TRISOMY21 CLUSTER EBRA CONSENSUS STATEMENT

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Overview TRISOMY21-CLUSTER was funded by EBRA in 2020 as a two-year networking action to enhance Down syndrome research in Europe.

Mission Establish a collaborative framework of coordinated actions of Down syndrome research in Europe.

Strategic objectives

- Expand existing and create new European Down syndrome research networks.
- Promote coordination and collaborations at both European and global level and contribute to European Policy.
- Increase translation of Down syndrome research into health interventions.
- Increase participation of industrial partners.
- Improve access to and optimise the use of research infrastructures and data.
- Explore funding possibilities for broader scale cooperation at global level.

Activities

- Consensus workshop.
- Thematic Workgroup on Down syndrome research priorities.
- Thematic Workgroup on strategy to link with policy makers and other relevant stakeholders.
- Public Forum of the EBRA Trisomy 21 cluster.

The first event was a meeting of TRISOMY21-cluster members with external stakeholders with the intention to reach consensus on the priorities, gaps and enabling actions.

TRISOMY21 consensus meeting

On November 12th, 2020, TRISOMY21- CLUSTER held the first meeting. The focus of the meeting was to bring together the leadership of the TRISOMY21-cluster and a number of relevant stakeholders, from funding agencies to patient's organisations and industry, to discuss priorities and opportunities for Down syndrome research and liaise with industry partners and patient representatives. During the meeting, consensus was built on research needs in the short and long term, and main objectives and priorities for action.

Meeting attendees The following TRISOMY21 stakeholder groups were represented during the meeting: Patient organizations, basic and clinical researchers, clinicians, industry, funders research infrastructures and data experts.

TRISOMY21 cluster: Mara Dierssen, Chair (Center for Genomic Regulation, Barcelona); Marie Claude Potier, Co-Chair (Institut du Cerveau et de la Moelle, Paris); Andre Strydom (King's College London); Jean Maurice Delabar (Institut du Cerveau et de la Moelle, Paris); Marzia Perluigi (University "La Sapienza", Roma); Eugenio Barone (University "La Sapienza", Roma); Elizabeth Fisher (University College London); Yann Herault (IGBMC, Strasbourg).

From EBRA: Kristien Aarts, Project manager EBRA, European Brain Council ; Fréderic Destrebecq, Executive director, European Brain Council

Stakeholders group: Philippe Amouyel, EU Joint Programme – Neurodegenerative Disease Research (JPND); Pat Clarke, Chair European Down syndrome Association; Marlies Dorlöchter, ERANET-NEURON; Monica Ensini, DG Research & Innovation at European Commission; Catherine Lemmonier, Jérôme Lejeune Foundation; Georgina MacKenzie, Wellcome trust; James Larkin, Innovative Medicines Initiative (IMI); Magda Chlebus, Executive Director, Science Policy and Regulatory (EFPIA and IMI); Bettina Ryll, Innovative Medicines Initiative (IMI); Amy Halls, National Institute for Health Research (NIHR, UK); Richard Oakley, Alzheimer's Society; Laurent Meijer, PERHA Pharmaceuticals; Hanna Churchill, Alzheimer's Society

Toward consensus

The research and coordinating objectives and priorities of TRISOMY21 cluster were discussed before and during the meeting with the invited stakeholders, identifying opportunities and challenges to go beyond the current limits of Down syndrome research and elaborating an **European Research Strategy**. These include (1) facilitating data and biosample availability and sharing, (2) increasing translation of basic science to clinical practices, (3) creating European and International joint funding initiatives and (4) supporting a multi-stakeholder Down syndrome research community.

The TRISOMY21 cluster aims to represent the research priorities of the entire Down syndrome research community. **The specific actions to achieve these general priorities will be discussed through two working groups**, the Thematic Workgroup on Down syndrome research priorities and the Thematic Workgroup on strategy to link with policy makers and other relevant stakeholders.

As part of the preparation for these specific actions, consensus aspects are acknowledged below and have been written by the leadership:

Basic Research in Down Syndrome

Research in the field of DS has generated new knowledge on disease mechanisms, leading to the discovery of druggable targets, compounds and procedures for treatment and has increased the quality of science in this field. This has opened unprecedented opportunities for individuals with DS and will provide many benefits for the general population and other conditions.

There is a need to continue reinforcing basic and pre-clinical research opportunities to increase our understanding of DS from the unknown molecular origin of the trisomy 21 aneuploidy to the pathophysiological mechanisms and preclinical proof-of-concept for therapies. We anticipate that those could also be beneficial in other intellectual disabilities, neurodevelopmental and neurodegenerative disorders.

Challenges for the future include (i) developing new experimental and theoretical approaches; (ii) increasing the pace of adoption of technologies such as iPSC, organoids, multi-omics, connectomics, computational neuroscience, single cell, molecular imaging, gene therapy etc.; (iii) attracting and retaining talented students, researchers and clinicians; (iv) accelerating the translation of novel therapies and biomarkers from the laboratory to the clinic; and (v) increase transversal and translational training efforts in complex diseases.

Clinical Research in Down Syndrome

Clinical research in the Down syndrome field needs reinforcement in three major research areas:

The lifelong nature of the disorder settles an important research need of extensive characterization from birth to adult life. This requires to define a more detailed clinical evaluation along lifespan, attached to a DS registry with a direct connection to a bioresource infrastructure to support longitudinal epidemiologic research and cross sectional studies.

Clinical trials on new age-specific drug treatments and neurotherapies are needed

Down syndrome is a complex disorder characterized by several comorbidities (psychiatric disorders, epilepsy and autism spectrum disorders, blood disorders, diabetes, obesity Alzheimer's disease etc.). These comorbidities settle another important research area and may enlighten the role of genes with pleiotropic function in DS and other conditions.

Studies for accurate stratification of patient populations to pave the way for personalized and precision medicine. Without an accurate and precise patient stratification model, researchers struggle to maximize the impact of their health intervention.

Challenges for the future: (i) the development of harmonised clinical evaluation protocols and dedicated ontology leading to the definition of a clinical path for DS; (ii) the creation of an European Down syndrome registry and a Down syndrome Clinical Trial Network (EU_DSCTN), given the uniqueness of Down syndrome and the recruitment complexity; (iii) the identification and incorporation in clinical practice of relevant disease and target engagement biomarkers; (iv) increasing the path to personalised and precision medicine; (v) increasing the pace of data and biosample sharing; (vi) adoption of technologies such as neurotherapies, eHealth and mHealth, gamification and cognitive training systems; (vii) bioethical aspects; (viii) primary care training

Innovation and infrastructures

Infrastructures

The size and complexity of the biosamples and data needed to promote translational research extends far beyond the scope of individual research projects.

1. There is a need of funding for dedicated Down syndrome bioresource infrastructure, with associated data (medical/epidemiological, social), and databases independent of physical samples, and other biomolecular and bioinformatics research tools. including animal and cellular models repositories.

2. Given the recruitment complexity enforces the need of a Down syndrome specific registry including individuals of all ages, with a direct connection to the bioresource infrastructure.

3. Deeper insights into clinical and preclinical data (multilevel including multi-omic, brain imaging, behavioural phenotyping) that may generate findings on lifetime evolution, drug mechanisms, novel targets for therapy, comorbidities, prognosis and outcome require developing long-term biomedical digital data preservation strategy for Down syndrome is very important to improve data quality, provide traceability and support reproducibility.

We need agreement between funding agencies and the Down syndrome scientific community to accommodate "bottom-up" integration and "top-down" financing of databases and biorepositories on an international scale.

Innovation

Delivery of medical care is changing, requiring transition to care facilitated by eHealth/mHealth platforms and digital healthcare. Creation of virtual Down syndrome centres to optimize and deliver care but also to collect useful clinical information across time.

Challenges for the future: (i) EU research infrastructures to support Down syndrome research; (ii) create a Down syndrome registry extending on existing registries including all ages, with a direct connection to a bioresource infrastructure; (iii) Create bioresource infrastructures; (iv) long-term preservation of Down syndrome biomedical research data and secure virtual workspaces to integrate and manipulate data, with shared software programs (e.g., bioinformatics tools), to facilitate the FAIR (Findable, Accessible, Interoperable and Reusable) use of data for near- and long-term research needs; (v) develop incentives to support and promote bioresources and data sharing

Down Syndrome Research Networks

The Down syndrome field needs to build a highly connected research community. A first initiative to create this interactive group has been the creation of the European local chapter among members of the Trisomy 21 Research Society to promote collaboration among institutions and investigators.

The establishment of cooperating networks of preclinical laboratories and clinical research centres could help integrate preclinical findings using clinical samples for biomarker analysis, integrate molecular characterization, pharmacology, biology, and imaging into clinical trials and create a pipeline for drug development and validation.

The European Research Networks would offer a unique opportunity to bridge hospitals and clinics with experts of DS, to perform academic clinical trials (phase 1) with innovative therapies, share data acquired during routine clinical work for data analytic sciences and homogenize the "rare disease" status for DS to leverage orphan drug designations and patent protection for increased investment.

Challenges for the future: (i) support the development of translational research networks at the European and global level; (ii) create an integrated preclinical-clinical program promoting cooperative agreements for research into preclinical and clinical aspects; (iii) funding opportunities to participate in global initiatives inside and outside the Down syndrome field (complex disorders; rare diseases; developmental diseases etc.)

Patients and Industry Involvement

Down syndrome organisations are major stakeholders that have a key role in advocacy and awareness. The Trisomy 21 Research Society (www.t21rs.org) as already built strong means for engagement and involvement of persons with Down syndrome and their families, but they should be strongly involved in the process of research prioritisation and design.

Down syndrome is a new extremely attractive field for investment by industry and new technology companies. Industry is recognizing the need to focus more on disease-modifying therapies that target specific mechanisms of disease and the underlying pathophysiology, which is very strong in the Down syndrome field already leading to promising therapeutic targets. This should be promoted through dedicated funding programs.

Challenges for the future: (i) involvement of Down syndrome organisations in research prioritisation through participation in funding decisions; (ii) involvement of persons with Down syndrome and their families as partners to researchers, clinicians and industry; (iii) implementation of adequate tools for co-creation research; (iv) increasing SMEs and biotechnology companies entering the field, allowing truly innovative approaches through specific funding programs (IMI); (v) means to promote access of industry to preclinical trial capabilities and expertise distributed throughout the TRISOMY21 network and to support the participation of industry to translational initiatives; (vi) educate on path to industry (spin-off, start-up); (vii) Involvement of regulatory agencies (EMA).

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