

Fellowship Project Award: Clinical Training and Project Entitled ‘*In Vivo* Assessment of Bone Microarchitecture Using HR-pQCT in Hemophilia Patients’



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During my hematology residency, I discovered bone and joint health are important factors impacting morbidity and quality of life in hemophilia patients.

Osteoporosis in hemophilia patients is an emerging concern. I initiated a project investigating the prevalence of low bone mineral density (BMD) and characterization of bone mineral loss in severe hemophilia patients using novel 3D imaging of bone microarchitecture by high resolution peripheral quantitative computed tomography (HR-pQCT).

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My goal is to become a clinician researcher and leader in the management of acquired and congenital bleeding disorders with specific expertise in bone and joint health and other age-related changes in hemophilia patients. I plan to achieve this by completing two years of hemostasis training under the mentorship of Dr Man-Chiu Poon. The training experience will focus on development of expertise in the comprehensive management of patients with congenital and acquired bleeding disorders with a curriculum tailored to my interest in bone and joint health, and age-related changes in hemophilia patients.

Research:

1. Complete project investigating bone and joint health in hemophilia patients using HR-pQCT.
2. Collaborative meetings with Drs Steven Boyd (basic scientist/investigator for Bone Imaging Laboratory), and Greg Kline (endocrinologist) will help my understanding of structural bone changes.
3. Establish linkage with subspecialties such as endocrinology, orthopedics, rehabilitation medicine, and physiotherapy for potential collaborative projects/guidelines specific to the bone and joint health of hemophilia/bleeding disorder patients.

Clinical experience:

1. Attendance at biweekly adult hemophilia/bleeding disorders clinics alternating with biweekly pediatric hemophilia/bleeding disorders clinic. The adult comprehensive care clinic cares for approximately 420 patients, while the pediatric comprehensive care clinic cares for approximately 90 patients
2. Regular on-call duty for hemophilia patients and inpatient hemophilia/hemostatic disorders consultations.
3. Visit other centres of hemostasis excellence nationally and internationally to obtain clinical experience and establish collaborative interests with other hemophilia treatment centres.
4. Regular meetings with Dr Poon to discuss clinical cases and hemostasis topics. These meetings will provide opportunities to assist in managing difficult hemostasis cases and to ensure a representative curriculum of hemostasis topics are covered. We also have a quarterly city-wide hemophilia clinic journal club.

Academic responsibilities:

1. Participate in formal and informal hemostasis teaching of medical students, residents and fellows.
2. Educate other healthcare providers (adult hematologists, surgeons, emergency physicians, nurses, and physiotherapists) about the appropriate management of bleeding disorders. Specific focus on hemostasis and thrombosis issues of surgical and orthopedic procedures in bleeding disorder patients.

Laboratory interpretation:

1. Attend weekly formal hemostasis and molecular hematology laboratory interpretation sessions with Drs Poon and Xiu Jiang (hematopathologist)
2. Evaluate the role of new modalities in global hemostasis testing in diagnosis and monitoring of congenital and acquired bleeding disorders.

Early Career Investigator Award: Functional Assessment of Hemophilic Ankle Arthropathy in Children



Dr Sebastien Lobet,
University Clinic St-Luc, Brussels, Belgium



Hemophilia is characterized by recurrent joint bleeding episodes, leading to irreversible chronic arthropathy. Advances in replacement therapy have resulted in reduced bleeding frequency and preservation of almost clinically normal joints in children with hemophilia.

However, the ankle joint seems to be an exception to that rule since children with hemophilia still exhibit onset of ankle arthropathy despite regular prophylaxis administration of coagulation factor concentrates. As a consequence the ankle is now the paramount joint affected in patients under 20 years of age suffering from severe hemophilia. The reasons for this reluctant bleeding pattern affecting the ankles are still not understood and should be investigated.

Musculoskeletal outcomes of hemophilic arthropathy have been assessed using clinical and radiological assessment methods. However, as these scores are based on the status of individual joints, they do not integrate the inter-related impact of multiple-joint arthropathy on musculoskeletal function. Furthermore, these scores are generally assessed in a supine position and do not integrate the pain induced by a weight-bearing activity.

In this context, three-dimensional gait analysis (3DGA) allows the objective quantification of motion in patients with hemophilia. It consists of simultaneous analysis of joint kinematic (modelling of joint active movements), kinetic (study of the force interactions of the foot with the ground) and metabolic measurements (calculation of energy consumption) during walking.

I started a PhD thesis in 2008 at the Catholic University of Louvain with the research topic the functional assessment of hemophilic arthropathy by 3DGA. During the past 4 years of combined research and clinical work, I have accumulated data showing that 3DGA is a reproducible

and powerful tool to assess abnormal gait patterns and the effects of disease progression in adult patients with hemophilia but also the impact of conservative orthopedic treatment in patients suffering of ankle arthropathy.

With respect to the pediatric population, preliminary data from our group suggest that specific gait variables are impaired in clinically asymptomatic children with previous history of joint bleeds. In a second project, our observations of alterations of the rheological properties of muscles in children with hemophilia support the hypothesis that despite intensive replacement treatment,

subclinical changes may affect not only the joint itself but also the surrounding soft tissues.

In this context, development of sensitive assessment tools appears critical to evaluate the integrity of not only articular but also extra-articular structures in patients with hemophilia. To further complement this research work, we intend to conduct an ambitious multicentric study to better understand the biomechanical consequences and adaptations of ankle

arthropathy in children. This project aims to explore several aspects of ankle function (visco-elastic properties of muscles as well as motion of the small joints of the foot) that have never been explored before. We also intend to compare this functional assessment with a thorough radiological evaluation by magnetic resonance imaging and ultrasound.

This project will be conducted in the frame of a post-doctoral fellowship at the Faculty of Human Movement Sciences of the Katholiek University of Leuven, Belgium.

Children with hemophilia still exhibit onset of ankle arthropathy despite regular prophylaxis

Special Project Award: Induction of Tolerance to FVIII by *In Vivo* Antigen Delivery to Immature DCs



Dr Neil Josephson,
Puget Sound Blood Center, Seattle, WA, USA



The greatest challenge to hemophilia care in the developed world is to improve treatments for individuals who develop high titer anti-factor VIII (FVIII) inhibitory antibodies.

Unfortunately, little progress has been made in our ability to eradicate inhibitors since the first immune tolerance induction (ITI) protocols were introduced over 30 years ago. These regimens, which rely on frequent infusions of high doses of FVIII, fail in a significant percentage of poor prognosis individuals; and even when successful ITI can take years to be effective and is prohibitively expensive. Therefore, new approaches for tolerizing hemophilia A patients with inhibitors are urgently needed.

Our group hypothesized that tolerance to FVIII could be generated more efficiently and reliably by employing approaches of antigen delivery that are inherently more tolerogenic than intravenous infusion of naked protein. To test this hypothesis we developed methods to promote FVIII antigen processing and presentation by immature dendritic cells (DCs) in hemophilia A mice. Our published results showed that this strategy was effective, even in animals with pre-formed immune responses against FVIII. However, the clinical feasibility of the methods we evaluated may be significantly limited because they require genetic modification and *ex vivo* culture of primary cells. The approach for delivering FVIII antigen to immature DCs proposed in this application avoids all *ex vivo* cell manipulation.

DEC-205 is an endocytic receptor expressed at high levels on immature DCs. Other groups have demonstrated tolerance induction to foreign antigens linked to antibodies (Abs) specific for DEC-205. Therefore, we hypothesize that *in vivo* delivery of anti-DEC-205 Abs linked to immunogenic domains of FVIII will induce tolerance

to FVIII. Because almost all of the antigenic epitopes responsible for inhibitor formation are contained within the FVIII A2 and C2 domains, our initial approach will be to generate and test fusion proteins that link these regions of FVIII to the Fc portion of an anti-DEC-205 Ab. We will evaluate efficacy of fusion Abs infused into naïve hemophilic mice prior to immunization with FVIII and in mice that have pre-formed high titer inhibitors. To investigate the mechanisms of immune suppression we will perform cytokine profiling of T cells in treated and control mice and adoptive transfer studies of specific T cell populations into naïve secondary recipients just prior to immunizing them with FVIII.

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Our strategy for FVIII tolerance induction requires that treated individuals have an adequate reservoir of immature DCs to process and present the delivered antigens. Environmental cues influence the activation and maturation state of DCs and there is abundant clinical data demonstrating a role for inflammation in promoting inhibitor formation.

There is also emerging evidence showing that inhibition of DC activation can improve tolerance induction to foreign antigens. Therefore, the second part of our studies will evaluate whether pharmacological inhibitors of DC activation improve the efficacy of tolerance induction by anti-DEC-205 fusion Abs. Our eventual goal is to develop a clinical treatment for inducing tolerance to FVIII that is more efficient and reliable than current ITI protocols.

Caregiver Award: Hemophilia Wellbeing Index: An International Survey



Prof Eduardo Remor
Autonomous University of Madrid, Spain



This project is a proposal for an International Survey on Hemophilia Wellbeing with the follow aims:

- Understand the wellbeing status of the hemophilia population (over 16 years old)
- Establish a wellbeing index baseline for hemophilia patients
- Create reference norms for future cross-cultural studies
- Achieve insights need to improve wellbeing and healthcare satisfaction.

The methodology to access this information will include a brief internet website survey with worldwide access in different languages (English, Spanish and Portuguese, initially). This method of collecting data carries many advantages. It is fast, low cost and allows access to diverse and worldwide populations. The survey will be built with new tools for structuring surveys and managing large datasets. All the procedures regarding ethical standards, research conduction and data safety will be attended.

To gather this valuable information the survey will include as the main survey outcome the Hemophilia Well Being Index (HWBI). The HWBI is a brief multilanguage psychometric sound patient-reported outcome, developed from an international basis; specifically for the assessment of subjective well-being of patients with hemophilia. The instrument has already been psychometrically tested in an international sample of 342 patients with hemophilia from different countries: Argentina, Brazil, Chile, Spain, Nicaragua, Panama, Uruguay and Venezuela.

The measure has shown excellent psychometric properties, including reliability and reproducibility, with evidence for construct validity in terms of concurrent (SF-

36, EQ-5D) and discriminant (clinical hemophilia markers) validity. The instrument is available in Spanish; Portuguese and English language versions, and the psychometric study is current in press (Remor, E. International Journal of Behavior Medicine, Springer).

The scope of the project is the worldwide hemophilia population (other coagulation disorders may potentially be included), who are able to read and understand English, Spanish and Portuguese. Addition of other languages to the survey is potentially feasible, due to the shortness of the survey. Efforts will be made to achieve at least 1000 responses.

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The originality and novelty of this project consists in the focus on subjective wellbeing. Until now, important knowledge has been accumulated but restricted to quality of life and the impact of hemophilia health status and markers on quality of life outcomes. Quality of life and

wellbeing are related concepts but not the same. Each one explains unique and different variances in health-related outcomes. This new focus on wellbeing status is potentially broader and it will be the first time that wellbeing status is empirically measured in hemophilia population; reference norms will be established, and insight about the domains linked to the lack of wellbeing will be identified. These results may help to draw guidelines for its improvement.

This project will also support the network within hemophilia centers and local hemophilia organization worldwide already established in past years through international multidisciplinary efforts. This project is endorsed by both the university where the applicant is a faculty member and the Iberoheemofilia network website (www.iberoheemofilia.net) established in July 2000.