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European Paediatric Translational Research Infrastructure

Paediatric Medicines Discovery Platform

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Paediatric Medicines Discovery Platform

Aim:

Offer access to academic drug discovery facilities specialized to paediatric diseases,
Provide integrated services, coordinating efforts among European Centres of Excellence,
Implement cutting edge technologies, to accelerate discovery and preclinical drug development in paediatrics

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Scientific context analysis

- The same principles outlined for drug discovery in adults are applied to paediatric drug discovery, yet with several **key differences**.
- A range of **unique characteristics** demonstrated by this specific group offer a framework for identifying gaps in discovery efforts pursuing paediatric drug development and providing a **dedicated** and **original** research platform in the EU.

Scientific context analysis

- Several highly abundant paediatric diseases are **exceedingly multifactorial**.
- Most existing disease **models are inadequate** to capture the unique **developmental status** of paediatric patients.
- **Personalized medication** approaches in **paediatrics** are not widely exploited at present.
- Several paediatric diseases are categorized as **rare diseases**.

Paediatric drug discovery demonstrates **serious gaps** as compared to respective efforts focusing at adult pathologies and represents an exceedingly challenging domain with **great potential** for **innovation** and **contribution to public health**.

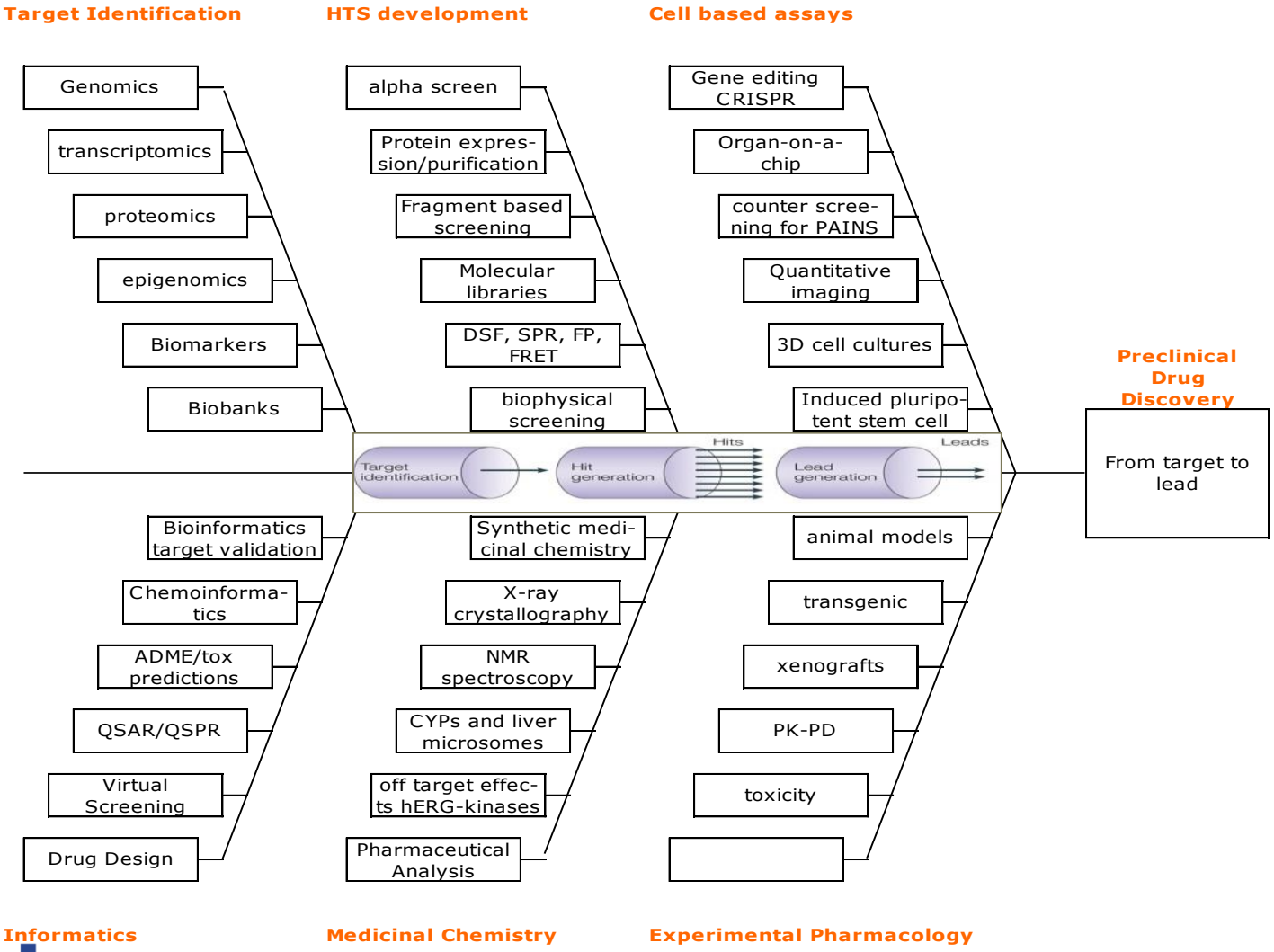
Scientific aims of the Platform

- By combining **basic and applied research** over a multitude of **interdisciplinary fields** spanning from bioinformatics and developmental biology to advanced animal models, EPTRI will facilitate **drug development** directly **focusing** on **paediatric populations** and not through extrapolation from corresponding studies on adults.
- EPTRI aims to develop a new **quadruple helix** structure where **government**, **academia**, **industry** and **citizens** work hand in hand.

Gaps identified

- Lack of **standardized animal and cellular models** of paediatric diseases available
- Lack in **research on specific mechanisms** that lead to development of paediatric diseases
- **Tests** usually not **validated** and therefore results obtained with aforementioned models in different laboratories not comparable
- Limited **special instruments** for work with **immature animals**

Preclinical Drug Discovery



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User needs

Target validation

It is of major importance to increase understanding on the disease mechanisms and use this knowledge to provide **new targets** for efficient therapeutic intervention.

This is of special importance in paediatric drug discovery as molecular targets are **highly diverse** and **partitioned along the different ages** of the young individuals.

Proper drug target selection and validation are crucial to the discovery of new drugs for specific diseases.

User needs

In silico drug design, informatics

At present, **preclinical stages of drug discovery** are **significantly shortened** by effective implementation of a diverse array of state-of the-art computational technologies.

These computational algorithms have a considerable impact for predicting capacities of small molecules to interact *in silico* with a given drug target in a therapeutically relevant manner.

As a result, they can be of **utmost importance** in the discovery of new and promising paediatric drug candidates.

User needs

High-throughput bioactivity screening

Hit identification is pivotal to early stage drug discovery.

An array of biological techniques is available for **optimal exploration** of chemical space.

Biophysical and biochemical techniques are particularly useful in drug discovery efforts dealing with **emerging and underexplored drug targets** such as **those related in paediatric-relevant initiatives**.

User needs

Chemical libraries and synthetic medicinal chemistry

Synthetic medicinal chemistry is **key component** of every drug discovery endeavor.

Furthermore, accessible chemical space is notably increased by **several public or commercial compound libraries along** with a wide array of smaller focused libraries or others facilitating **drug repurposing**.

User needs

Cellular models

Determining drug effects in human is the most confident way to **validate drug targets** and **understand disease mechanisms**.

Candidate drugs can be assessed using **advanced cellular models**.

Distinct features of **emerging technologies** such as **iPSC and 3-D systems** can advance early stage drug development studies of genetically defined **pathological phenotypes** for screening.

Access to **specialized paediatric material** through **dedicated biobanks** may offer critical advantage toward **targets of paediatric interest**.

User needs

Advanced screening approaches

Two distinct approaches adopted by modern drug discovery in assessing lead compounds: **phenotypic** (cell-based or *in vivo* systems) and **target-based** (isolated targets and chemical probes) discovery.

Advanced experimental systems elaborated for providing models to **study paediatric diseases** and **human development**.

Techniques that **can substitute for difficult** *in vitro* assays such as **droplet microfluidics and organ-on-a-chip**.

User needs

Animal Testing

Animal experiments are essential for translation of drug discovery studies from **bench to bedside**.

Several **limitations** in paediatrics are related to involvement of adult animals, preclinical/translational studies done in non-corresponding developmental stages of lab animals and use of more experimental groups and longer follow-up.

However, in vivo studies comprise a **method of choice** for preclinical evaluations in drug discovery.

Areas of services provided

In silico Virtual screening for primary hit discovery and hit-to-lead optimization design

In Silico Hit Discovery: *Computational screening of compound libraries against targets of interest and prioritization of molecules based on predicted binding affinities against specified drug target.*

In Silico Hit-Lead Design: *Construction and validation of quantitative computational models based on molecular simulations for derivation of structure-activity relationships and lead optimization.*

Chemo-informatics – in silico prediction of ADME properties & toxicity

Development of QSAR models *for the in-silico prediction of key physicochemical properties of lead compounds related to pharmacokinetics including absorption, distribution, metabolism and excretion.*

Computational assessment of ***toxicological risks*** *using QSTR, read-across, dose-response and toxicogenomics analysis approaches, filtering of compound libraries, prediction of off-target effects, identification of reactive species and Pan-Assay Interference Compounds.*

Areas of services provided

Target validation

Genetic approaches *to target validation by using RNA interference, gene knock-out and knock-down studies, antisense technology.*

Bioinformatics, *analyses for identification of candidate target genes.*

Target characterisation *expression, purification and structural determination*

Chemical approaches *for target validation by development of* ***chemical probes*** *for specified protein target.*

Cell based assays, Stem cells, Specialised cell models

Screening of small molecules on **paediatric diseases cell models**. *Screening on specific models for* ***muscular dystrophies, brain injury, apoptosis, cancer etc***

Development of stem **cell based organoids** *and specific paediatric drug discovery screening. 3-dimensional cell cultures, microtissue products, nano-culture spheroid plates, micropattern plates, polymer nanofiber plates and low-density 3-D cell suspension media*

Development of **preclinical disease models** *(oncology,) on the basis of biobank samples. Development of cell lines as models for specific paediatric diseases* **based on patient samples**.

Areas of services provided

Animal models

Test of selected New Molecular Entities on paediatric diseases animal models

Mouse model of premature ageing (Hutchinson-Gilford Progeria)

Drosophila model for Congenital disorders of glycosylation (CDGs);

Mouse model for Duchenne Muscular Dystrophy (mdx)

Mouse, rat, hypoxia

Transgenic mice, xenografts

Drosophila model of motor neuon disease in particular hereditary spastic paraplegia genes

Periventricular leukomalacia, cerebral ischemia

Mouse models of primary immunodeficiency

Mice ADPKD model; juvenile rabbit BPD model; rabbit CDH model; PREPL mice model;

Zebrafish Dravet model

Murine medulloblastoma model.

Mouse model of PCD with hydrocephalus and infertility

Areas of services provided

Animal models

*Animal testing of **New Molecular Entities** on **Zebrafish** models for **paediatric cancers, cardiovascular, neurological disorders***

*Animal testing of New Molecular Entities on mouse model for **epilepsy***

*Animal testing of New Molecular Entities on for **Rare Diseases** such as Aniridia, DMD, CCHS, MNGIA, ADA-SCID.*

*Animal testing of New Molecular Entities on preclinical animal models of **paediatric solid tumours**.*

*Animal testing of New Molecular Entities on Progeroid **laminopathies, lipodystrophy (FPLD2) and LMNA-related muscular dystrophies**.*

Areas of services provided

Animal models

*Animal testing of the previously developed **New Molecular Entities** for the assessment of toxicity and ADME properties*

Pharmacokinetic studies

Metabolism studies

Assessment of toxicity

Resource description

Facilities-technologies

- Available confirmation from **110 distinct research institutes** eager to contribute to the platform.
- The principal research topics involved in drug discovery (discovery of **new hit compounds** for **emerging paediatric drug targets** and subsequent biological evaluation in advanced **assay settings**) are well offered by the **institutes** and the **expertise** of the involved research collaborators.
- The defined gaps with respect to paediatric **drug discovery** in the EU research system are **reasonably addressed** by the platform.

Resource description

Facilities-technologies

iPS and intestinal organoid technology

flow-based cytometry

molecular imaging

next-generation sequencing

Selective Plane Illumination Microscope (SPIM-light sheet)

developmental zebrafish models

experiments on zebra fish embryos exposed to compounds

developmental zebrafish models

placental and umbilical cord models

proteomics

cell sorting

laser capture microdissection

advanced imaging

transgenic and gene targeting animal facilities

histology suite

bioinformatics services

genomics (ChIP-seq)

transcriptomics (RNA-seq)

proteomics (iTRAQ labeling combined with mass spectrometry)

Resource description

Facilities-technologies

imaging facility equipped for live cell and whole-embryo experiments, Quantitative Ion imaging

computing infrastructure for data storage, image analysis and 3D image visualization

isolation / expansion mesenchymal cells from bone marrow, umbilical vein, Wharton's jelly and fat

Small rodents, lagomorphs and immunodeficient animals facility

NGS genomic technology based on NextSeq500 + MiniSeq

NGS sequencing Illumina platforms

Fluidigm C1 system for Single cell assays

high-capacity robotic systems for DNA and RNA extraction, liquid handling and NGS library preparation

Whole Genome and Exome seq, ChIP-seq, DNAse-seq, FAIRE-seq, STARR-seq, RNA-seq

Orbitrap Elite™ Hybrid Ion Trap-Orbitrap system

Map II-8 robot, MALDI-TOF-TOF, LC-nESI-QIT MSN, LC-nESI-QqTOF MS-MS and LC-MALDI spotting system.

Resource description

Facilities-technologies

Sanger sequencing based on ApiSi Biosystems 16-capillary AbiPrism 3130Xl Genetic Analyzer sequencer and different thermocyclers.

gas chromatographs with mass spectrometers (Agilent)

HPLC with detection of fluorescence

spectrophotometric and electrochemistry

Capillary electrophoresis with spectrophotometric and laser-induced fluorescence detection

mass spectrometry plasma source coupled (ICP-MS) UHPLC / MS-MS system.

Pathology platform with tissue processors, microtome, cryostat, immunostainers, microscopes and SP8 confocal microscopy system with STED super-resolution.

confocal microscopy unit with confocal Nanoscopy, visualization of individual molecules inside the cells and a resolution of up to 60 nm.

Molecular modeling infrastructure.

NMR (200, 400, 600 MHz)

Feasibility Study

DEVELOPMENT OF NOVEL DUAL-TARGET MODULATORS ENHANCING MITOCHONDRIAL FUNCTION AS A THERAPEUTIC APPROACH FOR DUCHENNE MUSCULAR DYSTROPHY

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Feasibility Study

Background of proposed study

- Duchenne muscular dystrophy (DMD), **rare but severe** genetic disease.
- Impairment of normal muscular tissue functionality, leading to inevitable death.
- Most drugs presently used for DMD **are clinically used for different indications**, such as steroids, and implemented as to schemes targeting at **slowing progression** of DMD.

Feasibility Study

Scientific rationale and objective

DMD currently has **no cure** and therapeutic treatment aims at prolonging survival of pediatric patient.

Great need for developing potent drugs for this disease impacting lives of so many people and their families.

- Several proteins explored for their tractability to act as drug targets for DMD.
- However, field is **underexplored** and **challenging**.

Feasibility Study

Collaborators	organisation name and role	Country
Emmanuel Mikros	ATHENA RC	GREECE
Pietro Spitali	LUMC	THE NETHERLANDS
Stefan Knapp	Goethe Universität, Frankfurt	GERMANY
Leonardo Scapozza	University of Geneva	SWITZERLAND
Petr Džubák	Palacky University in Olomouc	CZECH REPUBLIC
Claudio Passananti	CNR-IBPM	ITALY
Toshifumi Yokota	University of Alberta	CANADA
George Paliouras	Duchenne Data Foundation (DDF)	THE NETHERLANDS
Giovanni Migliaccio	Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF)	ITALY

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Feasibility Study

Study design

Considered targets are:

- Metabolic enzymes related to H_2S production(CBS)
- Thiolase that is a part of the mevalonate pathway
- ATP synthase and creatine kinase related with energy production
- Family of histone deacetylases (HDAC) epigenetic targets
- Mitochondrial targets related with macro-autophagy bnip3 and beclin1
- Distinct members of Akt-mTOR pathway such as FOXO3.

Feasibility Study

Study design

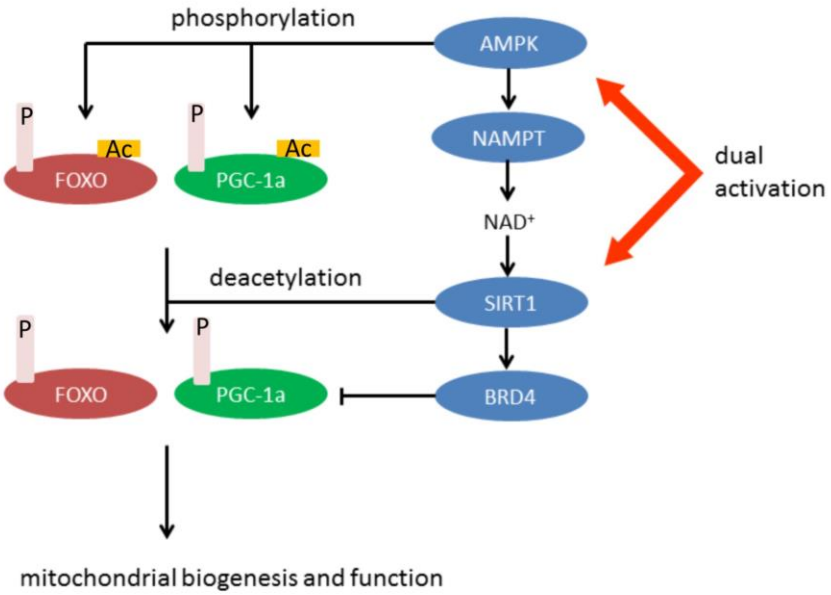
Discussed targets:

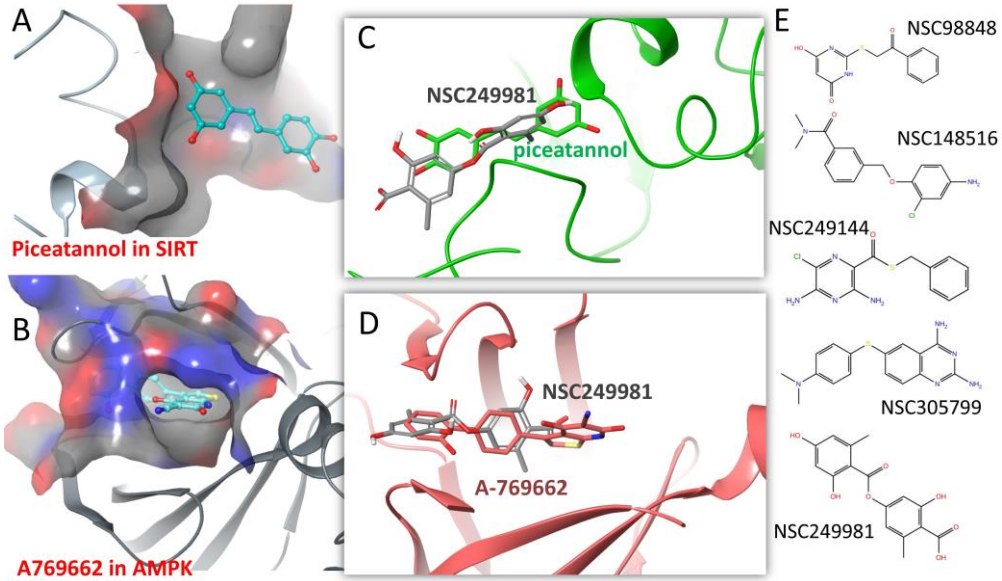
1. Activation of **SIRT1** (epigenetic target, deacetylase involved in gene expression regulation)
2. Activation of tissue specific isoforms of **AMPK** kinase (ser/thr protein kinase regulating homeostatic cellular energy)

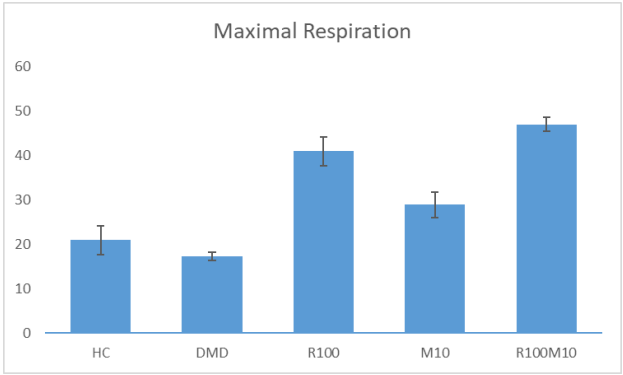
Both pathways have been suggested to be involved in DMD pathology while they comprise attractive target areas (kinases and epigenetics).

Feasibility Study

Study design







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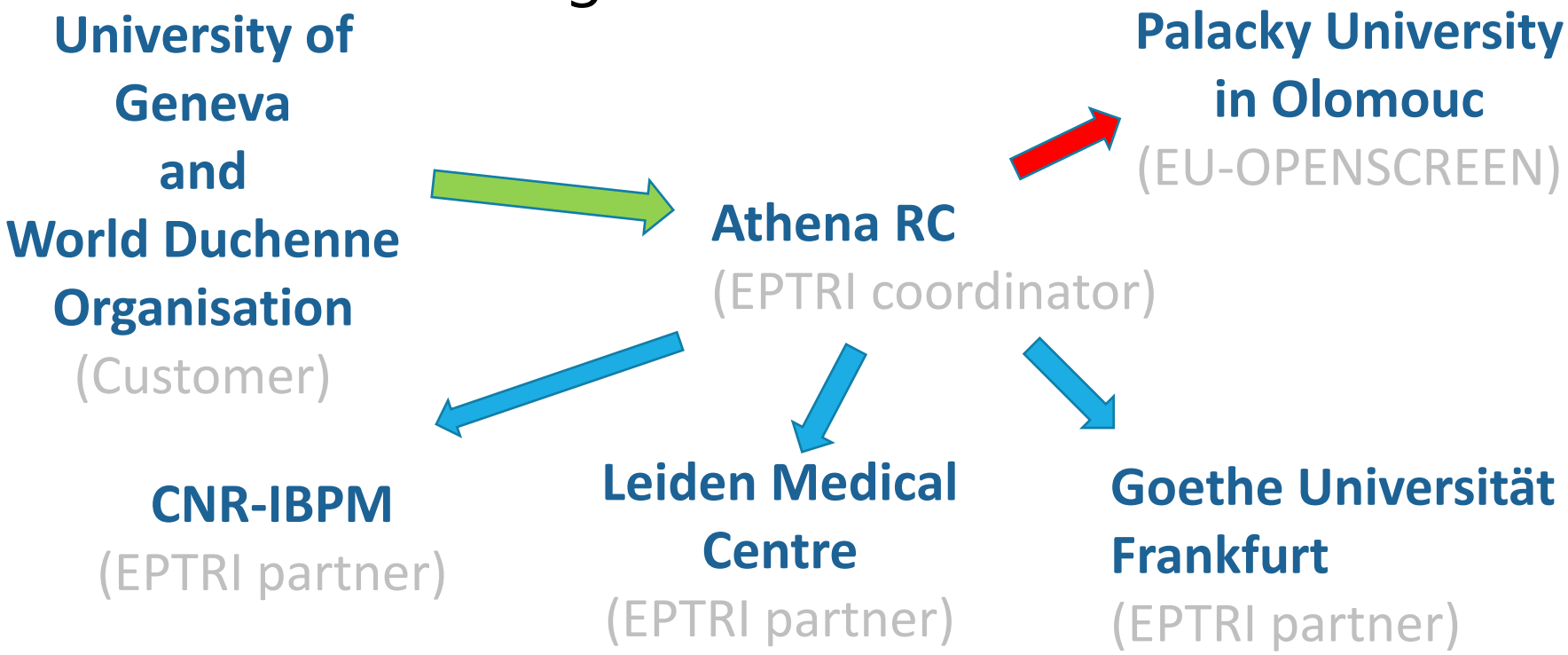
Involvement of the EPTRI

Partners of EPTRI in collaboration with external scientists will efficiently perform a study of common interest and exchange know-how.



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EUROPEAN JOINT PROGRAMME
RARE DISEASES

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RARE DISEASES

Pre-proposal application form
EJP RD JTC 2020

1.a. Project title:	**DEVELOPMENT OF NOVEL DUAL-TARGET MODULATORS ENHANCING MITOCHONDRIAL FUNCTION AS A THERAPEUTIC APPROACH FOR DUCHENNE MUSCULAR DYSTROPHY**
1.b. Project acronym:	**DMitoHeal**

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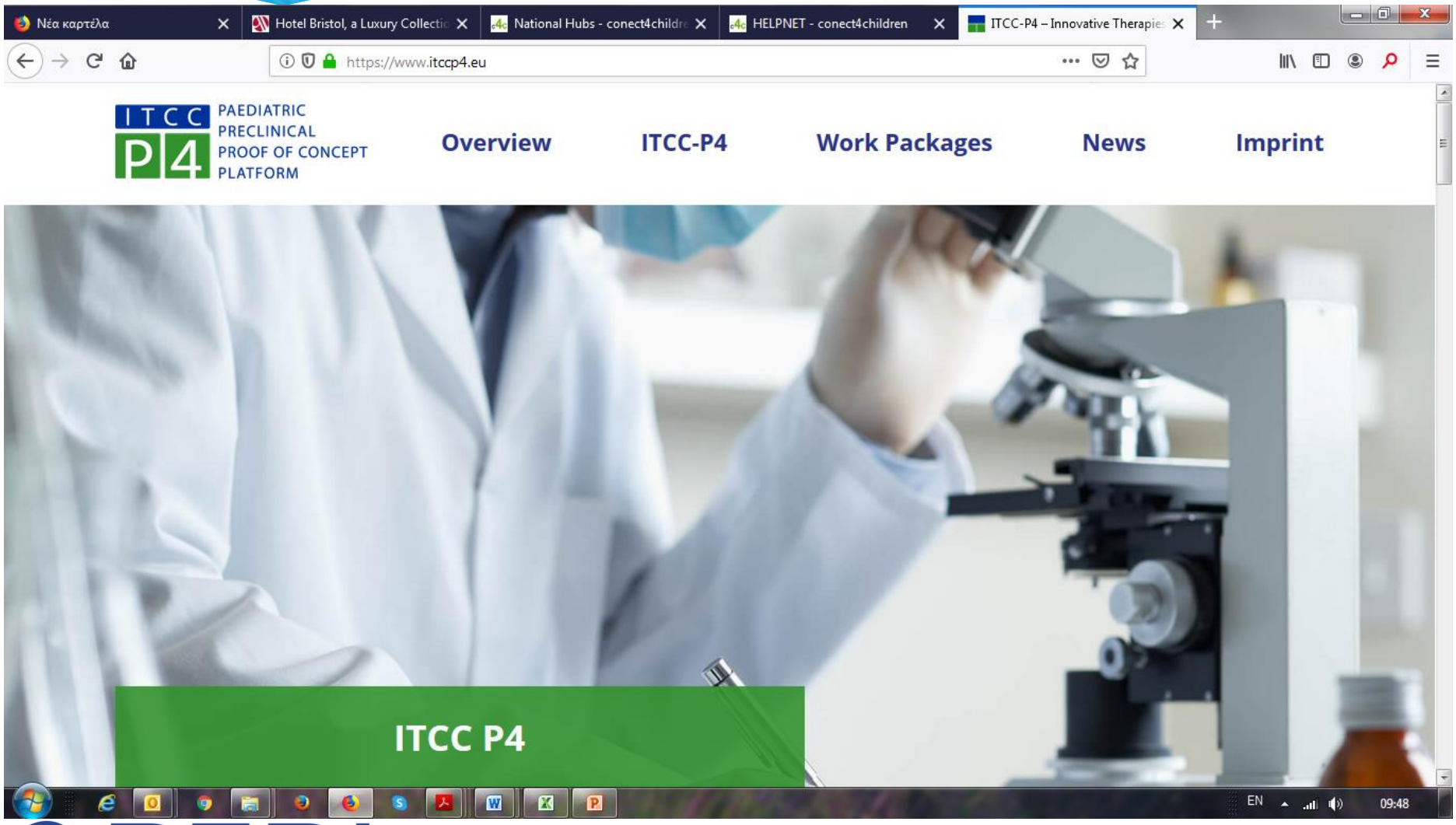
SWOT

- Strengths related to **scientific importance**
- Weaknesses related to **administrative fragmentation** and **sustainability**
- Opportunities **ethical obligation** and to a considerable extent attached to **scientific innovation**
- Threats related to **competition**

Competition



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Competition

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SWOT

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