDDs, diagnosis often occurs many months after the first clinical signs are observed, thus delaying prompt intervention (Novak et al, 2017). Early detection of NDDs is one of the major challenges, with the highest odds of producing ground-breaking changes in child healthcare (Novak et al, 2017), since the response to intervention is more significant the earlier the therapy is initiated (Johnston et al, 2009; Heckman, 2008).

In the first months of life, a careful neurodevelopmental assessment combined with specific technical tools such as neuroimaging, neurophysiological tests, and genetic tests, provide important information to support the early detection of atypical development. Unfortunately, this level of clinical accuracy is only possible in a minority of the cases, namely in the presence of significant risk factors that identify infants at very high risk of NDDs (e.g. preterm birth, birth asphyxia, syndromes, neonatal seizures). Clinical screening tools generally show very low predictive value and reliability, particularly in the phase of emergence and establishment of the first clinical signs (Lee et al, 2015). Advances in technology have been shown to significantly improve medical care of patients, however,

there is a lack of integration of available technology into the assessment of infant development from birth to adult age.

Based on these premises, we have developed an unobtrusive technological approach for the quantitative assessment and longitudinal monitoring of biomarkers of neuro-motor-development in children from birth to adulthood. The proposed approach is designed to support and integrate the traditional assessment of milestones of motor development (i.e. general movements, sitting, horizontal displacement, standing, walking, handling), as well as to provide a deeper insight in the underlying control.

The acquisition protocol was designed to be easy to implement, child friendly, and require little time, to guarantee applicability and acceptance, while guaranteeing the reliability of the extracted biomarkers. In particular, videos from a commercial camera for general movements and motion data from wearable inertial sensors for other tasks are recorded by clinicians or carers during routine ambulatory assessment at programmed time-points. Quantitative metrics are extracted from video and kinematic signal processing as biomarkers of biomechanical performance, variability, fluidity, and coordination of motion, as well as complexity and automaticity of motor control (Bisi et al, 2019; Bisi et al, 2020), providing a characterization of the neuro-motor development that integrates clinical assessment.

The longitudinal implementation of the full approach allows to track the developmental trajectory from birth to adult age, but modular implementation of the full protocol is possible to target a specific population and/or research question.

The proposed assessment in currently applied to children:

- born preterm from birth to 36 months (video- and sensor-based assessment);

- affected by severe neurologic/rare disorders from 5 to 18 years (only normal gait in Mowat-Wilson, Dravet, and Chiari syndrome);

- affected by minor musculoskeletal deformities from 5 to 16 from 5 to 18 years (normal and tandem gait in scoliosis, flat foot, club foot);

- during pre-school and school age from 4 to 18 years (posture, normal and tandem gait, object handling).

SPEAKER: LUCA SANGIORGI

Wearable Sensors for Monitoring Osteogenesis Imperfecta in Children: A Pilot Study.

Marina Mordenti[1], Alice Moroni[1], Manila Boarini[1], Giulia Rogati[1], Roberto Ramaglia Amadasi[1], Francesca Gurioli[1], Marta Calzolari[1], Alberto Leardini[1], Luca Sangiorgi[1]

1 – IRCCS Istituto Ortopedico Rizzoli

Osteogenesis imperfecta (OI) is a rare bone disorder causing fractures, deformities and short stature due to bone fragility. OI typically progresses during childhood, with partial stabilization in adulthood, and has significant clinical and genetic variability.

Long-term OI management requires a multidisciplinary approach, including rehabilitation. Technological advancements are improving patient care, with Inertial Measurement Units (IMUs) becoming increasingly used as wearable sensors. Despite some limitations, IMUs offer a cost-

effective alternative to lab-based gait analysis and support rehabilitation and daily exercise, providing step-by-step, game-based guidance.

The present pilot study on OI children aims to investigate the impact of IMU technology on remote monitoring.

The study, supported by the project 4FRAILTY, funded by Italian Ministry of Education, University and Research - PON R&I grant ARS01_00345, CUP B76G18000220005 - was conducted at IRCCS Istituto Ortopedico Rizzoli, an OI reference center, and aimed to enroll OI "walking" children to undergo a kinematic analysis via an IMU-based motion tracking system.

Patients were equipped with 5 IMUs (Euleria srl, Rovereto, Italy) secured to specific anatomical segments using adjustable bands. They performed motor tasks representative of daily living activities (e.g. walking) and selective joint exercises (e.g. knee flexion/extension). The study also aimed to assess patients' health-related quality of life via EuroQoL-5-Dimensions Young version (EQ-5D-Y) and balance confidence in performing activities via the Activities-specific Balance Confidence Scale (ABC Scale). A patient satisfaction questionnaire was used to evaluate the IMU approach.

The study enrolled 10 children with OI type I according to Sillence classification (7M, 3F, mean age 11.8 years). Two of them performed a subset of motor tasks due to non-OI-related issues.

In a preliminary analysis on 4 patients, the seated knee extension exercise resulted in an average range of motion of 94.9 ± 10.8 deg, while the standing hip extension and abduction exercises yielded 29.8 ± 13.5 and 23.8 ± 7.5 deg, respectively.

The EQ-5D-Y showed that no participants reported problems with mobility, self-care, or usual activities. However, difficulties were reported in the pain/discomfort (40%) and anxiety/depression (80%) dimensions. The mean EQ VAS score was 87/100 (IQR 65–100), indicating a generally high self-rated health status, and confidence in performing daily activities without experiencing unsteadiness using the ABC scale was 83/100 (IQR 74–90), indicating a high level of self-perceived balance and stability.

All participants reported good/high feasibility of the motor tasks and exercises in the satisfaction questionnaire. In addition, 80% said they would be willing to use the IMUs if they were available in local clinics and for domestic use.

This pilot study shows that IMU's game-based approach is an innovative tool to promote exercise in rare children. While OI children reported good overall health and functional independence, many experienced pain/discomfort and emotional distress. The high ABC scale scores indicate confidence in balance and stability during daily activities, despite physical and psychological challenges. These findings highlight the need for targeted interventions to address pain and mental well-being in this population.

IMUs are an easy-to-use, accessible alternative to gait analysis in fully equipped laboratories, encouraging local healthcare providers to adopt these systems for easier, more widespread monitoring. Only patients needing in-depth assessment will be referred to hub hospitals, optimizing resource allocation and care. Furthermore, remote digital communication lets clinicians advise and assess patient from a distance, reducing the need for patient journeys to centers of expertise, which can be complex and expensive.

SPEAKER: CHEMS HACHANI

Optimizing Pediatric Clinical Trials: Leveraging Milo AI for Efficient Recruitment and Data Management in Assessing Hypertonic Inhalation.

Chems HACHANI[1]

1 – Eclevar Medtech

Pediatric clinical trials require efficient recruitment and data management. This 4-week, prospective, open-label, randomized, multicentric, parallel-arm study evaluates the performance and safety of HYPERTONIC INHALATION (3%, 6%, 7% sodium chloride) in infants, children, and adults with cystic fibrosis (CF) or non-CF bronchiectasis (NCFB). Conducted by [Confidential Manufacturer] with Eclevar MedTech at UK sites, the trial utilizes the Milo AI platform to enhance participant selection and data handling. Milo captures clinical audio from patient visits, interprets it, and integrates summaries into its electronic data capture (EDC) system. This EHR-to-EDC process auto-populates case report forms, with human oversight ensuring precision. In a 360-patient cohort, Milo boosted recruitment efficiency and data integrity. This approach underscores AI's ability to optimize clinical trials, providing robust evidence of device performance and safety per EU MDR 2017/745 standards

POSTER SECTION

The Impact of Digital Technology on Cognitive and Emotional Development in Children: A Narrative Review.

Sergii Tukaiev[1], João Miguel Alves Ferreira[2]

1 – Institute of High Technologies, Taras Shevchenko National University of Kyiv; 2 – Faculty of Medicina, University of Coimbra, Coimbra, Portugal.

Background: The increasing integration of digital technology into children's daily lives has sparked discussions on its potential cognitive and emotional consequences.

Aim: This narrative review explores the impact of digital device usage on attention regulation, executive functions, and emotional wellbeing in paediatric populations.

Results: While some studies highlight cognitive benefits, such as improved problem-solving and digital literacy, others point to risks, including attention deficits and increased emotional dysregulation. Factors such as screen time duration, content quality, and parental mediation play crucial roles in shaping these effects. The review also examines the moderating influence of socioeconomic status and family environment on children's digital engagement and developmental outcomes. Findings suggest that a balanced approach—promoting digital literacy while setting healthy boundaries—is essential to harness the benefits of technology while mitigating its risks.

Conclusion: Understanding these dynamics can inform paediatric psychological interventions, educational policies, and parental guidance strategies, fostering healthier cognitive and emotional development in the digital age.

Bridging the Gap: A Digital Platform for Early Pediatric Mental Health Care.

Hila Segal[1,2], Arriel Benis[3], Shirley Saar[1,4], Iris Shachar-Lavie[1,5], Silvana Fennig[1,4]

1 – Schneider Children's Medical Center; 2 – Shalvata Mental Health Center; 3 – Holon Institute of Technology; 4 – Tel Aviv University; 5 – Israel Ruppin Academic Center

Background: The prevalence of mental health disorders among children and adolescents presents a significant public health challenge. Children exposed to mass disasters, such as armed conflicts or natural disasters, are at a particularly high risk of developing mental health problems, necessitating prompt and robust intervention. The acute need for early intervention in these situations is well recognized, as timely support can mitigate long-term negative outcomes. Pediatricians are particularly suited to delivering such interventions due to their role as primary health care providers and their frequent contact with children and families. However, barriers such as limited training and resources often hinder their ability to effectively address these issues.

Objective: This study aimed to describe the rapid development of a digital mental health tool for community pediatricians, created in response to the urgent need for accessible resources following the October 7th terror attack in Israel. The goal was to create a comprehensive resource that addresses a wide range of emotional and behavioral challenges in children and adolescents, with a particular focus on those affected by armed conflict and significant trauma exposure. In addition, the study aimed to evaluate the platform's usability and relevance through feedback from primary users, thereby assessing its potential for implementation in routine pediatric practice.

Methods: Developed through collaboration between pediatricians and mental health professionals at Schneider Children's Medical Center in Israel, the platform consists of 15 structured modules covering key pediatric mental health concerns such as sleep disturbances, anxiety, school refusal, eating behavior changes, and emotional dysregulation. Each module includes clinical guidance, initial intervention strategies, parental psychoeducation, and referral recommendations. The usability and relevance of the platform were evaluated through structured feedback from a focus group of seven primary care pediatricians.

Results: Early evaluations demonstrated high satisfaction among pediatricians in terms of usability (mean 4.57/5), content relevance (4.71/5), and layout suitability (4.66/5). Participants emphasized the importance of concise, actionable content tailored to time-constrained clinical environments. The findings highlight the platform's potential to enhance early mental health intervention, addressing a critical gap in pediatric primary care.

Future Directions: Recognizing the broader need for integrating mental health into routine pediatric care, we are currently in the process of enhancing accessibility and user engagement. Future iterations will focus on interactive features, real-time clinical consultations and updates, and multilingual support, ensuring widespread applicability throughout Israel. Additionally, further research will assess the impact of the platform on pediatric practice and clinical outcomes.

Conclusion: This initiative demonstrates the feasibility of a responsive and targeted digital mental health platform during periods of heightened need, emphasizing the essential role of pediatricians in delivering timely and proactive care, both in routine situations and during crises.

Diagnosis of Iron Deficiency Anemia in Children Using Conjunctival Photography: A Color Intensity Analysis Approach.

Ozan Emre EYUPOGLU[1]

1 – Istanbul Medipol University

Objective: This study aims to diagnose iron deficiency anemia in prepubescent children by using photographs of their conjunctiva. This method targets diagnosing iron deficiency anemia without the need for blood samples or kits. Early diagnosis aims to prevent problems related to iron deficiency in children and support healthy growth and development processes.

Method: The study included 100 girls and 100 boys aged 3-10 years. High-resolution photographs of the conjunctiva were taken using a smartphone or digital camera. These photographs were transferred to the Image J program, and the intensities of the red (R), green (G), and blue (B) color components were analyzed. The obtained color intensity data were compared with ferritin values to create calibration graphs. From the created calibration graphs, when the mean value of the color intensity of the conjunctival photograph of any child whose anemia status is unknown was placed, the ferritin value and thus the anemia status were determined. Statistical significance between control and healthy groups was given using the Student's t-test. Children with multiple medication use and those with diseases other than iron deficiency anemia were not included in the study.

Results: This method provides a sustainable and inexpensive approach to diagnosing iron deficiency anemia. The color intensity analysis of conjunctival photographs yielded results consistent with hemogram data. The study was successful in diagnosing iron deficiency anemia with an accuracy rate of 82.37%. Thus, early diagnosis of iron deficiency anemia was made possible, and the healthy growth and development processes of children were supported.

Feasibility and Preliminary Efficacy of Sailing-Based Rehabilitation for Adolescents with Rare Skeletal Disorders: A Single-Center Pilot Study.

Manila Boarini[1], Federico Banchelli[1], Davide Scognamiglio[1], Silvia Fittipaldi[1], Giuseppina M. Farella[1], Daniela Platano[1,2], Giulia Rogati[1], Enrica Di Sipio[3], Giacomo Villa[3], Lisa Berti[1,2], Alberto Leardini[1], Silvana Sartini[1], Annalisa Scopinaro[4], Luca Sangiorgi[1]

1 – IRCCS Istituto Ortopedico Rizzoli; 2 – Università di Bologna; 3 – Euleria srl Società Benefit; 4 – UNIAMO Federazione Italiana Malattie Rare

Background: Rare Skeletal Disorders (RSDs) are characterized by skeletal deformities, chronic pain, and disability, significantly impacting physical and psychological well-being. Individuals with RSDs often experience social isolation, reduced independence, and barriers to accessing coordinated healthcare. Conventional rehabilitation primarily targets motor function in controlled settings but may not fully address psychosocial well-being. Adventure-based interventions incorporating physical activity and group engagement may offer additional benefits. Sailing-based rehabilitation integrates motor training with dynamic environmental adaptation, teamwork, and psychological stimulation. This study assessed the feasibility, safety, and preliminary efficacy of a sailing-based rehabilitation intervention in adolescents with RSDs, integrating objective motion analysis and patient-reported outcomes.

Methods: This single-center, non-randomized, single-arm feasibility study included eight participants aged 12–18 years with RSDs who completed the intervention on two adapted sloops under certified instructors' supervision. Feasibility was assessed through recruitment, retention,

adherence, and satisfaction. Safety was evaluated by recording adverse events. Secondary outcomes included health-related quality of life (HRQoL), psychological well-being (assessed via EQ-5D-5L, PODCI, RSES, YP-CORE, and TSK), and physical function measured using inertial measurement unit (IMU)-based motion analysis. Data were analyzed descriptively, and changes over time were evaluated using the Wilcoxon signed-rank test.

Findings: The intervention demonstrated 100% retention, compliance, and adherence, with only mild adverse effects reported. Post-intervention assessments revealed improvements in HRQoL (VAS, p=0.10), happiness (p=0.06), proprioception (p=0.01), postural stability (p=0.01), gait quality (p=0.04), and upper limb function (p=0.02), though some benefits diminished at three-month follow-up. The structured and immersive nature of sailing, requiring real-time adaptation to wave-induced motion and team-based coordination, contributed to these positive outcomes. The integration of IMU-based motion analysis provided objective quantification of physical improvements, while validated patient-reported outcomes captured psychosocial changes. IMUs enabled precise, remote monitoring of participants' motion performance by tracking kinematic parameters such as joint angles, balance, and movement symmetry in real time. This approach allowed for a comprehensive assessment of physical function outside conventional clinical settings, offering insights into neuromuscular adaptation and motor learning.

Conclusion: This study is the first to systematically explore the feasibility and safety of a sailing-based rehabilitation intervention for adolescents with RSDs. Findings suggest that this intervention is feasible, safe, and potentially effective in promoting both physical and psychological benefits. The structured yet adaptable format of sailing may offer a replicable model for integration into diverse therapeutic settings. By demonstrating that a structured sailing intervention can enhance quality of life, motor function, and psychological well-being in adolescents with RSDs, this study supports the inclusion of holistic, experiential therapies in rehabilitation practice. The use of IMU-based motion analysis underscores the feasibility of remote monitoring, allowing clinicians to track physical improvements objectively and tailor interventions accordingly. Future research should explore scalability, long-term efficacy, and integration into healthcare policies. Further studies, including larger controlled trials with extended follow-up, are needed to confirm these preliminary findings and optimize intervention protocols for broader clinical application.

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Artificial Intelligence in Pediatric Health: Linking Toxicology and Disease Research via Web Platforms.

Nicola Gambarcota[1], Fulvio Ciriaco[2], Nicola Amoroso[3], Daniela Trisiciuzzi[3], Maria Vittoria Togo[3], Fabrizio Mastrolorito[3], Antonella Liantonio[3], Paola Imbrici[3], Giuseppe d'Orsi[4], Massimo Carella[5], Orazio Nicolotti[3], Cosimo D. Altomare[3]

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In the quest for innovative tools to advance drug discovery, repurposing in pediatrics, and toxicological endpoint prediction, we have developed three publicly accessible web platforms: PLATO, TISBE, and CIRCE. PLATO (Polypharmacology pLATform for predictiOn) is a ligand-based predictive platform designed for target identification and bioactivity assessment. It serves a dual purpose: narrowing down potential protein drug targets and computationally estimating biological

affinity values. PLATO is particularly effective in reverse screening for drug repurposing, identifying promising candidates for pediatric disease treatment. TISBE (TIRESIA Improved on Structure-Based Explainability) is a cutting-edge tool for predicting developmental toxicity—an essential factor in ensuring maternal and child health. It is highly effective in assessing chemical safety for pediatric populations while ensuring transparent and interpretable predictions through an explainable machine learning approach. CIRCE (Cannabinoid Iterative Revaluation for Classification and Explainability) is a multi-layer machine learning framework designed to predict selective and unselective CB1/CB2 binders. By computing Shapley values, CIRCE identifies the key molecular features influencing predictions and enhances model interpretability. Given the putative critical role of the cannabinoid system in pediatric conditions such as refractory epilepsy or tuberous sclerosis complex, CIRCE facilitates the design of CB1/CB2 binders and aids in repurposing existing drugs for pediatric treatments. Collectively, these platforms represent a significant step forward in pediatric drug research and repurposing, offering powerful computational tools for discovering and validating therapeutic options while ensuring safety and efficacy through explainable AI methodologies. The platforms are accessible at the following links:

PLATO is free available at https://prometheus.farmacia.uniba.it/plato/
TISBE is free available at https://prometheus.farmacia.uniba.it/tisbe/
CIRCE is free available at https://prometheus.farmacia.uniba.it/circe/

“Kick-off Meeting of the OrphaDev4Kids Patient Expert Committee (PEC)”

SPEAKER SECTION

SPEAKER: ALEKSANDER WISNIEWSKI

Building the POLPEDNET KIDS: Enhancing Clinical Studies through Young Patient Involvement in Poland.

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The POLPEDNET KIDS advisory group, launched in Poland, gathers insights from a unique blend of participants including healthy children, patients, and those currently or previously involved in clinical trials. This initiative aims to make clinical research more inclusive and reflective of the diverse needs of patients. Since its launch in May 2024, the group has grown to include 30 members aged 8-17, who meet monthly to delve into discussions on clinical trials, drug development, and the design of innovative medical technologies.

An author-created questionnaire has been developed to evaluate the interest potential of a group across various areas of medicine. This tool is designed to assess and understand the specific medical fields that members of the group are most engaged with and curious about. The initial novel questionnaire provided critical insights into the members' knowledge and preferences. Around 68% of the group members were aware of clinical trials, and 16% had a personal connection to someone who had participated in one. These figures highlight a substantial base level of engagement with clinical research among the participants.

When queried about their interests in specific medical fields, 60% of the young people expressed a fascination with genetics, reflecting a strong inclination towards understanding the building blocks of life and its applications in medicine. Artificial intelligence in medicine also attracted the interest of 20% of the members, indicating a growing curiosity about the integration of technology and healthcare.

The forward-thinking nature of the group was further demonstrated in their responses to potential future technologies. A significant 66% believed in the possibilities of deploying medical nanorobots and using holograms in treatment, showcasing their openness to revolutionary healthcare solutions. Moreover, when asked about hypothetical technologies that could cure currently incurable diseases, 56% hoped for the development of instant cure drugs, 28% envisioned organ-producing machines, and 12% were intrigued by the idea of body-repairing robots.

These preferences underscore the group’s visionary outlook and readiness to engage with complex, future-oriented medical technologies. The coordinator of POLPEDNET KIDS actively promotes these insights among pharmaceutical companies, emphasising the importance of integrating young people’s perspectives into the development of modern therapies. This advocacy ensures that the voices of young patients are heard in the realms of medical research and device innovation, potentially shaping the direction of future healthcare advancements.

The POLPEDNET KIDS initiative stands as a pioneering example of how inclusive children’s and young adults involvement can significantly enrich the medical research landscape. By bridging

youthful creativity with scientific inquiry, the group not only empowers its participants but also sets the stage for transformative advances in healthcare. As this initiative continues to evolve, it promises to have a significant impact on the development of patient-centred medical research and healthcare solutions, ensuring that the future of medicine is as diverse as the population it serves.

POSTER SECTION

Dexmedetomidine as a Promising Neuroprotective Sedoanalgesic in Neonatal Therapeutic Hypothermia: A Systematic Review and Meta-Analysis.

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Background: Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and neurodevelopmental disabilities. Therapeutic hypothermia (TH) is the standard of care, but optimized sedoanalgesic strategies remain critical. Dexmedetomidine shows promise as an alternative to traditional sedatives, but its role in this context remains systematically underexplored.

Objective: This meta-analysis evaluates the safety and efficacy of dexmedetomidine in neonates undergoing TH for HIE.

Methods: A systematic search of Medline, Scopus, EMBASE, WOS, ClinicalTrials, and Cochrane Library identified studies published from January 2014 to October 2024. Studies focusing on dexmedetomidine in neonatal TH with relevant outcomes were included. Selection followed PRISMA guidelines, with independent quality assessments. The protocol was registered in PROSPERO (CRD42024605817). Results are presented as meta-analyses or evidence-based discussions when pooling was unfeasible.

Results: Seven studies involving 609 neonates were included: four cohort studies (n = 486) and three case series (n = 123). Dexmedetomidine provided comparable sedation to traditional agents (MD = -0.01 [-0.68 - 0.66], p = 0.99) and significantly reduced seizure risk (OR 0.31 [0.10 - 0.98], $p < 0.05$) with a non-inferior safety profile. Trends suggested shorter duration of mechanical ventilation and time to full enteral feeding. Substantial heterogeneity in dosing protocols highlights the need for standardization.

Conclusions: Dexmedetomidine appears to be a safe and promising sedative in neonatal TH for HIE, with potential neuroprotective, respiratory, and gastrointestinal benefits. Despite limited evidence and the absence of randomized clinical trials, its non-inferior efficacy and safety warrant further exploration and urges the development of standardized dosing protocols.

Psychological Wellbeing and Adherence to Paediatric Treatments: A Biopsychosocial Perspective.

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Background: Paediatric treatment adherence remains a critical challenge in healthcare, influenced not only by medical factors but also by psychological and social determinants.

Aim: This study explores the role of psychological wellbeing in promoting adherence to treatments among children with chronic conditions, using a biopsychosocial framework. Psychological

resilience, emotional regulation, and caregiver-child dynamics significantly impact a child's ability to follow medical recommendations. Through a literature review and case analyses, this study highlights the necessity of integrating psychological interventions into paediatric care. Strategies such as psychoeducation, cognitive-behavioural approaches, and structured social support can enhance treatment compliance and overall health outcomes. Additionally, the importance of interdisciplinary collaboration between paediatricians, psychologists, and social workers is emphasized to ensure holistic and patient-centred care.

Conclusion: Understanding the psychological dimensions of adherence can inform more effective healthcare strategies, ultimately improving quality of life for paediatric patients and their families.

Accessing the intrathecal space in a porcine paediatric model: description of the techniques, cerebrospinal fluid profiling and gene therapy applications.

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The piglet has emerged as one of the most complete and accurate models for neonatal and paediatric translational medicine due to genetical, anatomical and physiological similarities with humans. The porcine brain resembles humans in terms of weight, volume, cortical surface area, myelination, composition and electrical activity, and its development extends from prenatal to early postnatal life. Moreover, due to their longer lifespan, pigs are a great model to study inherited/genetic conditions. All of the above have contributed to the interest toward piglets for gene therapy for neurological disorders. In such scenario, it became pivotal to validate reproducible techniques to access the intrathecal space allowing for cerebrospinal (CFS) sampling and local drug administration. This abstract describes two techniques developed for Cisterna magna (CM) puncture and lumbar spinal catheter placements, as well as some applications.

The CM study, divided into a cadaver phase and an in vivo one, was conducted on 2-30 days-old piglets: after hand palpation of the occipital protuberance, a line identifying the median spinal plane was marked; a second one was then traced between the cranial margins of the atlas wings. A 22G×75mm spinal needle was introduced along the median line to a depth of 4mm, 5mm posteriorly to the intersection of the two lines; the tip of the needle was directed cranioventrally using the cranial margin of the wings as an external landmark. The technique allowed the safe CSF collection in all animals [1].

The second study, once again divided into a cadaver and an in vivo phase, identified the L2-L3 intervertebral space as the best one for percutaneous insertion of spinal catheter, reaching the CM, in 30 days-old piglets. Again, the newly developed technique allowed for safe placement of the device in all subject. The proposed technique requires less skilled operators when compared to the other existing method, which involves surgical approach, and potentially leads to fewer complications [2].

The above-mentioned methodologies were then used in a trial aimed at creating a comprehensive map of Central Nervous System (CNS) transduction by eight recombinant adeno-associated virus (rAAV) serotypes upon cerebrospinal fluid administration in neonatal piglets. rAAV9 showed the

highest transduction efficiency and the widest distribution capability, robustly transducing both glia and neurons, including the motor neurons of the spinal cord [3]. Alongside, pre-injection CSF samples from 5, 30 and 50 days-old subjects were used for a metabolomic quantitative profiling of their composition, that highlighted several differences between ages, potentially related to the tightening of the blood-brain barrier [4].

According to the author's experience, focussing on the set up and standardization of the methodologies to be used to deliver drugs intrathecally and to collect uncontaminated CSF samples, is a mandatory preliminary step allowing for smoother, more refined trials, in full compliance with the 3Rs principle. Moreover, the in-depth quantification of the CSF composition represents a critical tool to better understand the physiology of such an important lab animal, especially prior to establishing and phenotyping disease models.

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