Trisomy 21 Research Society 2020 Annual report

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General information

The Trisomy 21 Research Society (T21RS) is the first non-profit scientific organization of researchers studying Down syndrome, founded to promote basic and applied research on Down syndrome, stimulate translational research and apply new scientific knowledge to develop improved treatments and cures.

The society aims to:

- Facilitate the permanent interaction between researchers studying Down syndrome by means of our website, scientific meetings, publications in journals and the two-yearly T21RS International Conference.
- Establish common protocols both for basic research (mice studies, stem cells studies) and translational research (for clinical trials with biomarkers, cognitive paradigms etc.).
- Support education and training of young researchers in all stages of their careers, including undergraduates, graduates and postdoctoral fellows that are interested in Down syndrome, by providing training programs and grants to young scientists Stimulate research on Down syndrome.
- Explain (recent) findings in Down syndrome studies to the general public and to inform legislators and other policymakers about new scientific knowledge and recent developments and their implications for public policy and society.
- Promote the interaction between scientists and patient associations, foundations and pharmaceutical industries

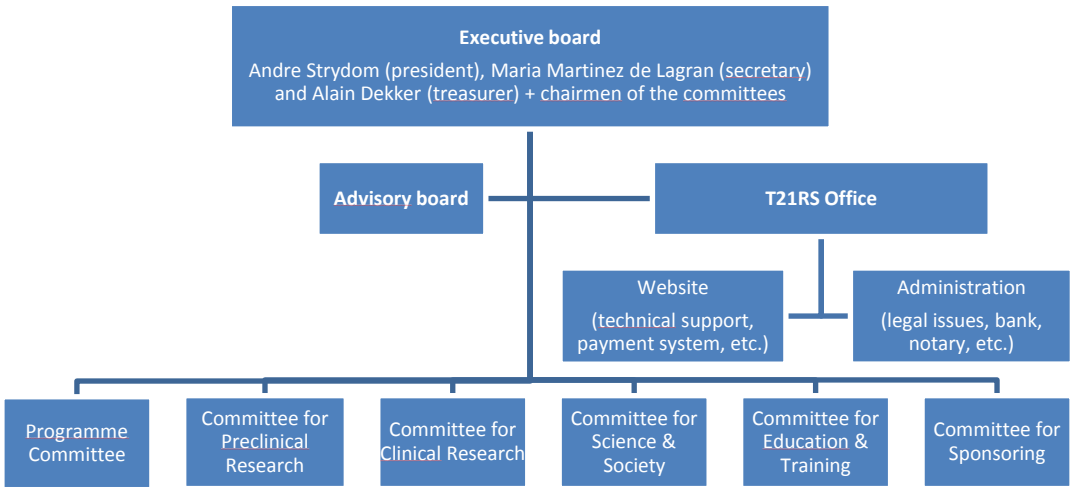
The society was created in April 2014 and statutes were registered on 17thApril 2014 in Groningen, The Netherlands, under the auspices of Mr. Albert Kraster, civil-law notary practicing in Groningen and member of The Royal Dutch Association of Civil-law Notaries. These statutes were revised the 11th July 2017. The Executive Board of T21RS produced a Governance document in line with these statutes to facilitate operation which will be revised every 2 years. The society is a non-profit organization for the stimulation of scientific research on Down syndrome, operating under Dutch law. The original deed in Dutch and the English translation can be downloaded from the society website, t21rs.org, as well as the Governance document. In 2020, the Executive Board of T21RS created a Policy of Conflict of Interest also available in the society website. Finally, a privacy policy is available on the website according to EU General Data Protection Regulations.

The society has organized three T21RS International Conferences:

1. 2015 edition in Paris, France (June 4-8 2015)
2. 2017 edition in Chicago, USA (June 7-11 2017)
3. 2019 edition in Barcelona, Spain (June 5-9 2019).

Executive board of T21RS

The executive board is formed by the president, secretary and treasurer of T21RS as well as the chairs of the committees



President:
Andre Strydom (King's College London, UK)

Secretary:
Maria Martinez de Lagran (Center for Genomic Regulation, Barcelona, Spain)

Treasurer:
Alain Dekker (University Medical Center Groningen, Groningen, the Netherlands)

Committee chairs:
Program Committee: **Elizabeth Head**
Committee for Science & Society: **Anne-Sophie Rebillat**
Committee for Sponsoring: **Jean Delabar**
Committee for Education and Training: **Sandra Guidi**
Committee for Pre-clinical Research: **Elizabeth Fisher**
Committee for Clinical Research: **Alberto Costa**

An electronic ballot was organized on January for the election of the new chairs of the Program committee and Science & Society committee and President Elect. Of the 247 members, 171 (69,2%) voted, and the candidates obtained the following votes:
Program committee: Dr. Yann Hérault from Institut de Génétique et de Biologie Moléculaire et Cellulaire (France) 26 (24.3%), Prof. Ann-Charlotte Granholm from Knoebel Institute for Healthy Aging (US) 25 (23.4%) and Prof. Elizabeth Head from University of California Irvine (US) 56 (52.3%). **Elizabeth Head** became the chair of the Program committee of T21RS.

Science & Society committee: Dr. Renata Bartesaghi from University of Bologna (Italy) 35 (32.7%), Dr. Anne-Sophie Carret-Rebillat from Institut Jérôme Lejeune (France) (with co-chair Dr. María Carmona-Iragui from Sant Pau Hospital (Spain)) 62 (57.9%) and Dr. Jacqueline London from University of Paris (France) 10 (9.3%). **Anne-Sophie Rebillat** became the chair of the committee for Science & Society of T21RS.

President Elected (2022-2023): Dr. William Mobley from UC San Diego (US) 64 (59.8%) and Dr. Weihong Song from University of British Columbia (US) 43 (40.2%). **William Mobley** became the President-elect of T21RS.

Local chapters consist of local community of scientists interested in Down syndrome research with the aim of promoting activities organized by T21RS members to engage local communities. The local chapter provide opportunities to educate and inform the public about the importance of Down syndrome research through outreach activities. In 2020, China (chaired by Dr. Yong Dai) and Europe (chaired by Dr. Marzia Pierluigi) have joined as T21RS local chapters (see Sponsorship and Membership Committee section).

In August 2020, T21RS launched a call looking for new chair and members for the communication workgroup. The Executive Board selected Dr. Michael Yaeger (University of Colorado, Denver, USA) as the new chair replacing the past one, Dr. Mari Luz Montesinos (University of Sevilla, Spain). Five new members joined also to the communication workgroup (see Communication Workgroup section)

T21RS activities

T21RS launched two calls during 2020 for awards worth 500 EUR for the organization of scientific or dissemination events to contribute to increase the public visibility of Down syndrome research and of T21RS. Applicants should be T21RS members. Executive board awarded 5 applications in the call launched on March, but one of the awardees reimbursed the money due to the inability to organize the event due to the Covid-19 pandemic. In the call launched on September, 3 applications were awarded (see below).

In the year 2019, the Committee for Education and Training launched the Annette Karmiloff-Smith and Michael Harpold Outstanding Thesis Award Program, for outstanding Ph.D. thesis defended during the period January 1, 2018 to December 31, 2019. The name of the award was to honor the memory of those prestigious scientists and members of the T21RS, who highlighted in the field of Down syndrome research. In 2020, an evaluation committee formed by three members of the Executive Board selected 2 applicants as winners of the prizes of 1,000 EUR each (see Education and Training Committee section).

The Education and Training Committee have organized 6 webinars to support the dissemination of the latest research developed in the field of Down syndrome (see Education and Training Committee section).
In 2020, T21RS launched the new website with more information of interest for the members and easier to use and search (www.t21rs.org).

The 2020 year has been marked by the COVID-19 pandemic. T21RS has launched several initiatives to better understand the risk and to inform appropriate recommendations to protect individuals with Down syndrome against COVID-19, and to understand vaccination side effects and immune response. Many of the T21RS members are now part of a T21RS COVID-19 Taskforce (see below).

Report of the President

The past year has been one of the most challenging in recent memory, with the global SARS-CoV-2 pandemic affecting the way we work and interact with others. Sadly, many families and people with Down syndrome have lost their loved ones to COVID-19, and others have been severely affected by the impact of lockdowns in many countries. We have also lost an outstanding scientist, Professor Angelika Amon, a cell biologist at MIT who worked on chromosome imbalance.

Despite the many challenges during 2020, the society has continued to expand our engagement activities with the international community of researchers committed to understanding the effects of trisomy 21, as well as with our many stakeholders, to support the next generation of investigators, and to encourage collaboration.

COVID-19 Initiative

In order to respond to the pandemic, we launched a **COVID-19 initiative** to oversee activities aimed at addressing specific concerns:

1. Whether individuals with Down syndrome are more vulnerable to severe outcomes because of co-occurring conditions
2. Whether those with Down syndrome are at an increased risk for complications arising in the context of SARS-CoV-2 infection
3. Whether there are atypical responses to treatments of COVID-19 among individuals with Down syndrome,
4. Whether their response to current vaccines and side effect profiles, are different from other people.

We designed and delivered an **international survey** of the impact of COVID-19 on people with DS, an effort led by Stephanie Sherman, Alberto Costa of the T21RS Committee for clinical research, Mara Dierssen (past-president and preclinical committee representative) and Anne-Sophie Rebillat and Maria Carmona-Iragui from the T21RS Committee for Science and Society. We are grateful for the support and funding for the survey from Down Syndrome Affiliates in Action (DSAIA), Down Syndrome Medical Interest Group-USA (DSMIG-USA), GiGi's Playhouse, Jerome Lejeune Foundation, LuMind IDSC Foundation, Matthews Foundation, National Down Syndrome Society (NDSS), and the National Task Group on Intellectual Disabilities and Dementia Practices (NTG).

The results of the survey were published in the Lancet's EClinicalMedicine and disseminated via webinars co-hosted with several of our stakeholder partners (EDSA, DSRF, The Matthew Foundation and Lumind RDS). It also attracted considerable interest in the media, with news reports in Fox News, MSN, CNN, and many others.

Meanwhile, the T21RS preclinical committee spearheaded efforts for a rapid review of the literature to understand susceptibility to COVID-19, under leadership of Eitan Okun (Israel). The findings of this comprehensive review was published recently - https://doi.org/10.1007/s12017-021-08651-5; an important future resource for understanding the vulnerabilities to novel infections in people with Down syndrome. Another report more specifically focused on immunological issues is currently in submission.

We established a **COVID-19 stakeholders group**, chaired by the president and Stephanie Sherman with input from many of the Down syndrome associations across the world. Their inputs and insights were immensely helpful to refine our questionnaires, and to understand the implications of our survey findings. Our survey results and work with the stakeholders group resulted in the release of several infographics, highlighting risks and symptoms associated with COVID-19 in Down syndrome individuals, as well as two **statements** – one on isolation of individuals with Down syndrome, and another to promote the prioritization of vaccination. These helped stakeholder organizations to advocate for appropriate care and support for people with Down syndrome and their families. In addition, we endorsed the **Down syndrome and COVID-19 Q&A** initiated by the Global Down syndrome foundation.

We also established a **COVID-19 Impact workgroup** that is coordinating efforts to research the psycho-social impact of the pandemic.

Work is also ongoing to support studies of the immunological response to vaccinations of people with Down syndrome.

Finally, we have initiated a **vaccination prioritization tracker**, to promote vaccination priority for people with Down syndrome across the world (https://www.t21rs.org/covid_vaccination/).

Other new activities and initiatives

1. **Redevelopment of the T21RS website**
   A new website was built by BCO Congresos, the company that takes care of the technical secretariat of the society, with expert coordination from Maria Martinez de Lagran (T21RS secretary) to be more eye-catching and user-friendly, and now includes regular news updates, as well as several pages on the work of the COVID-19 Initiative.

2. **Membership value**
   We continue to support **T21RS grants** for the organization of scientific events by our members, with 500€ grants per successful applicant. This program is designed to contribute to the funding of technical and scientific activities such as talks, meetings and events, which will contribute to increase the public visibility of Down syndrome research and of T21RS. The range of activities funded included local activities on specific topics to multidisciplinary activities with a strong international participation.

   We have expanded the number of **T21RS chapters**, initially initiated by Jean Delabar, which now include Latin America, India, China and Europe Chapters. The chapters promote activities organized by T21RS members to engage local communities.

We have hosted a successful series of **webinars** on a range of cutting-edge topics, ranging from controversies in animal modelling to results of the T21RS COVID-19 surveys. Webinars are organized by Sandra Guidi and free to attend for members, and are uploaded to our website after a week for general access.

3. **Improving communication:** The Communication Workgroup (see report below) has a new chair, and continued to help prepare regular newsletters, and have developed new communication strategies which will be implemented over the next year. The **monthly newsletter** continues to foster communication, discussion and debate on research topics amongst the T21RS members. Members have actively contributed news items on engagement activities, notable findings, and new grant successes.

4. **T21RS committees** (see details below) have continued to work on promoting pre-clinical and clinical research on Down syndrome at international level, and to promote educational activities. The Science and Society committee has actively engaged with stakeholders in our COVID-19 initiative, helping to rapidly disseminate information to our members and the public via our website, news reports, and webinars. The Membership committee has supported to the creation of new chapters.

5. We have updated our **governance document** (in line with the statute) to ensure an appropriate focus on diversity and inclusion, as well as to allow for more active engagement with industry.

6. **Institutional relationships and advocacy**: the T21RS has taken a leadership role in contributing to efforts to highlight the need for more research in Down syndrome. This has included participation in an EBRA workgroup on priorities for Down syndrome research in Europe, and a response to the NIH call for contribution to T21RS's response to NIH's RFI: [NOT-HD-20-013, "Request for Information (RFI): Invitation to Comment on Updates to NIH Research Plans on Down syndrome] with input from both the preclinical and clinical committees. We have also participated in a consultation with the FDA to consider issues related to trials in Alzheimer's disease in Down syndrome.

Bi-annual conference, June 8-10 2021:

The 4th T21RS International Conference will take a Virtual form. The organising committee is chaired by Jorge Busciglio. The programme has been developed by Elizabeth Head and the programme committee, and includes 3 plenary speakers, 5 symposia and a data blitz (a series of 2-minute talks, each covering just a single powerpoint slide) to offer a fast-paced overview of some of the most exciting research presented by promising junior investigators, as well as a strong Science and Society programme with participation by a drama and dance group from India.
Due to the unusual circumstances, the in-person conference in California has been delayed to 2022, and we look forward to meeting everyone then.

Committee reports

I –Program Committee

The Program Committee was formed in April 2020 to help craft the scientific content of the T21RS meeting that was initially proposed for Long Beach, California. Unfortunately, due to the COVID-19 pandemic, in person meetings were canceled and we moved to a virtual format. The program is significantly shortened but exciting. We anticipate an in person meeting in June 2022 in Long Beach, California.

Program Committee members, location and area of research:

Title	Name	Location	Area of Research
Chair	Elizabeth Head	USA	Aging and Alzheimer disease
Past Chair	Anita Bhattacharyya	USA	IPSc/Molecular
Past President	Mara Dierssen	Spain	Preclinical
Member	Yann Herault	France	Mouse models/preclinical research
Member	Kelly Sullivan	USA	Inflammation/biomarkers/leukemia
Member	Floriana Costanzo	Italy	Child and Adolescent Neuropsychiatry
Member	Brian Skotko	USA	Clinician, medical geneticist
Member	Maria Carmona	Spain	Neuroimaging and biomarkers
Member	Daniel Satge*	France	Cancer in DS
Member	Tao Ma	USA/China	Alzheimer's disease (AD) and Down syndrome/mouse models

*left committee January 2021

The duties of this Committee included 1) coordination of submission of symposia proposals, 2) review and selection of symposia sessions, 3) providing feedback and suggestions for the schedule and for the plenary speakers, 4) selection of abstracts from junior investigators for a Data Blitz session.

The Program Committee has selected three outstanding plenary lectures (Drs. Handen (USA), Dr. Potier (France) and Dr. Sherman (USA)). It has selected 5 symposia proposals that cover a wide breadth of topics from molecular to clinical studies. The symposia all include diversity in terms of sex, geography and junior/senior investigators. The Program Committee has also dedicated time for a T21RS General Assembly and for an exciting Science and Society session.

In addition to the 10 members of the Program Committee, we included the local Organizing Committee, led by Dr. Jorge Busciglio (UCI). Given the virtual format, however, the duties of this committee were significantly reduced. The vibrant content of the upcoming meeting shows that our community continues to thrive, despite the significant curtailment of research activities.

We anticipate preparing a manuscript describing the proceedings of the meeting, to be written in fall of 2021.

II - Committee for Science & Society

Science & Society Committee Members

Chair of the committee:
Anne-Sophie Rebillat (France)

Co-chair of the committee :
Maria Carmona-Iragui (Spain)

Members:
Peter De Deyn (The Netherlands), past chair of the committee
Lotta Granholm (USA, Sweden)
Sebastián Videla (Spain)
Isabel Barroeta (Spain)

Alain Dekker (The Netherlands), Juan Fortea (Spain) and Cindy Lemere (USA) did not renew their participation

NB: Maria Carmona-Iragui and Anne-Sophie Rebillat are also members of the Executive Board, of the Covid-19 DS task force and respectively of the Program Committee (Maria) and of the Clinical Committee (Anne-Sophie)

This committee works to explain recent scientific findings and promote access to research for people with Down syndrome (DS)

Initiatives and achievements in 2020

1) **T21RS Covid-19 initiative**
In the extraordinary context of the Covid-19 pandemic, T21RS mobilized all its forces to lead research on the impact of Covid-19 on subjects with DS.
Maria and Anne-Sophie took part in around 30 meetings of the T21RS Covid-19 DS task force in 2020 to share experience and to implement the Covid-19 and DS T21RS survey that they helped to disseminate. They contributed to sharing the results of the survey with the community, particularly in their respective countries

2) **T21RS Science & Society Bulletins**
No bulletin has been published in 2020 but several reports have been collected to implement bulletins in 2021 (thesis from Kunnie Ando, Alexandra Botte and Andrea Giacomini)
   - Kunnie Ando: Synaptojanin 1, a key Down syndrome protein, is upregulated and is associated with Alzheimer lesions in Alzheimer disease brains (teams of Dr. Marie-Claude Potier (Institut du cerveau, at Paris, France) and Dr. Jean-Pierre Brion (Université Libre de Bruxelles, Belgium)

- Alexandra Botte: Ultrastructural and dynamic studies of the endosomal compartment in Down syndrome (team of Dr. Marie-Claude Potier, Institut du cerveau, at Paris, France)
- Andrea Giacomini: The sooner the better: a “magic formula” to cure intellectual disability in Down syndrome? (team of Prof. Renata Bartesaghi, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy)

3) T21RS Science & Society Symposium 2021

Defined in the articles of association, T21RS aims, among others, to promote the understanding of, and involvement in Down syndrome research among the public, as well as stimulate interactions between scientists and Down syndrome (family) associations. Next to publishing Science & Society Bulletins, the Committee, therefore, organizes a bi-annual T21RS Science & Society Symposium. Due to COVID-19 pandemic, a virtual T21RS International Conference is organizing for 2021. This committee is preparing the Science & Society Symposium of the virtual conference 2021.

4) New T21RS website

Contribution to the content of the new T21RS website launched in 2020

5) Regular meetings

The committee decided to meet regularly approximately every 3 months, the first meeting was held on September, 9th, 2020

6) New members

The committee is actively looking for new members and welcomed Isabelle Barroeta, from Spain

III - Committee for Sponsoring

Sponsoring Committee Members

Chair of the committee:

Jean Maurice Delabar (FR)

Members:

Yong Dai (CN)
Pablo Helguera (AR)
Hampus Hillerstrom (USA)
Sujay Ghosh (IN)
Marzia Pierluigi (IT)
Marie-Claude Potier (FR)
Carmen Martinez-Cue (SP)
Michelle Whitten (GDSF, US)

An active communication between members was maintained through conference calls and emails

Sponsoring activities

During 2020 research of sponsors had three objectives

1. to maintain functioning of the society to cover basic expenses (web, technical secretariat)
2. to fund travel grants and awards for young researchers
3. to prepare funding of the Long Beach meeting (fourth T21RS International Conference) which will be on line in June 2021

T21RS sponsors can be classified in four groups: the first one is the circle of founding members Lumind, Global Down syndrome, Lejeune Foundation, Matthews Foundation, Trisomie 21 France: 2020 was the first year of the novel 5 years founding agreement: during the second part of 2019 4 of them renewed their commitment and accepted to sign an agreement for the years 2020-2024. Discussion for renewing this agreement with Global Down syndrome was initiated.
Another main supporting member was recruited: Down Espana signed an agreement for 2020-2024.

The second group concerns foundations that give a specific support meetings and travel grants.

The third group is the institutional granting agencies.

The fourth group put together pharmas with interest in developing treatments for Down syndrome : Aelis Pharma, Fontup

Membership activities

The committee was active proposing new benefits for members including grants to support Scientific events.
The committee organised also to recruit new members and initiated the creation of two new local chapters: in China (chaired by Dr Yong Dai, Shenzhen people's hospital) and in Europe (chaired by Dr M Perluigi, Sapienza University of Rome).
The committee continued the update of a contact list of more than 1000 names of researchers, clinicians and associations.

Local chapter activities

China- Chair: Dr. Yong Dai

Webinars
We participated in T21RS executive board meeting on November 4, 2020.

Meetings:
One meeting "2020 Annual Meeting of Medical Genetics Professional Committee of Shenzhen Medical Association & Academic Conference of Trisomy 21 Syndrome Research Society in China Chapter" held on November 28th, 2020 in Shenzhen, China. The next meeting will be soon scheduled in the second half of 2021.

Contacts:
We have two WeChat groups, which have more than 300 candidate members and we want to apply for 10-15 standing committees and 1-2 secretaries for China Chapter. We will continue to promote communication & cooperation of researchers & doctors and Academic communication

India- Chair: Dr. Sujay Ghosh

Researchers-Parents Meet January 18, 2020.
The meeting was organized at the University of Calcutta. The aim was to involve more families in the research initiative and to uphold the activities of T21RS across the world.

International Conference: February 10-11, 2020
The theme of the conference was "Down syndrome research: Indian Initiative in the global perspective". The conference was graced by Prof. Stephnaie Shreman, Emory University, Atlanta, USA and Prof. Eleanor Feingold, Pittsburgh University , USA. Other speakers were Indian researchers. The two days conference was ended with wonderful cultural performances by the children with Down syndrome.
Scientific Webinar: July 30-31 2020.
Two days International Webinar. The speakers were Prof. Andre Strydom, Prof. Monika Lakhanpaul, Prof. Stephanie Sherman, Prof. Mara Dierssen.

Local Chapter Meeting: 24th December 2020

Members of Local Chapter met to fix the forthcoming activities and also took initiative to register the body under the Indian Society registration act. Also discussed the potential sponsors for the activities and prospective joining of the members in the forthcoming T21RS Virtual conference 2021.

Update of Contact list

The contact list is under preparation.

Europe- Chair: Dr Marzia Perluigi

Webinars

I coordinated the event organized on line by the Italian DS group held on October 16th 2020
"Down syndrome and Alzheimer disease: advancements in preclinical and clinical research" with presentations by: Yann Yerault, Eugenio Barone, Fiorenza Stagni and Alain Dekker. The session was open to all EU members

Meetings:

We had one meeting among members to introduce the activities of the Chapter. The next meeting will be soon scheduled (possibly first week of March) to discuss novel initiatives among members and to support EBRA activities.

Contacts:

The list of Current MEMBERS of the EU chapter is available on the web: i.e. those that agreed to participate to the EU chapter. We will implement the list in 2021.

Contact for the committee for sponsoring and membership:
sponsoring@T21RS.org

IV - Committee for Education and Training

Education and Training Committee Members

Chair of the committee:

Sandra Guidi (University of Bologna, Italy)

Members:

Renata Bartesaghi (University of Bologna, Italy)
Carmen Martinez Cué (Univesity of Cantabria, Spain)
Fiorenza Stagni (University of Bologna, Italy)

The T21RS Committee for Educational and Training will:

- organize training schools for young scientists interested in Down syndrome
- establish a network of host laboratories working on Down syndrome, where visiting young scientists may expand knowledge in different methodological and conceptual issues regarding Down syndrome
- provide grants to students to enable them to attend scientific conferences regarding Down syndrome
- issue thesis prizes in order to stimulate research on Down syndrome.
- Organize regularly webinars to support the dissemination of the latest research developed in the field of Down syndrome

Initiatives and achievements in 2020

- In the year 2019, the Committee for Fellowships, Education and Training had launched the "**Annette Karmiloff-Smith and Michael Harpold Thesis Award Program**", for outstanding Ph.D. thesis. Two prizes of 1,000 EUR each can be awarded. We received 9 applications. The evaluation committee, formed by three members of the executive board of the Society, have drawn up a ranking based on the score obtained by using an evaluation form specific for this purpose. The winners were: Dr. Andrea Giacomini with a Ph.D. thesis entitled "Pharmacotherapies targeted to neurogenesis in order to rescue cognitive performance in Down syndrome" and Dr. Rosalyn Hithersay with Ph.D. thesis entitled "Exploring executive functioning and frontal cortical activity using functional near infrared spectroscopy". The winner of the two awards will be announced during the next T21RS meeting.

- In synergy with the Committee for Science and Society, the Committee for Fellowships, Education and Training has invited the two winners of the 2019 Competition to write a short outline of their thesis work to be published in the **Bulletin of T21RS**.

- During the last year the Education and Training Committee organized a **series of webinars** aimed to give at our members, particularly to the young, the opportunity to take part in an exclusive discussion. We hosted leaders of several specific research fields to discuss together the most recent results in clinical and preclinical Down syndrome research. The webinars are hosted on Zoom platform and lasted about one

hour; 45 minutes of presentation and 20 minutes of discussion with the attendances. Generally, the attendances were about 70 people each webinar from all over the world.

- January 30th 2020: “Activation of the ISR mediates the behavioral and neurophysiological abnormalities in Down syndrome”, speaker Prof. Mauro Costa-Mattioli (Baylor College of Medicine, Houston, Texas);

- April 28th 2020: “Modeling Down Syndrome Using Human iPSC-Based Cerebral Organoid and Chimeric Mouse Models”, speaker Prof. Peng Jiang (Rutgers University, New Jersey);

- June 10th 2020: “The Endolysosomal pathway in Down syndrome”, speaker Dr. Marie-Claude Potier (Institut du Cerveau et de la Moelle épinière - Hôpital Pitié-Salpêtrière, Paris, France). Webinar organized in collaboration of LonDownS Consortium.

- July 22nd 2020: “The Covid-19 pandemic and protection of individuals with Down syndrome: from the biological risks to treatment” (organized in synergy with the T21RS COVID-19). In the first talk Prof. Eitan Okun (Bar Ilan University, Ramat Gan, Israel) and Prof. Mara Dierssen Sotos (Center for Genomic Regulation, Barcelona, Spain) talked about: “The biological risk of Covid-19 infection in people with Down syndrome”; in the second talk Prof. Anke Huels (Rollins School of Public Health, Emory University, Atlanta, Georgia, USA) talked about “The results of the T21RS Covid-19 survey in Down syndrome”; in the last talk Dr. Anne-Sophie Rebillat (Institute Jerome Lejeune, Paris, France) and Dr. Diego Real de Asúa (Hospital Universitario de La Princesa, Madrid, Spain) talked about “Clinical cases of Covid-19 in people with Down syndrome”;

- October 20th 2020: “Strengths and Limitations of Down Syndrome Mouse Models”, speaker - Prof. Randall J. Roper (Indiana University-Purdue University, Indianapolis);

- December 1st 2020: “Present and future challenges for modelling Down syndrome in model organisms”, speakers Prof. Roger Reeves (Johns Hopkins University School of Medicine, Baltimore) and Prof. Yann Herault (Institute of Genetics Molecular and Cellular Biology, Strasbourg).

V - Committee for Pre-clinical Research

Preclinical Committee Members:

Chairs of the committee:
Elizabeth Fisher (UK)

Co-chair of the committee:
Eugene Yu (USA)

Members:
Antonarakis, Stylianos (Switzerland)
Bhattacharyya, Anita (USA)
Delabar, Jean-Maurice (France)
Dierssen, Mara (Spain)
Fisher, Elizabeth (UK)
Haydar, Tarik (USA)
Herault, Yann (France)
Mobley, William (USA)
Potier, Marie-Claude (France)
Puig, Vicky (Spain)
Reeves, Roger (USA)
Roper, Randall J (USA)
Yu, Y. Eugene (USA)

New fellows: (Joined in September, 2020)
Sujay Ghosh (India)
Antonella Tramutola (Italy)

The Committee is pursuing its objectives to help standardize high quality preclinical research into Down syndrome, including by facilitating access to important resources, and helping provide essential robust data for those resources including controls.

Initiatives and achievements in 2020

• **Training the next generation of DS researchers**
To bring early stage researchers onto the T21RS Preclinical Committee, in order to gain 'managerial' experience of working with the T21RS community. After inviting expressions of interest, in summer

2020 we welcomed Drs Sujay Ghosh (assistant professor, University of Calcutta) and Antonella Tramutola (postdoc, University of Rome La Sapienza) onto the Committee for a one-year term. In Spring 2021, we will welcome for one-year: Florencia Lulita (junior PI) and Hiruy Sibhatu Meharena (postdoc). We will invite new applications in late Spring 2021.

• **Our committee made an important contribution to T21RS's response to NIH's RFI:** [NOT-HD-20-013, "Request for Information (RFI): Invitation to Comment on Updates to NIH Research Plans on Down syndrome].

The Lifetime Trajectory of Persons with Down syndrome

T21RS Consensus Suggestions

Down syndrome (DS) arises from having three copies of human chromosome 21, and is the most common genetic form of intellectual disability, affecting up to six million people worldwide. Furthermore, lifespan has increased dramatically such that people with DS can live well into their 60s in the developed world. **Thus, the world-wide prevalence of DS is still increasing**.

DS is not just characterized by intellectual disability but involves dysfunction and pathology in different organs/systems in different people – it is a **highly variable syndrome**. This variability can teach us about aberrant pathways associated with DS while providing potentially important information about these pathways in those without DS. In particular, there is current intense interest in the early-onset Alzheimer's disease that is a key feature of DS and ageing.

Despite the common occurrence of DS, the visibility of people with DS in all societies, and the well-known genetic cause, we have remarkably little reliable quantitative data on the life-time trajectory of persons with DS. This dearth of data severely hampers our attempts to model and understand mechanisms underlying this disorder, to optimize therapeutic, facilitative, and educational interventions, and to apply our findings to the non-trisomy 21 population.

We are confident that it is URGENT and IMPORTANT to concentrate on long-term studies of the life-time trajectory of people with DS. We propose the following focused RESEARCH THEMES to address key gaps in knowledge:

THEME 1: **To decipher the intrinsic variability of DS features and occurrence of comorbidities through detailed longitudinal clinical characterization of individuals linked to large-scale biobanking**

We propose the collection of samples from sufficiently powered cohort(s) of individuals with DS. The cohort(s) should between them cover all ages but ensure sufficient numbers under 20 years of age. It would be important to ensure equal sex distribution in order to study sex differences, as well as sufficient numbers of individuals from different ethnic groups to allow for exploring potential differences. Of key importance is the need to undertake comprehensive clinical assessment of individuals that are linked to patient samples, to give us the full picture of life-time trajectory, and accurate numbers for prevalence of features in specific populations. Given the range of phenotypes of relevance in DS, it is likely that different cohorts may have specific priorities, but consideration should

be given to comparable data collections, particularly at the clinical level, to allow for combined analyses. With this in mind, it will be necessary to link with existing cohorts and to support international collaborations. Data will give us insight into all aspects of DS including intellectual function, as well as cardiac function, otitis media, gut function, musculoskeletal function, obesity, diabetes, etc. To fully capitalize on the 'phenotypic' study of the individuals in this cohort, we need DNA sequences to give us genetic and molecular insight, cell line collection (fibroblasts, iPSCs) for validation, and we can add these to existing resources such as NIH-approved ES cells. Biomarker collection should include blood samples, and potentially other samples such as hair or saliva. There is a great shortage of such human material especially in combination with fine-grained clinical and non-clinical assessment. Such material is essential for validating findings and capitalizing on DS variability to improve clinical outcomes. Samples must be ideally be collected longitudinally so that we can study effects of ageing.

THEME 2: **To provide robust data on neurodevelopmental trajectory, including speech and language development, oral praxis, and the co-occurrence of psychiatric disorders such as attention-deficit/hyperactivity disorder, autism, mid-life depression, or the rare cases of developmental regression with a specific focus on longitudinal neuropsychological testing** of individuals with DS and family members over their lifetime. E-health systems could be part of this effort to avoid "standalone" testing effects. Neurodevelopmental disorders with identified genetic etiologies present a unique opportunity to study gene–brain–behavior connections.

THEME 3: **To define nervous system development and function in individuals with DS through the use of current and new technologies** into the field of DS research, including advanced neuroimaging, electrophysiology, histopathology, metabolomics, microbiome studies, human iPSC studies etc. Clearly for some studies such as neuroimaging, small cohorts will be analyzed but projects must be statistically valid and with defined sex and ethnicity, to establish data to address variability in DS.

THEME 4: Develop and expand fundamentally new approaches to researching DS including the discovery and development of animal and cellular models. Under this theme it would be critical to encourage the discovery and careful characterization of new developmental and neurodegenerative phenotypes in animal and cellular models, which would facilitate future preclinical research on pharmacological and genetic interventions.

THEME 5: Define in vivo mechanisms and long-term therapy, in model systems such as mouse, rat, non-human primates, that reflect human clinical phenotypes in DS allowing longitudinal analysis and mathematical modelling and to create opportunities for translational medicine. Note that many vitally important studies, such as brain connectomics, gene knock-down, local field potential electrophysiology, single-cell patch clamp recordings, monitoring the effects and attempts to ameliorate early-childhood stress, and large (pre-natal) developmental studies cannot be undertaken in humans.

The five themes are *priorities* to be studied under the heading: **what are the characteristics of the life-time trajectory of persons with DS?** Other aspects, such as the well-known reduction in prevalence of certain solid tumors in DS are important, but the lack of knowledge of the effects of trisomy 21 on and individual's life-time trajectory holds us back currently, and needs to be addressed immediately, for the long-term. Inadequate specific information is available about the prevalence and patterns of health conditions of people with DS, which are barriers that hold back effective interventions.

We also believe that it is URGENT and IMPORTANT to produce information with the high potential to provide short-to-mid-term benefits to individuals with DS and their families. To this end, we propose the following focused preclinical and clinical research themes to address these unmet needs:

THEME 1: Fund focused workgroups to study the expansion of the idea of the potential creation of Centers of Excellence for Down Syndrome Research and Care for adolescents and adults. Such centers of excellence would have a strong life-science research component and would not only provide dependable primary great shortage of such human material especially in combination with fine-grained clinical and non-clinical assessment. Such material is essential for validating findings and capitalizing on DS variability to improve clinical outcomes. Samples must be ideally be collected longitudinally so that we can study effects of ageing.

THEME 2: **To provide robust data on neurodevelopmental trajectory, including speech and language development, oral praxis, and the co-occurrence of psychiatric disorders such as attention-deficit/hyperactivity disorder, autism, mid-life depression, or the rare cases of developmental regression with a specific focus on longitudinal neuropsychological testing** of individuals with DS and family members over their lifetime. E-health systems could be part of this effort to avoid "standalone" testing effects. Neurodevelopmental disorders with identified genetic etiologies present a unique opportunity to study gene–brain–behavior connections.

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1. Fund focused workgroups to study the expansion of the idea of the potential creation of Centers of Excellence for Down Syndrome Research and Care for adolescents and adults. Such centers of excellence would have a strong life-science research component and would not only provide dependable primary and/or specialized care to adolescents and adults with DS, but would also be a reliable source of critically needed information on physical activity, diet, body composition, healthy aging, women's health (including sexual and reproductive health and early menopause), and post-school-age behavioral and psychological issues. Such centers would also provide caregiver support in the form of reliable information on research, evidence-based clinical practice, and availability of social services.
2. Fund focused clinical and pre-clinical workgroups to better understand comorbidities associated to DS, such as immunity/autoimmune issues, moyamoya disease, musculoskeletal dysfunction, cancer subtypes, ocular and other visual system disorders, obstructive sleep apnea, obesity, psychiatric comorbidities including regressive behaviors, and the molecular basis for the clinically observed protection from atherosclerotic disease.
3. Fund the expansion of current clinical care guidelines for adolescents and adults with DS.
4. Fund training programs for a new generation of clinicians and researchers (including, but not limited to, pediatricians, internists, family practitioners, basic and translational scientists) through doctoral and postdoctoral fellowships to create the workforce necessary to discover and translate new biomedical findings.
5. Fund the expansion of preclinical and clinical pharmacological research on approved drugs focused on DS. This research would involve both small safety and efficacy studies as well as pharmacokinetic and pharmacodynamics studies. Such research would address two unmet needs: (1) they would allow

us to find new uses for existing drugs for those with DS; and (2) they would determine whether widely-prescribed dosages of existing drugs are appropriate for patients with DS in the context of known organ dysfunctions, altered body fat distribution, and lower metabolic rate that are commonly associated with DS.
6. Promote research on intervention strategies based on non-pharmacological approaches, including, but not limited to technological approaches to stimulate brain function.
7. Promote research to explore specific characteristics of psychiatric disorders in DS in developmental age and the effectiveness of different treatments for these disturbances in children and adolescents with DS. We know, for example that DS is associated with major language delay: production is more impaired than comprehension, but great individual variability exists. The integration of contributions deriving from different research areas as cognitive neuroscience, behavioral neuroscience, and experimental neuropsychology could provide substantial insights for the identification of early predictors of language in individuals with DS and of focused interventions, moving toward personalized medicine for DS.
8. Continue the basic and clinical studies of Alzheimer's disease molecular and cellular mechanisms to identify biomarkers and fund pilot projects of potentially disease-modifying therapies for Alzheimer's disease in persons with DS.
9. Promote care procedures, research, professional training and cultural approaches on DS in low and middle-income countries (LMICs). Given that most studies of DS are performed in high-income countries with good resources, minimal data are available on the survival and treatment of children with DS from LMICs. The joint action by scientists and clinicians coming from different countries with different incomes, would allow the development of sustainable diagnostic protocols and early intervention procedures to be administered globally.

• **International meetings:** Preclinical committee submitted an application to SfN 2020 to host a Down Syndrome Social on behalf of T21RS and the application was approved by SfN Program Committee. As SfN2020 was cancelled because of the global Covid-19 pandemic, we plan to submit another application for a Down Syndrome Social for a future SfN conference.

• **Development of the modified ARRIVE guidelines specifically designed to facilitate research using mouse models of Down syndrome.** Related to that, the labs of our committee members, Drs Randall Roper and Mara Dierssen published a manuscript entitled "Behavioral phenotyping for Down syndrome" in "Current Protocols in Mouse Biology" (Vol., 10, Issue 3).

• **Our committee members presented at T21RS-hosted webinars on new development of animal model-based research on Down syndrome.**

• **Our committee explored better ways to identify sources of Down syndrome patient-derived iPS cells and fibroblasts and to facilitate the deposition and distribution of these cells at public domains to increase availability of cells to all researchers.** To be most useful to the research community, donor

clinical information should be attached to the cell lines, preferably using a mechanism that allows for the addition of future records from the same individual. A multi-site collection plan, including several cohorts characterized by longitudinal neuropsych or imaging methods should be established.

• **A manuscript entitled "Specific susceptibility to COVID-19 in adults with Down syndrome" has been prepared and submitted for possible publication in NeuroMolecular Medicine.** The preparation of this manuscript was led Dr. Eitan Okun and contributed by a significant number of our committee.

• **To promote the interactions between preclinical and clinical researchers,** we have planned the first meeting for March, 2021, which will be joined by the Preclinical Committee and Clinical Committees.

VI - Committee for Clinical Research

Clinical Adult Committee Members:

Chair of the committee:
Alberto Costa (USA)

Co-chair of the committee
Stephanie Sherman (USA)

Members:
Juan Fortea (Spain)
Tonnie Coppus (The Netherlands)
Benjamin Handen (USA)
Elizabeth Head (USA)
Sharon Krinsky-McHale (USA)
Andrew Nowalk (USA)
Huntington Potter (USA),
Michael Rafii (USA)
Anne-Shopie Revillat (France)
Wayne Silverman (USA)
Weihong Song (Canada)
Andre Strydom (UK)
Shahid Zaman (UK)

The T21RS Clinical Committee is a platform to encourage the development, discussion, and dissemination of translational research efforts across the T21 research community, families of individuals with Down syndrome and self-advocates, and clinicians serving patients with Down syndrome.

Initiatives and achievements in 2020

In 2020, we accomplished the following:

1. Together with the Clinical Child Developmental Subcommittee, several members of the Adult Clinical Committee used their expertise to provide input to **COVID-19 related projects** that were ongoing through the T21RS COVID Taskforce. This effort has already resulted in a publication in the Lancet e-journal *EClinicalMedicine* and is continuing through a new international survey on the COVID-19 vaccination of individuals with Down syndrome. In addition, Dr. Anne-Sophie Rebillat has contributed an article to the T21RS describing her experience treating patients with Down syndrome and COVID-19.

2. The Adult Clinical Committee has established a **workgroup to help brainstorm a program for a Joint Research Event with the DSMIG-USA**. This workgroup is comprised of the following Adult Clinical Committee members: Dr. Anne-Sophie Rebillat, Dr. Zaman Shahid, Dr. Ben Handen, and Dr. Huntington Potter. This Joint Research Event is now likely to take place in the spring of 2021 in a virtual meeting format. This effort should advance the goal of "working with Down syndrome organizations and clinician groups to ensure availability of high-quality evidence to support health of individuals with Down syndrome and guide treatment."

3. The Adult and Child Developmental Committees have planned a **joint meeting of the T21RS Preclinical and Clinical Committees**, which should advance the goal of "linking with other committees for combined responses to common issues." This joint meeting is scheduled to take place on March 23, 2021, and should help strengthen the relationship between the two committees and lead to a day-long research retreat in which various topics of common interest between clinical and preclinical researchers in the T21 research field will be discussed in depth.

Budget justification for Yr2021: request 1500 EUR
This budget will provide support to two virtual meetings: (1) The Joint Research Event with the DSMIG-USA; (2) A potential Research Retreat of the T21RS Preclinical and Clinical Committees.

Developmental Clinical Research Subcommittee Members

Chair of the subcommittee:
Stephanie Sherman (US)

Members:
Cécile Cieuta-Walti (CA; FR)
Floriana Costanzo (IT)
Jessica Hunter (US)
Julie Korenberg (US)
Silvia Sacco (FR)
Stephanie Santoro (US)
Brian Skotko (US)
Rafael de la Torre (ES)
Stefano Vicari (IT)

The goal of this subcommittee of the T21RS Clinical Committee is to increase our knowledge of the cognitive and behavioral trajectory of children and adolescents with Down syndrome (DS) and deepen our understanding of the effect of various comorbid disorders on these trajectories and on the quality of life.

Initiatives and achievements in 2020

In 2020, we accomplished the following:

1. Dr. Jessica Hunter, a committee member, led the effort to achieve our prioritized task of 2019 to **catalog existing DS cohorts** with respect to collected phenotype and genotype data. She developed a REDCap survey to do this and it was disseminated to the T21RS and the DS Medical Interest Group (DSMIG) memberships in 2019-2020. At this time, 22 cohorts have been described in the database. Parallel to this effort, NIH created a working group to also establish a database to catalog existing cohorts. Dr. Hunter provided our REDCap database as a foundation for this effort and the NIH working group modified and extended it.
2. The Committee has developed a **"use case" to show the value of using the existing cohorts for collaboration**. The focus will be on KBIT-2, an instrument widely used to assess cognitive level among children with DS. The goal will be to describe the distribution of scores (standardized and raw scores) across the ages and identify associated covariates. There were eight cohorts that include KBIT-2 data, totaling 789 cases. Currently, data from five of the eight cohorts (n=461 cases) have been centralized. Hurdles to obtain the other cohorts primarily relate to lack of resources (e.g., time or personnel available to pull the data). The goal for 2021 is to analyzed and publish the results from the use case.

3. The Committee also used its expertise to provide input to **COVID-19 related projects** that were ongoing through the T21RS COVID Taskforce. In addition, Drs. Floriana Costanzo and Stefano Vicari described their project to assess the psychopathological impact on children with DS due to the pandemic. Their goal was to identify other possible collaborators who had common goals. Based on this discussion, the T21RS COVID-19 Taskforce is now helping to organize this effort further.

4. Discussions were initiated to determine methods to **increase outreach to all people with Down syndrome to provide research opportunities**. An example of an approach was provided by Dr. Rafael de la Torre, which is in its design phase. This approach and others will be cataloged as a start to address this complex issue.

Budget justification for Yr2021: request 1500 EUR
Support a person to conduct the data management for the use case to promote the facilitation of collaborative research projects using the Existing Cohorts Database.

VIII- Communication Workgroup

Communication workgroup members:

Chair of the workgroup:

María Luz Montesinos (Spain) (until October 2020)
Michael Yaeger (USA) (since October 2020)

Members:

Claudia Cannavo (UK)
Lisi Flores (Canada) (since October 2020)
Sujay Ghosh (India) (since October 2020)
Eric Hamlett (USA)
James Hendrix (USA) (since October 2020)
Blandine Ponroy (Canada) (since October 2020)
Ilias Ziogas (Italy) (since October 2020)

1. We are in charge of producing a **monthly Newsletter**, which is distributed to the T21RS members who signed to receive it and among a list of interested persons who subscribed through our web site.

2. We **update the web site** with news, events and job offers when solicited.

3. Finally, we act as **Community Managers of the T21RS Twitter account**. We have presently 527 followers.

FINANCIAL REPORT

01-01-2020 – 31-12-2020

1. Treasury

T21RS is the first non-profit scientific society (*Dutch:* vereniging) for Down syndrome research. T21RS is officially established in Groningen (NL), and operates under Dutch law.

Official statutory address:	T21RS Groningen Office University Medical Center Groningen Hanzeplein 1 9713 GZ Groningen The Netherlands
RSIN identification number (NL):	853938283
KvK Chamber of Commerce number (NL):	60501162
Current treasurer (2016-2021):	Dr. A.D. (Alain) Dekker University Medical Center Groningen, The Netherlands
Past-treasurer (2014-2015):	Dr. A.M.W. (Tonnie) Coppus Radboud University Medical Center Nijmegen, The Netherlands
Operational currency:	Euro (€)
Number format:	Continental European Example: 40.000,25 *(forty thousand and twenty-five cents)*

2. Summary of 2020

Given the fact that the T21RS International Conference is organized every two years, 2020 can be considered a quiet off-year in-between the Barcelona conference (2019) and the California edition (originally scheduled in 2021). It was expected that 2020 would be a preparatory year for the T21RS International Conference 2021. Due to the COVID-19 crisis, however, it was decided to postpone the “live” meeting until 2022. Therefore, 2020 has been an even more quiet year in financial terms. Income in 2020 primarily concerned membership fees and annual support from Founding Members and Supporting members. Expenses primarily concerned operational costs and awards.

3. Revenues

Revenue in 2020 primarily consisted of 1) membership fees and 2) general financial support for the society by Founding and Supporting members.

1) Membership

T21RS distinguishes two types of membership: a) full membership for researchers and clinicians, and (b) associate membership for DS associations/foundations. A 50% reduced membership fee applies to individuals living and working in countries with low-, low-middle and upper-middle income economies (as defined by the Worldbank).

1a) Full member (for researchers and clinicians)

- Master/PhD student € 40,-
- Postdoctoral fellows € 80,-
- Academic staff members / clinicians € 100,-

1b) Associate member € 50,-

2) Founding members and Supporting members 2020

T21RS is very grateful to a number of non-profit organizations that financially support the continuation of the society and its aims. In 2020, this concerned:

- Fondation Jérome Lejeune (France): € 5000,- Founding Member
- Lumind-IDSC Foundation (USA): € 5000,- Founding Member
- Trisomy 21 France (France): € 5000,- Founding Member
- The Matthews Foundation (USA): € 2500,- Founding Member
- Down España (Spain): € 5000,- Supporting Member

Lumind-IDSC also coordinated a grant of € 8650,- for a COVID-19 & Down syndrome research project.

Revenue in 2020 primarily consisted of 1) membership fees and 2) general financial support for the society by Founding and Supporting members.

4. Expenses

Expenses primarily related to operational/running costs, including the development of the new website, website maintenance, banking fees and the technical secretariat of the society. Other expenses related to the T21RS Award for Scientific and Dissemination Events and the T21RS Thesis Award.

5. Profit and loss statement

This statement only provides an overview of income/expenses directly through the T21RS Bank Account.

Profit and Loss Statement

For the period from 01/01/2020 to 31/12/2020

Accrual basis

	31/12/2020
Income	
Financial support (founding/supporting members)	**22 500,00**
Financial support (specific project allocation)	**8 650,00**
Interest	**7,95**
Membership fees	**14 656,49**
Other	**477,00**
Total — Income	**46 291,44**
Less: Expenses	
DS-GO21 Project expenses	**235,80**
Operational costs	**14 524,14**
T21RS Event Awards	**3 000,00**
T21RS Thesis Awards	**2 000,00**
Total — Expenses	**19 759,94**
Net profit (loss)	**26 531,50**

6. Balance

Balance Sheet

As at 31/12/2020
Accrual basis

	31/12/2020
Assets	
Cash & cash equivalent	**327.866,69**
Net assets	**327.866,69**
Equity	
Retained earnings	**26.531,50**
Starting balance equity 01/01/2020	**301.335,19**
Total - Equity	**301.335,19**
Total equity	**327.866,69**

7. Conclusion

The year 2020 has been closed with a net profit of € 26.531,50 resulting in a positive balance of € 327.866,69.

8. Discussion and outlook

Due to the corona crisis, expenses in 2020 were less than expected given the fact that the preparation of the T21RS International Conference has been postponed. Instead of a “live” meeting in 2021, the meeting is postponed until 2022. The resulting net profit in 2020 will be used to further strengthen the financial reserve of the society and boost new initiatives in the upcoming years to fulfill the aims of the society. The financial buffer of the society is at a level that ensures continuation of the society, accounting for uncertainty of external financial support and potentially upcoming economically bad times.