

Lisbon MC-WG Meeting Minutes, 27-28 February, University of Lisbon, Institute of Molecular Medicine

MC Meeting

Quorum present - Participation of 2/3 of 27 participating countries, representing 19 countries.
Countries present at MC meeting in Lisbon: SE, FR, FI, HU, UK, NL, DE, DK, BE, PL, IT, GR, TR, IE, ES, NO, MK, BG, PT

Agenda is approved as well as the minutes of last meeting.

2 NNC have joined the Action (Observers: Russia and Ukraine)

3 new full members to the Action: Hungary, North Macedonia, Cyprus

1 IPC application pending (India)

STSM update: so far 3 STSM completed, one more approved.

Still available for this GP: 4.990€ for STSMs (2 more STSM) before the end of April.

Payment only comes after the mission is completed, through e-cost (Thomas Ritter comments).

Conference update: EVER meeting in Nice 2019, special interest session in congenital aniridia with several participants from ANIRIDIA-NET.

Grant management update: the more money we spend the more money we get, so spend more money! There is a change of grant holder manager, GP2: Ms Sabrina Weber, Sabrina.weber@uk-koeln.de

ITC update: We didn't have any ITC grants in GP1. Proposal from Sara: apply not only to eye research meetings, but also any other "broader field" congresses (stem cell meetings, etc).

Idea to foster participation in ITC grants: send emails to national societies of ITCs countries indicating the availability of grants. Maybe inform EU Cornea and ARVO organizers. Also a reminder email to all ANIRIDIA-NET participants informing about the grants.

Publications update: 2 thus far, 1 in revision ("Early phenotypic features of aniridia-associated keratopathy and association with PAX6 coding mutations ophthalmology-PAX6 mutational status" and "The spectrum of PAX6 mutations and genotype-phenotype correlations in the eye"). Other interesting publications on aniridia: "Aniridia With PAX6 Mutations and Narcolepsy", "Global and age-related neuroanatomical abnormalities in a Pax6-deficient mouse model of aniridia suggests a role for Pax6 in adult structural neuroplasticity".

Dissemination update: Website is up and running, costs for updates and maintenance covered until Nov-2020. The idea to produce a video to inform and raise awareness about aniridia has been approved.

Training Schools update: There are two planned schools: 3 day training on GMP manufacturing for ocular surface in Granada-September/October 2020 (J. Martínez); 3-4 day in Lugano, Barcelona/... (Vito Romano).

WG3 – Stefano Ferrari

- 30 people in the WG, a list presented
- 3 STSMs involving members of WG3 already in GP1
- Action: ask whether 16 – 20 March STSM (Bulgaria to Italy) should be postponed and for how long to still be in GP1
- 2-3 months STSM possible, very important and we should take more advantage of these
- Immunosuppression for allogenic CLET, when you take it away the graft fails
- Shortt et al. Daniels J, published in Stem Cells Transl Med that in aniridia, CLET grafts fail
- Could there be a better cultivation method?
- Discussion on allogeneic in general, that it has poor outcomes regardless of culture protocol or immunosuppression
- What is a standardized immunosuppression regime?
- Is the problem rejection or something else as well?
- CLET in aniridia, allogeneic – doesn't matter whether aniridia, even chemical burns have similar outcomes
- Mor: Need to discuss protocols for immune suppression
- Are we actually transplanting the stem cells? Or do the cells just stimulate host cells to reactivate the niche?
- A paper to be submitted out of an STSM between Maastricht and Veneto Eye Bank, can report this in our COST annual report
- STSM from Bulgaria to start soon
- Stefano presented the PRER review paper proposal and draft – it is not a standard review but an opinion by experts in the field

Daniel Aberdam – WG5

- Most WG5 members could not attend the meeting, 22 people in the WG
- EU Rare Grant 2020 application was written and submitted recently
- Writing a review on 'remaining open questions on aniridia pathophysiology', with L. Latta et al., will now distribute to other members to contribute
- STSM – Germany to NL, aims to understand differences between healthy and aniridia limbal cells, in terms of single-cell RNAseq (patient-derived cells)
- Healthy limbal cells from cadavers, aniridia limbal cells after surgery in Homburg
- Presented some results from the single-cell RNAseq analysis
- Can continue with a new STSM to follow-up on this work
- Daniel has a model in Paris, of PAX6 haploinsufficiency in corneal epithelial cells
- Repurposing of existing drugs for aniridia

Francisco Figueirido, UK

- LSCD is a major problem, 240 new cases/year in UK, orphan/rare disease
- LSCD management – tears, dry eye, epithelium, ocular surface unit, nerves and growth factors
- Phase II LSCD trial in UK, 23 patients, up to 7 years follow-up, no aniridia (only unilateral)
- CD200 maybe a better marker than p63 for LSCs

Juliana Martinez

- Andalusian Network for Advanced Therapies
- In ophthalmology, allogenic artificial cornea fibrin-agarose scaffold

- Presented results of transplantation in first 5 patients, 24 month follow-up

Thomas Ritter

- MSCs, immunomodulatory effect through secreted factors
- Allogeneic MSCs to modulate corneal graft rejection
- MSC trial in high-risk transplant patients to start soon, had MSC production problems
- TGF-beta stimulated MSCs give a profound therapeutic effect (rodent models)
- MSC-EVs – cell-free based therapy?
- Rat model of alkali burn on cornea, topical EV therapy vs PBS control, better epithelial healing and transparency after 1 week

Margarita Calonge

- Good results in allogeneic CLET, immunosuppression, only 1 case in 9 rejected
- Mycophenolate mofetil, cyclosporin, one other drug
- BM-derived MSCs – no need of immunosuppression
- Total LSCD model in rabbit, treated with MSCs adipose-derived on AM
- BM MSC randomized trial – GMP cell production
- Restoration of corneal epithelial phenotype, use IVCM to diagnose epi phenotype
- 1 aniridia patient, improved ocular surface after 1 year

Heli Skottman

- Use both hESC and hiPSC
- New population of stem cell populations in human limbus, evaluating in vitro and in vivo models

Sara Xapelli

- Neurogenesis – important for learning and memory, originate in brain
- Cannabinoid receptors involved in pain, food intake, learning memory, cognitive functions
- Vanilloid receptors – calcium channel
- Studying cannabinoid receptors CB1R and CB2R, BDNF – these modulate neurogenesis

WG2 – Vito Romano

- Update of GP1 goals, what has been done thus far
- Action items – follow up with EVICR.net to distribute the survey to their members

WG1 – Dominique Bremond-Gignac

- Guidelines update (should we call it a consensus statement?)
- AGREE II validation, six domains
- French guidelines have been published
- Group of experts: COST, AE, Geniris, ERN, etc.
- Presented draft – should call it a consensus paper now, as it cannot be a legally-binding 'guideline' which is tightly regulated in every member country
- Who wants to contribute, establish one editor per section (7 sections)
- Go through a Delphi System ?
- Maybe start with the existing draft

3rd MC and WG Meeting February 27th-28th
Faculdade de Medicina Universidade de Lisboa
Avenida Professor Egas Moniz, 1649-028 Lisboa, Portugal

Day 1 - Wednesday, February 27th - Working Groups 3, 4, 5; 3rd MC Meeting

9:15 Opening - Neil Lagali

- Logistics/Organization
- Attendance list signing
- National Rare Disease Day on Feb 29th

9:20 WG presentation Stefano Ferrari

- Collaboration between WGs 3+4+5
- Promoting/disseminating of the WG's work not going particularly well, groups are working together on improving that

9:30 WG 3 - Stefano Ferrari - "Stem cells and Regenerative Medicine"

- STSMs involving members of WG3:
 - Elena Daniele -> Stefano presents the purpose of this STSM, comparing the approaches regarding stem cell transplants in host and home institutions, hands on knowledge comparisons, looking for new approach, difference in cell cultures - detailed discussion regarding clinical trials in aniridia and allogenic limbal stem cell transplants failure, incl. aniridia and chemical burns, question of immunosuppression, between Neil, host institution, Stefano and other participants; Stefano underlines the importance of STSMs and its advantages
 - Arianne van Velthoven -> purpose of the STSM- how to properly culture limbal stem cells, hands on experience, Arianne can now begin her project and culture limbal stem cells on her own, paper in the works stemming from the STSM, question of funding through COST as open source publication
 - Yoana Kiselova -> delay in STSM because of the Coronavirus outbreak in Italy, flights to Italy cancelled in Bulgaria, question of postponing/ moving into GP2
- Publications of Review paper of the WG3 progress - submission into several periodicals

10:00 WG 5 - Daniel Aberdam - "Aniridia models for collaborative research"

- Presentation of the group members (22)
- Presentation of the WG5 own website
- STSM Lorenz Latta - presentation of the project aims, understanding of limbal stem cell biology as well as into pathophysiologic changes of the disease; presentation of the specific culturing procedure, presentation of the results, question of need for further STSM during GP2 based on the results
- Presentation of a further project/ proposal for European Joint Programme On Rare Diseases (ERA)
- Wish for more interaction within the group

10:15 WG 4 - Neil Lagali - "Transplantation, Inflammation and Immunity"

- retrospective studies as a first step for WG, attempt to build a data base of cases -> pan-european registry already existing, attempt to gain information from there, a short summary of the registry
- Bogumil informs about the possibility to access data in Poland,
- Margarita informs about the possibility to collect data in Spain,
- accessing data in Bulgaria might be challenging,
- no registry in Norway, but a possibility to collect data,
- Erika informs that there is no aniridia registry in Hungary, but there is a discussion of starting a registry in her home institute
- Mor proposes a tight collaboration in EU and bringing up the collection of data under one umbrella project/organization instead of singular data bases stemming from individual institutions
- Ivana proposes to involve medical professional organization/project to coordinate the collection of the data
- Summary -> individual participating countries should inquire about the possibility to access data bases or submit applications to access data to build a registry

10:30 coffee break

11:10 picture for the rare disease day February 29th for the action website

11:15 research presentations

11:15 - "Developments in Limbal stem cell transplantation" - Francisco Figueiredo

-> limbal stem cell deficiency, failure of corneal transplantations, LSCD management, ex vivo LSC research in Newcastle, Holocore Study, other emerging therapies for LSCD

11:40 - "Artificial cornea" Juliana Martinez Aienza

-> presentation of the Andalusian Network for the design & translation of advanced therapies, allogeneic Limbal cell + keratocytes treatments and presentation of the trial results for 5 patients with LSCD

11:50 - "Mesenchymal stromal cells and its secreted vesicles for treatment of ocular inflammation and injury" - Thomas Ritter

-> research topics in the home institution, allogeneic cells, prolongation of transplantation results, mechanisms in pre-sensitized corneal transplantation model

12:05 - "Mesenchymal stem cell transplantation for treatment of corneal failure due to limbal stem cell deficiency - congenital aniridia" - Margarita Calonge

-> tissue transplantation vs. cell transplantation, optimization of cell products, alternative stem cell sources -> limbal epithelial stem cells + mesenchymal stem cells (bone marrow extraction)

12:20 - "Modeling of limbal stem cell differentiation xxx" - Heli Skottman

-> intestinal limbal stem cells

12:35 - "Cannabinoids as xxx" - Sara Xapelli

-> cannabinoids in neurogenesis + use in PAX6

12:50 - "Bio energetic and metabolic regulation to improve adult neurogenesis in Ageing" - Susana Sola

-> diet influence and modulation of neurogenesis, TUDCA

13:10 Lunch Break

14:22 MC Meeting

14:22 Welcome to participants, tour-de-table, signing of the attendance sheet

14:30 Verification of the presence of two-thirds of the Participating COST Countries or, if applicable, a quorum

Present countries: Sweden, France, Finland, Hungary, Germany, England, Denmark, Belgium, Poland, Italy, Greece, Turkey, Ireland, Spain, Norway, Macedonia, Bulgaria, Portugal, The Netherlands

14:30 Adoption of agenda

14:32 Approval of minutes and matters arising from last meeting

14:35 Update from the Action Chair

- Status of Action - Neil Lagali -> start and end dates of Action, participating COST countries, participating NNC/ IPC institutions and Specific Organizations
- Short Term Scientific Missions (STSM): review of completed reports and new applications -> Thomas Ritter - three approved, one pending because of the Corona virus - host institution in northern Italy

14:43 Update from the Grant Holder: Action budget status -> Claus Cursiefen

14:49 Update from the COST Association, if a representative is present - no representatives present

14:50 Monitoring of the Action

- ITC update -> Sara Xapelli
- Update dissemination, website, logo, social media LinkedIn, Twitter -> Juliana Martinez Atienza
 - Suggestion for a Video supporting dissemination of the Action 18116
 - MC core group votes yes for a video in the next GP
- Publications Update -> Neil Lagali

15:23 Action Budget Planning, revised budget and GP1/GP2 budget planning

- suggestion of an extra/separate WG meeting
- Training schools budget -> suggestions to both increase and decrease the budget
- question of doing a webinar for clinical physicians
- Question of looking for trainers for a video webinar

15:33 Implementation of COST policies on:

- Promotion of gender balance and Early Career Investigators (ECI) -> discussion and underlining of importance of ECI
- Inclusiveness and Excellence -> discussion about the ITC - none in GP 1, reaching out to ITC countries to inform about the possibility of ITC in GP2 within their countries, possibility for early ITC for ARVO conference

15:40 coffee break

16:15 Post coffee break - another discussion about ECI and ITC and ways to spread the word

16: 30 Training schools proposals

16:38 Location and date of next meeting - presentation by Neil Lagali, Christina Grupcheva not present

- Varna, Bulgaria - difficult access, free venue
- Sofia, Bulgaria - yes when in the city center

16:50 Scientific planning

- Scientific strategy (MoU objectives, GP Goals, WG tasks and deliverables, WGs 1-6)
 - aniridia referral centers, compiling a list of aniridia treating institutes and their willingness to participate
 - question of how to go about building/ mapping an aniridia centers network which support the CA18116
- Long-term planning (including anticipated locations and dates of future activities) - training school possible locations: Liverpool, Barcelona, Milan, Lugano

- Dissemination planning

17:09 Requests to join the Action from:

- COST countries -> no new requests (after meeting: Croatia requests to join Action)
- Institutions in Near Neighbouring Countries, International Partner Countries, and/or Specific Organisations: EU agencies, European RTD Organisation, International Organisations -> no new requests

17:10 Summary of MC decisions

17:12 Closing

Day 2 - Thursday, February 28th - Working Groups 1, 2, 6 (clinical)

09:06 WG 2 - Vito Romano - "Clinic and Cohort studies"

- Goals for GP1:
 - List of referral centers for aniridia in each country and possible cohorts
 - List of proposals for possible prospective and retrospective studies
 - List of protocols used for biobanking in different labs
- Presentation of centers and countries the WG is in contact with
- Discussion about how to access new data from biobanks, Mor suggest narrowing down which data is of importance and how to define and compile it
- Dominique informs about biobanks in France and the Rare diseases organization (ERA)

9:28 WG 1 - Dominique Bremond Gignac - "Clinical practice guidelines for RD"

- Aims: provide easy access to relevant information for management of rare diseases + Assist physicians
- Presentation of the methods - grading system for evaluating papers and publications, integration of different groups of experts
- Goal is to publish the guidelines
- Presentation of the guidelines draft - defining of specific terms, discussion of regulations regarding the legal side of the guidelines
- Discussion of the legal connotation of the word "guidelines" which is strongly bound to official health system and usually used by and coming from health authorities
- Proposition to change "guidelines" to "consensus" or "recommendations"
- Estimation of the length of the consensus - approx. 20-25 pages
- Suggestion to refer to the existing French and Spanish guidelines

10:03 WG 6 - Christina Grupcheva not present, Neil is moderating the discussion - "Patient-driven research - Questionnaire"

- summary by Ivana: Max 40 questions, easy to answer, easy to understand

- Who is the target audience, which specific information should serve which specific purpose?
- Suggestion to engage European Patient Associations in order to receive feedback on the questionnaire
- Should the questionnaire follow the FDA guidelines? - Francisco alerts to a problem with terminology -> "questionnaire" suggests a clinical research -> suggestion to change the term to "survey"
- Requirement to receive ethical approval for the survey in light of future publication
- Presentation of the survey draft by Ivana: questions including medical history, surgeries, eye surgeries, family anamnesis, medication, prescription-free medication use, social history, social difficulties

10:30 coffee break

11:05 individual WG discussions

12:00 lunch break

13:30 Closing