Doctorate in Health and Technology, University of Bologna, Italy
Positions open to start November 2019

GENERAL INFORMATION

About this doctorate program

This PhD program has a duration of 3 years. The Doctorate in Health and Technology is an interdisciplinary program, where each PhD student has a supervisor from the technical area (engineering, chemistry etc) and one from the clinical or biological area.
https://www.unibo.it/en/teaching/phd/2019-2020/health-and-technologies
The objective of the interdepartmental Doctoral Programme in Health Sciences and Technologies is to train the next generation of leaders in industrial, clinical, and academic research. Our goal is to develop an organic research programme at the interface between engineering and medicine, which is inspired by the quantitative and integrative approach of physical sciences, and by the latest development in biomedical research, drive the development and clinical translation of disruptive health technologies.
The doctoral training programme will prepare students in conducting research which:

- Extend the comprehension of how human physiology and pathology work in term of physical and chemical mechanisms, and how these mechanisms respond when perturbed by external factors such as therapies, changes in life style, and environmental factors.
- Develop new technologies that by leveraging on this mechanistic understanding pursue a wide spectrum of applications relevant to human health, including prevention, diagnosis, prognosis, treatment, and rehabilitation.

How to apply:

Formal application must be submitted through the UniBo portal:
https://www.unibo.it/en/teaching/phd/information-enrolling-phd-programme/how-to-apply-phd-programme
Each student, depending on their degree, will be able to apply only for a sub-set of projects among those advertised for this PhD program; among them each student will be allowed to select three projects, and name them in order of preference; however, in some cases it might not be possible to satisfy all requests, and some students might be offered a research project different from those they selected.
The full call is available online:
https://www.unibo.it/en/teaching/phd/2019-2020/attachments/35th-cycle-call-for-application/@@download/file/35thCycle_CallForApplications.pdf

Profile of the candidate

We are looking for a highly motivated young researchers with a Master degree (or equivalent) in Mechanical Engineering, Biomedical Engineering, Physics, Material Science, or related disciplines, willing to study and do research at the leading edge of biomechanical engineering, in close contact with a clinical environment.
Individuals expecting to obtain their Master degree before 31 October 2019 can conditionally apply.

In order to be admitted to the selection, a student needs a five-year higher education degree, which includes at least one module for each of the following disciplines: mathematics, physics, computer science, biology, physiology, and anatomy.
Candidates must be fluent in English as it will be the language used to interact with supervisors and colleagues during the project, and to interact with partners. Although some understanding of Italian may be useful for daily living, this is not a mandatory requirement. Communication and teamworking skills are required in our international team.

Deadline:

Applications must be submitted through the Unibo portal by 15 May 2019, 13:00 Italian time (UTC +1)

Salary: 19 367 € per year before taxes.

More information:

For informal discussions please contact Professor Luca Cristofolini luca.cristofolini@unibo.it

PhD PROJECT #1:
Electrospun scaffolds for the regeneration of tendons and ligaments

Summary

Degenerative or traumatic lesions of tendons and ligaments are difficult to repair. Post-operative failures affect between 15% and 40% of cases (depending on initial indications). We developed a prototype of an electrospun scaffold replicating the hierarchical morphology and the mechanical properties of tendons and ligaments. This PhD project will further develop the prototype by increasing the bioactivity and enhance the integration of the constituent material with the surrounding tissues, and will bring this technical solution towards clinical application.

The following aspects will be investigated: optimization of the polymeric biomaterial and its functionalization to improve cell adhesion, recruiting and differentiation and to prevent inflammatory response, optimal technique for effective sterilization; means of surgical attachment to the host tissue.

The collaboration between the technical area (engineering and chemistry) with the clinical counterpart (orthopaedic surgery) will be a key point of this project.

Objectives of this project

The overall objective of this PhD project to bring a promising electrospun scaffold for the repair of tendons and ligaments from the current state of technical development (between TRL3 and 4) towards clinical application. The following specific objectives will be tackled:

- Optimization of the sterilization technique to ensure effective sterilization of the nanofibrous structure and preservation of the desired mechanical properties and biocompatibility properties
- Optimization of the surgical technique to attach the scaffold to the host bone, and/or the residual tendon/ligament, in collaboration with the orthopaedic surgeons to ensure adequate mechanical strength and lack of stress concentrations and surgical practicability
- Increasing scaffold bioactivity and integration in the surrounding tissues to prevent adverse response of host tissue and avoid inflammatory reactions.

This project covers some basic science (interaction between nanofibrous scaffold and host tissue), it focuses on technological development (implementing and testing different solutions on the scaffold) and has clinical relevance (develop the best solution for implantation).

Rationale and scientific background

The fact that different orthopaedic surgeons chose different strategies for the repair of damaged tendons and ligaments is an indicator that there is no consolidated and satisfactory technique. In fact, the post-operative outcome is far from satisfactory. Surgical treatments fail in 15% and 40% of cases (depending on the initial indications). Artificial implants fail mostly because of biomechanical mismatch (inadequate stiffness, limited strength etc). Xenografts often do not get properly integrated or even create rejection. Allografts offer better similarity, but are limited due to cost and availability. Autografts solve some of the problems above, but are associated with morbidity of the donor site and are limited in stock.

Bioresorbable scaffolds are a very promising option, as they are not limited in availability [1]. We recently developed a technique to manufacture electrospun scaffolds that replicate the morphology and the mechanical properties of the human natural tendons and ligaments [2,3].

To bring this project towards an animal trial and a future clinical application, there are some clear points that need to be fine-tuned. Specifically, as the key to success of such devices is integration with the host tissues, this project aims to understand how to prevent such common clinical complications, and to develop the extremities and the interfaces so as to grant success in case of implantation.

References

[1] Sensini, A., and Cristofolini, L., 2018, "Biofabrication of electrospun scaffolds for the regeneration of tendons and ligaments," MDPI Materials, 11(10-1963), pp. 1-43.

[2] Sensini, A., Gualandi, C., Cristofolini, L., Tozzi, G., Dicarlo, M., Teti, G., Mattioli-Belmonte, M., and Focarete, M. L., 2017, "Biofabrication of bundles of poly(lactic acid)-collagen blends mimicking the fascicles of the human Achille tendon," Biofabrication, 9(1), p. 015025.

[3] Sensini, A., Gualandi, C., Zucchelli, A., Boyle, L. A., Kao, A. P., Reilly, G. C., Tozzi, G., Cristofolini, L., and Focarete, M. L., 2018, "Tendon Fascicle-Inspired Nanofibrous Scaffold of Polylactic acid/Collagen with Enhanced 3D-Structure and Biomechanical Properties," Scientific Reports, 8(1(17167)), pp. 1-15.

Research project

The focus of the activities will be on optimizing and testing electrospun hierarchical scaffolds made of blends of natural (collagen) and synthetic (PLLA) polymers so as to ensure that they become suitable for implantation. This PhD candidate will spend 30-40% of his/her time in the biomechanical laboratory of prof. Cristofolini, 30-40% of the time in the Chemistry lab of prof. Focarete and the remaining 20-40% of in the clinical settlement, in collaboration with Rizzoli Orthopaedic Institute. Furthermore, an international secondment of 2+3 months at the University of Portsmouth is planned to complement the preparation of this candidate providing high-resolution imaging and cell culture, whereas an international secondment of 2+3 months at Erlangen University is planned to complement the preparation of this candidate on scaffold functionalization and biomineralization.

Activity 1 – CLINICAL TRAINING. Building the understanding of lesions of the tendons and ligament, about the current surgical techniques for reconstruction, and about the post-op failure mechanisms. This activity will be particularly intense during the 1st year, to acquire new clinical understanding. However, during the entire duration of development and validation activities will be closely connected to the clinical environment.

Activity 2 – STERILIZATION TECHNIQUE. Within this activity the candidate will first get familiar with the sterilization techniques that can be applied to this family of resorbable materials. Tests will be carried out to identify a technique and the parameters that grant adequate reduction of the bioburden, without compromising the mechanical properties and the biocompatibility of the scaffolds

Activity 3 –SCAFFOLD BIOACTIVITY AND INTEGRATION WITH HOST TISSUE. This activity will be carried out in parallel with the previous ones, with the aim to optimize the constituent material and increase the bioactivity of the scaffold and its integration with the surrounding tissues. Within this activity the candidate will get familiar with scaffold functionalization techniques.

Activity 4 – BONE INSERTIONS. The activities within this activity are fundamental to adapt the scaffolds and define the surgical technique that will provide adequate insertion in the host bone. This is currently one of the main surgical challenges. The input of the clinical supervisor is extremely important in this phase.

Innovation potential

This proposal mainly aims at technological innovation: this PhD project will provide significant advancement in the development and validation of nanofibrous scaffolds. In particular, currently no hierarchical scaffold is available for the regeneration of tendons and ligaments. This research will deliver unpreceded solution with highly biomimetic scaffolds. The main points of innovation will be:

- Advancing the development of electrospun hierarchical bioresorbable scaffold
- Developing and validating technological and surgical solutions for the attachment of such scaffolds to the host tissues
- Developing and testing innovative solutions to prevent inflammatory response and tissue adhesion

Furthermore, it is foreseen that this project will deliver scientific innovation providing new insights in the way host tissues (tendon, ligament, bone and enthesis) react to nanofibrous scaffolds

Expected results and applications to human pathology and therapy

This project is meant to develop a better solution for the repair and regeneration of lesions of tendon and ligaments, so as to overcome the critical limitations of the current commercial devices and surgical techniques. This will allow, in a perspective, to deliver better treatments both to young patients (typically affected by traumatic lesions) and elderly ones (presenting degenerative lesions).
While in the duration of this PhD project it is not realistic to start a clinical trial on humans, it will definitely open the way to a dedicated animal trial.

The research team

This candidate will have an engineering background. While this will facilitate him/her in grasping the technical part of the project, some time and effort must be dedicated at the beginning to improve his/her understanding of the clinical problem. This project is rooted between three groups:

- The group of **Prof. Focarete** (Chemistry Department) will provide the training and expertise on electrospinning, polymers, and treatment and modification of polymers.
- The group of **Prof. Cristofolini** (Department of Industrial Engineering) will provide "training through research" in the area of biomechanics and material characterization.
- The group of **Dr Traina** will provide training and supervision on the surgical procedures for tendon and ligament repair, on complications, and will supervise the design of the implantation technique.

Prof Focarete and Prof Cristofolini have been collaborating in the recent years for the development of the first prototype of this implantable scaffold. The success of collaboration is documented by a number of joint publications. Also: Prof. Traina and prof. Cristofolini have been intensively collaborating for years on research projects at the intersection between orthopaedic clinical application and biomechanics research. A strong integration of the two research groups has been achieved by involving the clinical staff in lab activity, and the lab staff in clinical research. This PhD candidate will enjoy this extremely stimulating interdisciplinary environment, and will share his/her research time between clinics (in tight collaboration with Rizzoli Orthopaedic Institute) and biomechanics lab.

The Polymer Science and Biomaterials group at the Chemistry Department "Ciamician", UNIBO has recognized expertise on structure-polymer correlation of natural and synthetic polymeric biomaterials. The group has strong knowledge of material design, material processing through conventional and advanced innovative technologies and nanotechnologies, material characterization and study of biodegradability. The group has demonstrated the capability to develop polymeric systems for drug delivery and as tissue models for tissue engineering. In collaboration with the Biomechanics lab of prof. Cristofolini the group has acquired knowledge to develop scaffolds with optimized biomechanical properties by playing on the choice of the more appropriate material and on the selection of the best morphological properties of the scaffolds.

The Biomechanics group is directed by prof Luca Cristofolini and prof Marco Viceconti and is part of the **Department of Industrial Engineering**. The group has been active for almost 30 years in the area of musculoskeletal biomechanics. The environment is informal and friendly, and collaborations are encouraged between team members, and between juniors and seniors. The biomechanics group is formed by Italian and International young scientists, and has strong ties with the clinics (e.g. Rizzoli Orthopaedic Hospital), with international partners (as part of collaborative projects), and with the industry (e.g. orthopaedic manufacturers, software developers). The focus of the group directed by prof. Cristofolini is on the multi-scale biomechanical characterization of skeletal structures and orthopaedic devices, and on the integration of *in vitro* tests and numerical modeling. Their main activities focus on preclinical testing of orthopaedic implantable devices, and validation of innovative surgical techniques. Their group, in collaboration with the Electrospinning group, recently developed and characterized innovative regenerative scaffolds. Furthermore, this group is acknowledged internationally for the applications of DIC to biomechanics.

The **Dept. of Orthopaedic-Traumatology and Prosthetic surgery** and revisions of hip and knee implants of the Rizzoli Orthopaedic Institute is nationally recognized for the treatment of severe orthopaedic conditions including joints tendon and ligament reconstructions (mainly in the lower limb). Its activity is mainly focused on surgical treatment of complex cases, analysis and data collection of multiple type of joint replacement surgery through different surgical approach and procedures. Comparison between different procedures and cases are routinely performed in order to continuously improve the patient's provision of care.

Specific skills useful for this PhD project

Desirable specific expertise preferentially required: good laboratory practice; mechanical testing and experimental stress analysis; chemistry; physicochemical characterization; handling and testing of biological tissue; orthopaedic biomechanics; mechanical properties of living tissues; statistics and design of the experiment.

PhD PROJECT #2:
Patient-Specific Spinal Surgery for Severe Scoliosis (PS5)

Summary
Scoliosis can be extremely threatening: pain, disability, compression of internal organs, breathing problems are just some of the consequences. In the most severe cases, corrective spinal surgery is the only viable option. In young and growing patients, adjustable devices must be used, that are mobilized over the months to correct the spine and follow the patient's growth. One main challenge for the clinical specialist is to choose the optimal treatment for each patient, for example how to plan the right amount of adjustment over time, so as to achieve the desired correction while avoiding complications and adverse effects. Currently, surgeons are guided only by intuition and experience. The aim of this PhD project is to develop and validate a modelling technology capable of generating patient-specific predictive models of the spine biomechanics that can be used as a treatment planning tools, by simulating different treatment options and predict the occurrence of adverse effects including spinal cord compression, facets impingement, excessive strain of the intervertebral discs, excessive stretch of the muscles.

Objectives of this project
The project aims to develop a treatment simulation environment to optimise the treatment of scoliosis patients. The research will articulate in the following phases:

- Collection of dedicated biomechanical information (stiffness of discs and ligaments, range of motion) through *ex vivo* testing of spine specimens.
- Development of the protocol to build patient-specific computer models of the spine biomechanics from medical imaging data (CT, MRI and X-ray).
- Use of the *ex vivo* experimental data to quantify the model predictive accuracy.
- Develop a treatment simulation environment, where the most common interventions are properly simulated, and adverse effects (if any) predicted.
- Use retrospective clinical data to establish the clinical accuracy of treatment simulation environment when compared with the actual outcome of a specific treatment in a given patient.
- Through these activities, the PhD student will gain skills in the area of biomechanics, in silico modelling, and orthopaedics (spine)that will make him/her employable in the academia, but also in device manufacturers and developer of medical software.

Rationale and scientific background
Congenital and idiopathic scoliosis can be extremely threatening when causing severe deformity. Pain, disability, compression of internal organs, breathing and cardiac problems are just some of the consequences. Corrective surgery is the only option in extreme cases: this consists in the implantation of screws (or hooks) and rods that restore alignment in the frontal and sagittal planes. The surgeon must find a compromise between extreme correction (ideally restoring "perfect" anatomy) and avoiding damage due to compression or stretching of the spinal cord or nerves. In young patients, an additional challenge derives from the changes over time due to growth. In these cases, the surgeon can use Magnetically Controlled Growing Rods that must be mobilized at time intervals to induce progressive correction and allow natural lengthening. Currently, no evidence-based tool is available to help the surgeon plan the optimal compromise. Surgeons can only follow their experience and, to some extent, a trial-and-correct approach [1]. This clearly exposes the patient to the risk of unnecessary pain, organ damage, and sub-optimal correction.

References:
1. A Gonzalez Alvarez, KD. Dearn, BM. Lawless, C Lavecchia, , T Greggi, DET Shepherd Design and mechanical evaluation of a novel dynamic growing rod to improve the surgical treatment of Early Onset Scoliosis. Material and Design 2018;155:334-45

Research project
The focus of the activities will be on developing a numerical model of the growing spine while undergoing correction. This PhD candidate will spend 60-70% of his/her time in the biomechanical laboratory developing *in vitro* tests (supervisor L. Cristofolini) and numerical models (supervisor M. Viceconti), 30-40% of the time

in the clinical settlement (Rizzoli Orthopaedic Institute) collecting and analysing retrospective patient cases. Furthermore, an international secondment of 4-5 months at a foreign clinical institution (for example, the Buda National Center for Spinal Disorders led by Prof Peter Paul Varga, in Budapest), preliminary step to develop a full scale multicentric clinical trial for the new technology after the end of the PhD project.

WP1 – BASIC CLINICAL TRAINING. Building the understanding of spinal deformity, surgical corrections, short-and long-term outcomes and complications. This WP will be particularly intense during the 1st year, to acquire new clinical understanding. However, during the entire duration of development and validation activities will be closely connected to the clinical environment.

WP2 – COLLECTION OF *EX VIVO* DATA. Within this WP the candidate will collect a set of biomechanical data from cadaveric spines from young donors. This will serve to initialize the models and identify the relevant parameters (WP3 and 3)

WP3 – PROTOCOL FOR PATIENT-SPECIFIC MODELLING. This will include the Development of the modelling protocol on retrospective data and the Development of ad hoc imaging protocols.

WP4 – EX VIVO VALIDATION OF PREDICTIVE MODELS. The candidate will use the experimental data collected in WP2, and the modelling protocol developed in WP3, to develop predictive models of the ex vivo experiments form CT data of the specimens and validate the modelling protocol by comparing the model predictions to the experimental measurements.

WP5 – DEVELOP TREATMENT SIMULATION ENVIRONMENT. Once the model is fully validated *ex vivo,* the candidate will develop the simulation of the various interventions available.

Innovation potential

There is an acute unmet need for proper planning tools in the treatment of sever scoliosis. While the biomechanics of the scoliotic spine is complex, in the last 20 years a massive amount of experimental and modelling work has been done, which can be capitalised here. We thus believe there is a significant innovation potential in this project. If reasonable predictive accuracies are achieved, after the end of the project we will explore the possibility to hand over the technology to a company, or to establish an exploitation team without our group. In both cases, a multicentric clinical trial will be required to demonstrate the efficacy of this new technology when compared to the current standard of care.

Meanwhile we will work to establish a planning service for Dr Greggi clinic, and for any other spine surgeon at the Rizzoli Institute, who is interested in using this technology to plan their interventions.

Expected results and applications to human pathology and therapy

In this case, the clinical impact is self-explanatory: if the technology works as expected, and provide sufficient accuracy to be clinically informative, this could radically change the standard of care for the handling of sever scoliosis cases.

The research team

This candidate will have an engineering background. While this will facilitate him/her in grasping the technical part of the project, some time and effort must be dedicated at the beginning to improve his/her understanding of the clinical problem. This project is rooted between different and complementary expertise:

- The group of Prof. Cristofolini (Department of Industrial Engineering) will provide “training through research” in the area of biomechanics and material characterization.
- The group of Prof. Viceconti (Department of Industrial Engineering) will provide “training through research” in the area of computational biomechanics and patient-specific modelling.
- The group of Dr. Greggi will provide training and supervision on the surgical procedures for the spine and on complications, and will supervise the design of the modelling strategy, and the retrospective validation.

This PhD candidate will enjoy this extremely stimulating interdisciplinary environment and will share his/her research time between clinics (in tight collaboration with Rizzoli Orthopaedic Institute) and biomechanics lab.

The Biomechanics group is directed by prof Luca Cristofolini and prof Marco Viceconti and is part of the **Department of Industrial Engineering**. The group has been active for almost 30 years in the area of musculoskeletal biomechanics. The environment is informal and friendly, and collaborations are encouraged between team members, and between juniors and seniors. The biomechanics group is formed by Italian and International young scientists, and has strong ties with the clinics (e.g. Rizzoli Orthopaedic Hospital), with international partners (as part of collaborative projects), and with the industry (e.g. orthopaedic manufacturers, software developers). The focus of the group directed by prof. Cristofolini is on the multi-scale biomechanical characterization of skeletal structures and orthopaedic devices, and on the integration of *in vitro* tests and numerical modeling. Their main activities focus on preclinical testing of orthopaedic implantable devices, and validation of innovative surgical techniques. Furthermore, this group is acknowledged internationally for the applications of DIC to biomechanics.

The Rachis Deformity Surgery of the Rizzoli Orthopaedic Institute is nationally recognized for the treatment of severe deformity in adult and young patients. The group directed by dr Greggi is constantly developing new surgical protocols to improve treatment of young and growing patients. Comparison between different procedures and cases are routinely performed in order to continuously improve the patient’s provision of care.

Specific skills useful for this PhD project

Desirable specific expertise preferentially required: good laboratory practice; mechanical testing and experimental stress analysis; handling and testing of biological tissue; orthopaedic biomechanics; mechanical properties of living tissues; statistics and design of the experiment; medical imaging.

PhD PROJECT #3: Innovative technique to repair osteoporotic fractures with bone substitutes

Summary

The second most common site for traumatic fracture in the elderly is the upper limb (proximal humerus and distal radius). Reconstruction of these fractures is currently performed with plates and screws. In both cases, healing failures (mainly pseudo-arthrosis) derive from lack of stabilization of the bone fragments, which is particularly frequent in case of poor bone quality and osteoporotic defects. As the current technique is dissatisfactory (adding more screws would not solve the problem) we will explore a different approach. A bone substitute will be used in combination or in replacement of plates and screws. This PhD project consists of three main actions: (i) biomechanical testing of different reconstruction techniques to identify the optimal ones; (ii) definition of surgical guidelines based on ex vivo fluoroscopic imaging (similar to the foreseen surgical protocol), in relation to biomechanical performance; (iii) definition and following of clinical trial on selected fracture cases.

This project originated from the clinical problem encountered by orthopaedic surgeons, will require significant input from the technical area, and will rely on collaboration with a biomedical company.

Objectives of this project

This PhD project addresses a clinical objective: developing and validating an alternative technique for the treatment of osteoporotic fractures of the upper limb. This project will start from preclinical *in vitro* testing, and will finally reach the first stages of clinical trial. The following specific aims will be targeted:

- Adapting the surgical technique through *in vitro* tests and biomechanical simulations. This will allow to define the biomechanical criteria for the use of the bone substitute, and will confirm which of the traditional osteosynthesis components can be avoided.
- Definition of the surgical guidelines to indicate the surgeon the optimal amount of bone substitute to be delivered in each patient under safe conditions. This part will integrate imaging techniques with biomechanical testing, so as to confirm the conditions to be achieved during surgery to grant optimal strength of the reconstruction.
- Testing the concept through a first clinical trial so as to provide clinical evidence about the safety and efficacy of this technique.

Rationale and scientific background

Proximal humeral and distal radial fractures account for about 25% of all fractures in the elderly and affecting approximately 142 out of 10,000 persons per year [1]. Locking plate fixation is considered the optimal treatment for these fractures, when possible. Incidence of complications increases according to patient's age, number of fragments, fracture pattern and dislocation [2]. Intra-operative risks of this technique include articular cartilage damage while drilling or inserting the screws [3]. This risk is increased as the surgeon may need to use multiple screws to stabilize the different fragments, since in osteoporotic setting the screws must be long enough to achieve fixation in the subchondral bone. The most common post-operative failure mechanism of plated proximal humeral fractures is a secondary loss of reduction [3]. Low bone mineral density (BMD) is the primary cause of this complication. In fact, one of the most common mechanisms of failure is a sliding of the fragment: osteoporotic bone has a weak mechanical structure, and repetitive loading damages the cancellous bone because of the high stress at the tips and threads of the screws.

In these fractures it is important to obtain immediate post-operative fixation strength, to early mobilize the shoulder and prevent post-operative stiffness. To reduce the incidence of mechanical failure, several augmentation techniques have been developed. While augmentation provides some improvements, it also has different specific drawbacks [3]. Recently some innovative products have been released, with the aim of conjugating the positive aspects of the different augmenting materials. In particular the biomaterial used for this study is a combination of beta-TCP (beta-tricalcium phosphate) and polymethylmethacrylate (PMMA), aiming to provide good initial mechanical property, and bone ingrowth with partial substitution over time [4].

Therefore, to improve the reconstruction technique for such fractures, alternative techniques are being sought. Rather than increasing the number of screws, the focus is shifting towards bone substitutes as means of initial fixation, and to promote bone healing [5]. The trauma surgeons in Rizzoli area are among the pioneers in this field.

References

[1] WHO, 2007. Assessment of fracture risk and its application for postmenopausal osteoporosis. Report of WHO study group, World Health Organization, Geneva.

[2] Gavaskar AS, Karthik B, Tummala N Second generation locked plating for complex proximal humerus fractures in very elderly patients. Injury 2016; 47(11): 2534–38

[3] Thanasas C, Kontakis G, Angoules A. Treatment of proximal humerus fractures with locking plates: systematic review. J. shoulder Elb. Surg. 2009;18(6):837–44.

[4] Dall'Oca C, Maluta T, Micheloni GM, et al. The biocompatibility of bone cements: progress in methodological approach. Eur. J. Histochem. 2017;61(2):2673.

[5] Kammerlander C, Neuerburg C, Verlaan J-J, et al. The use of augmentation techniques in osteoporotic fracture fixation. Injury. 2016;47:S36–S43.

Research project

This project aims at bringing towards the clinical trial a treatment solution that currently has been exploratively tested *in vitro*. This PhD project will start with training of the candidate (which must have a technical background) on the clinical problem (WP1). The candidate will then spend 60-70% of his/her time in the biomechanical laboratory of prof. Cristofolini developing and testing the treatments solutions (WP2 and 3). Finally, he/she will spend the remaining time in the Rizzoli Orthopaedic Institute, analysing the results from the clinical trial.

WP1 – CLINICAL TRAINING. The candidate first will need to get familiar with the types of fracture, treatment options, and failure scenarios. This activity will be particularly intense during the 1st year, to acquire new clinical understanding. However, during the entire duration of development and validation activities will be closely connected to the clinical environment.

WP2 – BIOMECHANICAL OPTIMIZATION OF REPAIR TECHNIQUE. This part of the project will explore different treatment options aiming to reduce/avoid the use of screws and plates in osteoporotic fractures of the upper limb, and to assess the biomechanical influence of using a bone substitute. The core of this WP is a series of biomechanical *in vitro* tests on cadaveric bone specimens.

WP3 – DEFINITION OF SURGICAL GUIDELINES. While WP2 concentrates on biomechanical optimization, this WP aims to identify the optimal indications for actual clinical implementation. The optimal types of reconstruction for the humerus and radius (not necessarily the same) will be addressed. Reconstructions will again be performed on cadaveric specimens, but using instrumentation and imaging as in real surgery, to define the ideal protocol.

WP4 – CLINICAL TRIAL. The best solutions (from WP2) will be applied to fracture patients following the guidelines (from WP3). Preliminary approval by the ethical committee and the relevant authorities has already been submitted for an initial clinical trial.

Innovation potential

This PhD student, in collaboration with the orthopaedic surgeons involved and the biomechanical group, will develop and assess a new solution for treating osteoporotic fractures. The combined use of an osteoconductive injectable bone substitute and classic screws, and the use of such bone substitute are a new concept for the treatment of this type of fractures. This project will therefore lead to technological innovation in the delivery and use of such cement (possibly requiring further development of the bone substitute itself, in collaboration with the Manufacturer).

Expected results and applications to human pathology and therapy

This project will develop and validate better treatments for osteoporotic fractures of the upper limb, that are currently difficult to treat, and have unacceptably high failure rate. It is expected that the innovative solutions proposed will improve fracture treatment in different ways:

- Lower incidence of articular damage due to intra-op cartilage drill-in
- Lower incidence of short- and mid-term failures (pseudarthrosis, malunions)
- Better bone healing thanks to the osteoconductive bone substitute.

The research team

This candidate will have a technical background. While this will facilitate him/her in grasping the technical part of the project, some time and effort must be dedicated at the beginning to improve his/her understanding of the clinical problem.

This project between a technical and a clinical environment:

- The group of Prof. Cristofolini (Department of Industrial Engineering) will provide "training through research" in the area of biomechanics and material characterization.
- Rizzoli Institute (dr Guerra and prof. Faldini) will provide training and supervision on the most frequent bone fractures, on the current techniques for osteosynthesis, and on the need for improvement; dr Guerra will contribute to the design of the reconstruction techniques, and on laying down the specifications for biomechanical testing.

Prof. Cristofolini has been intensively collaborating for years on research projects at the intersection between orthopaedic clinical application and biomechanics research together with dr Guerra and with prof Faldini. A strong integration of the two research groups has been achieved by involving the clinical staff in lab activity, and the lab staff in clinical research. The success of collaboration is documented by a number of joint publications. This PhD candidate will enjoy this extremely stimulating interdisciplinary environment, and will share his/her research time between clinics (in tight collaboration with Rizzoli Orthopaedic Institute) and biomechanics lab.

The Biomechanics group is directed by prof Luca Cristofolini and prof Marco Viceconti and is part of the **Department of Industrial Engineering**. The group has been active for almost 30 years in the area of musculoskeletal biomechanics. The environment is informal and friendly, and collaborations are encouraged between team members, and between juniors and seniors. The biomechanics group is formed by Italian and International young scientists, and has strong ties with the clinics (e.g. Rizzoli Orthopaedic Hospital), with international partners (as part of collaborative projects), and with the industry (e.g. orthopaedic manufacturers, software developers). The focus of the group directed by prof. Cristofolini is on the multi-scale biomechanical characterization of skeletal structures and orthopaedic devices, and on the integration of *in vitro* tests and numerical modeling. Their main activities focus on preclinical testing of orthopaedic implantable devices, and validation of innovative surgical techniques. Furthermore, this group is acknowledged internationally for the applications of DIC to biomechanics.

The **Dept. of Shoulder and Elbow surgery** of the Rizzoli Orthopaedic Institute continuously performs teaching and research activity. It participates to several national and international clinical studies, for example for the ultrasound guided treatment of calcific tendinopathy, the development of new materials for osteosynthesis of shoulder and elbow fractures. Several patents have been ideated and registered, such as a titanium mini-plate for surgical repair of the rotator cuff, a special postoperative brace for the shoulder, a self-threading titanium screw for a plastic plate. The Unit has a constant partnership with scientific laboratories to improve arthroscopic suture techniques in rotator cuff repair, for shoulder prosthesis design improvement, and in the field of regenerative medicine for poor quality or massive tears of rotator cuff tendons, for the study and treatment of osteoporosis.

The **I Clinic of Orthopaedic and Trauma Surgery** of the Rizzoli Orthopaedic Institute is nationally recognized for the treatment of severe orthopaedic conditions including joints diseases which require both primary and revision surgery. Its activity is mainly focused on surgical treatment of complex cases, analysis and data collection of multiple type of joint replacement surgery through different surgical approach and procedures. Comparison between different procedures and cases are routinely performed in order to continuously improve the patient's provision of care.

Specific skills useful for this PhD project

Desirable specific expertise preferentially required: good laboratory practice; mechanical testing and experimental stress analysis; handling and testing of biological tissue; orthopaedic biomechanics; mechanical properties of living tissues; statistics and design of the experiment.