Report of the short-term visit
ERN Exchange Programme 2021-2022

ERN ReCONNET

Name of the participant	Karelle Bénistan – Caroline Michot
Healthcare provider where the participant is employed	AP-HP (Assistance Publique – Hôpitaux de Paris)
Name of the Healthcare provider and Head of the Unit hosting the exchange visit Address Name of the Head of the Unit	Ghent University Hospital, Center for Medical Genetics Corneel Heymanslaan 10, 9000 Ghent, Belgium Head of the Unit: Pr Fransiska Malfait
Start date of the exchange visit	16.01.2023
End date of the exchange visit	20.01.2023

1. **Please introduce your position/employment (MD, HAP, patient, other) and years of practice of your profession:**

Karelle Bénistan, MD, head of the French Reference Center for non vascular Ehlers-Danlos syndromes (adult) – position since 20 years.
Caroline Michot, MD, French Reference Center for non vascular Ehlers-Danlos syndromes (paediatric) – position since 4 years.

2. **The objectives of the exchange visit were:**

The objectives of the exchange visit were to share organisational knowledge, clinical knowledge and good practices on Ehlers-Danlos syndromes (EDS) expertise and management. We expected from this exchange program the chance to compare our organisation of patients' care, our clinical experience in diagnosis and our patients' management.

To achieve these objectives, the planned activities were:

- Visiting the inpatient clinic (to see organisation, appointment management, patient's care pathway)
- Meeting all the different healthcare providers (different specialization),
- Sharing clinical experience with patient's care
- Sharing difficulties about EDS management
- Sharing good practices
- Discuss about EDS and HSD actualities

3. Please describe the activities performed during your exchange visit:

1st day: welcome meeting with the Pr Fransiska Malfait in her office in the medical genetic unit and overview of the timetable for the week of visit.

Meeting with Pr Sofie Symoens, head of the routine laboratory of molecular biology. We had the chance to visit the whole lab with her, which allows us to benefit from her explainations and to share our experiences in genetic testing / molecular aspects regarding Ehlers-Danlos (EDS patients). We have also discussed the limits of these molecular tests and the need to reinforce the possibility of functional testings. This 1st contact supports the importance of the relation between clinicians and expert molecular biologist.

2nd day: meeting with the research team, including the fundamental researchers and the clinical research team (especially the physiotherapists). We have had the great opportunity to attend the presentation of all the members of the research team, who each develops their research thematics, main results and perspectives of work. This has raised many ideas of future collaborations.
The presentations included: Dr Delfien Syx on the pain testing in mouse models for EDS, Dr Marlies Colman on clinical pain testing in cEDS patients, Lies Rombaut and Inge De Wandele (physiotherapists) on clinical studies in hereditary connective tissue disorders.
In the afternoon, we have had a long discussion/exchange session with Inge De Wandele on the organization of the patients' pathway in the unit and after the expertise in the unit.
We have also attended the meeting of the ERN ReCONNET group on classical EDS.

3rd day: one-on-one discussions with the PhD students who work in the diverse universitary research units related to hereditary connective tissue disorders:

- Michiel Vanhooydonck from the Bert Callewaert laboratory on the development and phenotyping of a quadruple KO of Smad3a/b and Smad6a/b zebrafish model of thoracic aortic dissection.
- Tamara Jarayseh from the Pr Paul Coucke laboratory on the development and phenotyping of a Tapt1 zebrafish model. Indeed, some humans with *TAPT1* mutations have bone fragility.
- This PhD student also works on the research of modifier genes in osteogenesis imperfecta (OI), using diverse OI zebrafish models.
- Sophie Debaenst from the Pr Paul Coucke laboratory on the proteomic analysis of the zebrafish vertebral column for different mutant of OI, in order to search for a biomarker able to predict the severity of OI.

All these zebrafish models will be great tools to study both physiopathology and to assess pharmaceutical compound efficiency.
After what, we have had a meeting with Pr Paul Coucke, head of one of the research laboratory and of the zebrafish facility of the Ghent university. We have had the chance to visit the whole building of research labs with him, which allow us to benefit from his explanations and to share fundamental data about connective tissues disorders. We had the chance to discuss very recent and not published works on the assessment of the physiopathology of these diseases, which is of great importance as it can raise hypothesis for future treatments. It will give us the chance of future research collaborations.
In the afternoon, we have had an informal discussion with Prof. Fransiska Malfait to discuss patients' care organization and pathways, ERN program, research projects (clinical and fundamental), EDS society program.

4th day: clinics with Dr Lies Rombaut, specialized physiotherapist in the unit of Prof. Fransiska Malfait. After that, we have attended clinics with one of the trainees of Prof. Fransiska Malfait. This

has given us the opportunity to exchange about the important points of the medical history to collect and mainly on the proper physical exam for 1st clinic and for follow-up.
Inge De Wandele, other specialized physiotherapist in the unit, has also made a physical examination for joint laxity on us, which has further explained the proper physical examination. She has also reviewed with us the headlines of management of Ehlers-Danlos (EDS) patients for physiotherapists.
In the afternoon, we have had one-on-one discussions with the PhD students who work in the diverse universitary research units related to connective tissue disorders:

- Karo De Rycke and Marina Horvath, from the Julie De Baker laboratory on the use of zebrafish as a tool to further assess the physiopatholgy of the cardiovascular abnormalities in fibrillinopathies and to develop a high-throughput screen of therapeutic drugs.
- Lisa Dangreau, from the Julie De Baker laboratory on the use of a zebrafish model of pseudoxanthoma elasticum to contribute to novel physiopathological insights and therapeutic strategies in ectopic mineralization.

All these zebrafish models will be great tools to study both physiopathology and to assess pharmaceutical compound efficiency.
Thereafter we have attended the ERN ReCONNET Board of Network meeting by visio.

5th day: goodbye to the team and last informal discussion with Prof. Fansiska Malfait.

4. Please describe below what you have learned and which new information/novelties you got during the exchange visit:

Clinical aspects for the Ehlers-Danlos (EDS) patients:

*Overview of the organization of the clinical unit on EDS in the medical genetics Unit: secretary, waiting room, examination room, 1st time clinics, follow-up clinics,… The department is doing a triage of the patients based on a questionnaire. The patients fulfilling some criteria really orientating towards a connective tissue disorder are seen by senior doctors and the others ones have an 1st appointment with a trainee, before to be seen by a senior doctor.
Exchange on the booklets of informations about EDS and HSD delivered to the patients (confronting to the one used in our center).

*Review of the clinical examination in case of suspicion of an EDS syndrome and deep functional assessment by physiotherapists.

*Discussion about what indications should lead to the offering of genetic tests (clinical criteria).

Molecular biology:

*Generalities and global presentation of a molecular biology facility.
Review of the important challenges in the organization of the workflow for a molecular biology laboratory, that is also in charge of PND, PGD, targeted panels on other different groups of diseases.

*Confirmation of the imperative need of common meetings between molecular biologists and clinicians for the classification of the identified variants with next generation sequencing technics.

*Importance of the functional tests to accurately classify the variants. The biochemical analysis (based on radioactivity assay) of collagen molecules developed since many years by the Ghent team is of very great interest for this.

*Existence of important technical difficulties to assess *TNXB* variants, due to the existing pseudogene, leading the Ghent team to stop to investigate this gene by targeted sequencing.

Clinical and Fundamental researchs:

*Opportunity to learn and to exchange on the most recent findings of the researchers on the EDS topics, both on patients and on animal models. The details of what we have learned will not be described as many data are not published to date.

The presentations concerned:

- Preclinical pain research in EDS with the current findings in mice. Actually the pain is a very predominant manifestation of EDS and the scientific question of the team about how the defect in extracellular matrix (ECM) can drive chronic pain in the EDS patients is of very great interest.
- Experimental pain assessment in classical EDS. This presentation has given us the opportunity to exchange on the actual question about the link between EDS and small fiber neuropathies and dysautonomia.
- "Follow You": multicenter investigation on musculoskeletal complains with a large battery of tests. This presentation was very interesting to discuss the most proper functional assessment to offer to the patients, in the perspective not only of clinical follow-up, but also for research basis.

The team is really involved in such specific evaluation and has already published studies, that we had the opportunity to discuss with them. We have learnt the importance of the assessment if the daily activity of the patients, in order to prevent deconditioning.

-Hypermobile shoulder. This presentation was very interesting and we have learnt many things on the normal and pathological movements of the shoulder, on the deep and precise assessment of this joint dysfunction and on the 3D scapular kinematics (very precise videorecording of shoulder movement). The results of these clinical studies show very important and direct applications for the rehabilitation of patients with shoulder instability.

*Opportunity to learn and to exchange on the most recent findings of the researchers on the hereditary connective tissue disorders (HCTD) topics, both on patients and on animal models (Cf section 3 and the lists of the one-on-one discussions with the PhD students).

5. Please describe below how you plan to implement what you have learned in your Healthcare provider/clinic/practice:

Clinical aspects for the Ehlers-Danlos (EDS) patients:

-We will think about modifying the organization of 1st clinics in our pediatric center (with the use of a questionnaire to see rapidly patients with criteria supporting a HCTD, and propose a teleconsultation as a screen for the others).

-We will work about our communication tools dedicated to patients (improve our booklet and create new ones more orientated towards the physiotherapy).

-We will try to work on a common database through the ERN network.

Molecular biology:

-We will continue to regularly discuss with our colleagues of molecular biology on the identified variants in our patients, as the visit has confirmed to us the importance of such meetings.

-We will search for a biochemistry department, if possible in our organization, to try set up biochemical testing of collagen molecules in order to improve the classification of the variants.

Clinical and Fundamental research:
We are thankful for the opportunity to meet diverse research teams on the HCTD topics and we will further keep in touch to develop common projects and collaborations.

6. Would you visit in the future the same center or another ERN centre for update/new topics?

This program was so interesting on a clinical and research point of view that we would like to repeat this experience, if it is possible.

7. Would you recommend the Exchange Programme to your colleagues? If yes, why?

Yes. As already mentionned, this week was a great opportunity on many aspects, so that it is really important to offer it to other teams. It will allow to really create a network of specialists of rare diseases, as it facilitates the relationships quite better than visioconference and as it will probably give rise to future collaborations.