# VICTOR HUGO

## I- Background

### 1- Why a western regional musculoskeletal network?

Currently, there is no network dedicated to musculoskeletal diseases in France. The musculoskeletal field (degenerative, inflammatory or infectious joint diseases; bone diseases) has the advantage to be already structured in the western region in the domains of care, teaching and research but its performance can be increased by a synergy beyond the borders of the specialities. A regional network carried by all teaching hospitals and all the western universities may help all clinicians, teachers or researchers to obtain a sufficient critical mass for synergic actions (for example, patients' recruitment in cohorts or sharing of knowledge in undeveloped domains on a site) and so to increase the visibility at the international level. The objective is to federate hospital departments and research teams at the regional level to bridge over their tasks.

- **Care:** Most of the teaching hospitals have musculoskeletal units and there is already an inter-regional collaboration in numerous domains (regional or national PHRC, regular exchanges on practices, common meetings). Some departments are recognized as reference centres or competence centres (autoimmune diseases, fibrous dysplasia and Mac Cune Albrigh,).

- **Teaching :**
  - HUGO is the geographical region for the residents in the west, with common teaching, including at least two annual face-to-face meetings, which allows a strong interaction between the teachers. There is however no homogeneity of teaching (differences of

support, differences of protocols of care, differences of implication in clinical research) between the various cities.

- The medical students of DFASM, also, have common activities (in particular the EBIR exam) but, globally, teaching is not homogeneous within the region, with disparities according to the priorities of the hospitals. The implication of the medical students in the clinical research is unevenly developed, explaining the lack of interest of certain physicians leaving hospitals for this domain, while emulation at the regional level would allow that students measure its importance.
- There are already Master's degrees and inter-university diploma (DIU) shared by different cities of the region but the visibility of the access to the teaching in the field of musculoskeletal research on the West, in spite of its importance, is not rather visible for the students. Better visibility would allow them to choose the adapted Master's degrees.

- **Research:** The clinicians and the researchers of the region specialized in the musculoskeletal domain work together, but mostly within the framework of limited partnerships. The critical mass and the complementarities in terms of units of research are nevertheless ideal for a synergy. Three Labex includes teams of VICTOR HUGO and numerous collaborations were weaved with the industrialists and the engineer schools of the region.

There is thus, today, no medical interdisciplinary formalized link at the regional level in the musculoskeletal domain. Such unification, in association with the units of research, would strengthen all groups.

## 2- According to what outlines?

Victor Hugo is a consortium of rheumatologists. The actors are:

- **Clinicians :**

The rheumatologists of all the departments of rheumatology of 6 western teaching hospitals and of main hospitals of the inter region (Chartres, Châteauroux, Dreux, La Rochelle, La Roche sur Yon, Le Mans, Lorient, Orléans, Morlaix, Quimper, St Brieuc, Vannes), in association with the office based rheumatologists (SRO), leaned to the Network of Rheumatology. PU-PH of the units of rheumatology of 6 teaching hospitals of the inter-region will be relays and will appoint the members of scientific council.

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|---|---|
| E LEGRAND | Rhumatologie Angers |
| M AUDRAN | Rhumatologie Angers |
| V DEVAUCHELLE-PENSEC | Rhumatologie Brest |
| A SARAUX | Rhumatologie Brest |
| D CORNEC | Rhumatologie Brest |
| B LE GOFF | Rhumatologie Nantes |
| Y MAUGARS | Rhumatologie Nantes |
| F DEBIAIS | Rhumatologie Poitiers |
| E SOLAU-GERVAIS | Rhumatologie Poitiers |
| A PERDRIGER | Rhumatologie Rennes |
| GUGGENBUHL | Rhumatologie Rennes |
| D MULLEMAN | Rhumatologie Tours |
| P GOUPILLE | Rhumatologie Tours |

- **Persons in charge of research units working with our group.** All the persons in charge of the research units quoted below will represent all the members of the units:

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|---|---|
| EA4658 : Groupe d'étude «Remodelage Osseux Et Biomatériaux » Gerom (D Chappard) | Angers |
| INSERM UMR 1101: Latim (E Stindel) | Brest |
| INSERM UMR 1078 (C Ferec, P Delépine, Elisabeth Leize-Zal ) | Brest |
| INSERM UMR 1227: LBAI (JO Pers) | Brest |
| EA 4325 : Laboratoire Brestois de Mécanique et des Systèmes (JY Cognard) | Brest |
| EA 3826 : Thérapeutiques Cliniques et Expérimentales des Infections (G Potel) | Nantes |
| INSERM UMR 957 : Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives (D Heymann) | Nantes |
| INSERM UMR 791 : Tissue Engineering (P Weiss, J Guicheux) | Nantes |
| EA 4708 : Imagerie Multimodale, Multiéchelle et Modélisation du Tissu Osseux et Articulaire I3MTO (E Lespessailles) | Orléans |
| EA 4331 : Laboratoire Inflammation, Tissus Epithéliaux et Cytokines (Litec) (JC Lecron) | Poitiers |
| CNRS Fre 3511 Institut De Physiologie Et De Biologie Cellulaires (IPBC) (F Becq) | Poitiers |
| EA 1254 : Microbiologie – Risques Infectieux (M Bonnaure-Mallet et A Gougeon) | Rennes |
| EA 1274 : Laboratoire Mouvement Sport Santé (P Delamarche, M Ropars) | Rennes |
| Plate-Forme Cire Inra (P Rosset) | Tours |

UMR CNRS 7292 : Génétique, Immunothérapie, Chimie et Cancer (GICC) (G Tours Paintaud)

Some of these units are in included in the LaBex IGO "Immunotherapy, graft, oncology" (EA2216), the LaBex Mabimprove (UMR7292), the LaBex Cami (UMR1101) "Computer assisted medical intervention" and the technological B-COM (UMR1101) research institute.

### 3- What themes in which units of research?

Themes developed in the units of research involved in four musculoskeletal domains are the following ones:

- Joint diseases (degenerative pathologies, inflammation, auto-immunity and immunotherapy of the adult and the child)
  - UMR 7292 (Tours) The GICC " Genetics, Immunotherapy, Chemistry and Cancer " is based on an interdisciplinary approach associating molecular biologists and geneticists, hematologists, immunologists, pharmacologists, chemists and clinicians. The laboratory studies the physiopathological mechanisms of certain cancerous diseases (leukaemia, gliomes, digestive cancers), inflammatory and immunological, to develop personalized therapeutics. It is organized in 3 teams CNRS (National Center For Scientific Research) and one EA. Team 1 : Antibodies, Fc receptors and clinical response - Team 2 : Leukemic Niche and redOx metabolism (LNOx) Team 3 : Tolemeres and Genome Stability and the EA 6306 Molecular and therapeutic innovation
  - UMR 957 (Nantes) "Bone physiopathology and Therapy of Primitive bone Tumours": The projects of research in the unit are devided in 5 themes: Caracterisation of the tumoral microenvironment, development of preclinical animal models, malignant osteolysis therapy and primary bone tumour combined therapies, primary bone tumour imagery and the development of new therapeutic, Development of clinical trials. Implication of the triad OPG/RANK/RANKL in osteolytic processes is also evaluated in joint diseases such as rheumatoid arthritis.
  - UMR 791 (Nantes) The Oniris-INSERM-University joint research Unit UMR-S 791 or Laboratoire d'Ingénierie Ostéo-Articulaire et Dentaire (LIOAD) Laboratory of bone, joint, and dental Engineering) is developing a research program for biomaterials and tissue engineering in the Nantes school of dental surgery. The unit's objective is to develop tissue engineering strategies for bone and joint regeneration. Its internationally recognized past concerns the field of bone replacement biomaterials (ceramics, calcium phosphate and

hydrogels). In association with therapeutic agents (antibiotics, bisphophonates and proteins), these biomaterials, developed in the laboratory, enable the regeneration of bone losses notably due to osteoporosis, by limiting bone resorption. Since the UMR was created in 2006, the research activity has been straightened out in tissue engineering and cell therapy. In order to improve regenerative medicine strategies, a cognitive approach has also been developped with the aim of better understanding the role of phosphate and its transporters in skeletal biology. Various osteochondrogenic cells (adult mesenchymal stem cells from bone marrow and adipose tissue) have been associated with synthetic matrices to carry out bone and cartilage tranplants. Clinical indications are mainly bone and cartilage regeneration when biomaterials alone are not sufficient. This strategy is recommended in orthopedics to fill in bone substance losses or improve osteosynthesis, notably in osteoporosis, but also in parodontology and dental implantology or in irradiated patients following cancer of upper aerodigestive tracts. The unit is also interested in cartilaginous damage understanding and regeneration (traumatology, osteoarthritis) and, more recently, the regeneration of the intervertebral disc through cell therapy. Pre-clinical modelling and research valorisation are very important in the unit activity. Many clinical applications have been developed in human and animal from its results.

- EA 4331 (Poitiers) "Laboratory Inflammation, Epithelial Tissues and Cytokines" (LITEC). It studies the role of cytokines in the induction of tissue inflammation, and the interactions between the inflammatory and epithelial cells. The fundamental aspects, the mechanism and physiology of inflammation are approached. The data obtained in vitro are compared with the pathological models, such as the psoriasis, arthritis and hepatic fibrosis associated with psoriasis, atopic dermatitis, skin carcinomas, gastrointestinal inflammation by Helicobacter Pylori.
- UMR 1227 (Brest) "Immunology, Pathology and Immunotherapy" (Brest): it studies the normal and pathological lymphocyte B in the autoimmune diseases (syndrome of Gougerot-Sjögren, lupus, rheumatoid arthritis). This search on the immuno pathology of the lymphocyte B extends since the fundamental approaches (epigenetic in the autoimmunity, the implication of the cytokine BAFF, the calcic channels and the lymphocyte B regulators) until the clinical applications (diagnostic tools, therapeutic assay, intravenous Immunoglobulins, evaluation of immunotherapy). The unit is a part of the LABEX IGO "Immunotherapy the West" where it coordinates the theme "regulating LB". A partnership exists with the Institute of Translational research In Diseases of the Blood

(IRTMS) which develops targeted anti-lymphocyte therapies B and anti-tumoral immunotherapy B.

- **Bone diseases** (joint and bone architecture, cells, disorders and fragilities)
  - UMR 957 (Nantes) " "Bone physiopathology and Therapy of Primitive bone Tumours": In the absence of a register, it is very difficult to accurately evaluate the incidence of primary malignant bone tumours. The number of new cases each year in France is estimated at 300 of which 50 % are osteosarcomas. The second most common primary malignant bone tumour is the Ewing's sarcoma. These two types of tumour generally affect young patients. The UMR 957 conduct basic, preclinical and clinical research in the study of pathogenesis of the osseous sarcomas to characterize the tumoral microenvironment, to develop new preclinical models of primitive osseous tumours to the small animal, to improve therapeutic existing and to test the efficiency of new pharmacological agents, to develop new therapeutic approaches of these tumours, to study the circulating tumoral cells, and to participate in clinical trials within the framework of national networks
  - EA 4708 - I3MTO - (Orléans) "Multimodal Imaging, Multiscale and Modelling of the bone and joint Tissues ". Its main objective is to validate new technonologies evaluating of musculoskeletal imaging, to evaluate the risk of fracture, to characterize the rheumatoid arthritis epiphysis bone and to characterize ostéocyte. Using multimodal imaging (optical and electronic microscopy, immunostaining, histology).
  - INSERM U 1078 (Brest). The "cell and tissue engineering" group studies the different aspects of the cell colonization of various orthopaedic substitutes. This group works on the cellularization of meniscal substitutes (synthetic scaffolds and human decellularized meniscus) to improve their long term fate. The recellularization of allogeneic osseous transplants for maxillofacial reconstructions or orthopaedic reconstructions is also studied to improve the integration of this kind of material. The culture and differentiation of mesenchymal stem cells (MSC) from bone marrow appears crucial since they are used to colonize these different substitutes.
  - FRE 3511 (Poitiers) CNRS "Institute of Cellular Physiology and Biology" (IPBC). The intercellular channels of the communicating junctions allow the direct transfer of ions, second messengers between the cytosols of most of the cells of the body. The functional change of the molecular components of these channels, called connexines, is known to lead pathologies including cancer. The team studies their implication in the carcinogenesis of invasive cancer cells gliomes and prostate cancer.

- EA 4658 GEROM (Angers and Nantes) “Remodelage Osseux et bioMatériaux” research focus on microarchitecture and bone remodeling and bone disease, Microarchitecture and bone remodeling in contact with biomaterials (bone grafts, implants and metal prostheses), Resorbable polymer biomaterial multiphase, experimental models of osteoporosis, Experimental models of bone lesions in multiple myeloma Bone cell adhesion, biomaterials and bone matrix and Mechanisms of bone metastasis.

➢ **Information** (imaging, movement, data)

- UMR 1101 (Brest) "Laboratory of Data processing Medical" (LaTIM). It develops multidisciplinary research in Information Sciences for health. LaTIM's research concerns the Continuous Optimization of Therapeutic Actions by the Integration of Multimodal Information: fusion of multi-modal, multi-scale, spatio-temporal (morpho-functional) information. This allows the development of models ranging from the molecule to the body, the organism and populations, based on a management strategy, organization and information security protocol providing a high level of quality in all the implemented processes and interventional and non-interventional therapies (solutions to the problems of quantitative multi-modality imaging PET / CT / MRI, determining and monitoring the therapeutic response as well as planning and dosimetry in radiotherapy, optimization of surgery through the implementation of innovative surgical procedures, functional and morphological optimization of implants, pre-evaluation and post-operative treatment procedures, development of specific biomechanical models with the inclusion of the musculo-ligamentous environment and evolution of pathophysiological models. These two axes are complemented by a transverse axis: Managing Shared Multimodal Medical Data for decision support.
- EA 1274 (Rennes) "Laboratory Movement sport health (M2S) ": Its global theme is the understanding of the human movement by associating skills in biomechanics and physiology. The main themes of research concern the adaptation and its physiological mechanisms to the exercise, the mechanical aspects of the movement, the metabolic and mechanical control of the movement, the optimization of the sports performance, the physiology of the physical exercise, and the quantification of the physical activity, the biometric sensors.
- INRA-CNRS-IFCE (Tours) "Physiology of the Reproduction and Behavior (UMR PRC) ". The department of in vivo imaging, installed in a building of 300 m ², with a system of Magnetic resonance imaging MRI and CT scan, strengthen equipments and the platform " Surgery and Imaging for Research and Education " (OILSKIN) created within the mixed

unit. Its objective is to make possible the use, on large-sized animal models (sheeps, goats and pigs), the progress of the imaging.

- EA 4325 Brest Laboratory of Mechanics and System (LBMS) (Brest). It was born in 2007 of the grouping of the laboratory MSN (ENSIETA), FILE (UBO), and the LRM (ENIB). Studies carried out in the LBMS lab involve analyzing the life span of naval structures. This scientific project is developed through acquiring general expertise both in the field of material, fluid and structural mechanics and in the field of electromechanical systems control and diagnosis. Thus, the range of potential applications includes other industrial activities (automotive, aeronautics, etc.). The MMA team, involved in the medical domain, evaluate the reliability and the durability of the structures, for example hip prosthesis.

- **Infectious diseases** (joint and bone infections of both adult and child)
  - EA 1254 (Rennes) "Microbiology - infectious risks". The team studies the expression of factors of virulence from various bacterial species responsible for human infectious pathologies. In our team project, bacteria are used like models for specifically investigating two major mechanisms of virulence: the toxin adhesion and secretion. Various methodologies used are shared; they are the transcriptomic, proteomic analyses of imageries and epidemiologic analyses of clinical stocks. Beside the traditional methods, new strategies for obtaining tools such as antibodies (patent deposited) are also developed, mutants (in progress). The objective of the team is to improve knowledge on the pathogenicity of micro-organisms targeted, in dealing with human infectious diseases.
  - UMR 1101 (Brest) “Laboratory of Medical Information Processindical" (LaTIM). The LaTIM is a joint unit (UMR 1101) consisting of INSERM, University of Western Brittany (UBO), and Telecom Bretagne (Institut Mines-Telecom) together with the University Hospital of Brest. It develops multidisciplinary research in Information Sciences for health. LaTIM's research concerns the Continuous Optimization of Therapeutic Actions by the Integration of Multimodal Information. In terms of methodology, the LaTIM aims to develop approaches for the fusion of multi-modal, multi-scale, spatio-temporal information. In terms of therapeutic actions, they develop both interventional and non-interventional therapies: Non-interventional therapies focus on the activities in the field of quantitative multi-modality imaging for diagnosis and therapy. This is to provide solutions to the problems of quantitative multi-modality imaging PET / CT / MRI (e.g. corrections related to differences in resolution, respiratory motion compensation, characterization of tumors), determining and monitoring the therapeutic response as well as planning and dosimetry in radiotherapy. This axis also develops a strong activity on numerical

simulations for imaging and radiotherapy, as well as the porting of these approaches on high performance architectures (GPU graphics cards). Interventional therapies relates to the field of orthopedics and physical rehabilitation, where the aim is to optimize surgery through the implementation of innovative surgical procedures, functional and morphological optimization of implants, pre-evaluation and post-operative treatment procedures, development of specific biomechanical models with the inclusion of the musculo-ligamentous environment and evolution of pathophysiological models.

- EA 3826 "Clinical and Experimental Therapeutics of Infections". The laboratory dedicates itself to the evaluation of antibiotics, combining 3 axis (in vitro, experimental animal and clinical) contributing to the knowledge on which are established the good use and the optimization of the prescription of antibiotics.

### 4- Organisation of the research in the Network

- The organization of the research in the network allows a link between all patients in the inter-region and laboratories of all universities.
- Four groups of clinicians will be responsible of the four clinical themes in connection with a member of each of the units of research.
- A scientific council of management will assure a bridge between these groups and will acts as an intermediary between clinicians and researchers.

## II- Objectives of VICTOR HUGO

We defined the needs for the researchers of these units in clinical data and equipment (biobanks, bank of image, etc.) then constituted the groups of clinicians-researchers who will find themselves for thematic meetings.

The objectives are:

- **To improve diagnosis and care** of musculoskeletal diseases constituting a considerable burden for the society: degenerative, inflammatory and autoimmune joint diseases, traumatic and not traumatic bone diseases, joint infections.
- **To promote innovation** in the HUGO's perimeter, allowing to create new synergies in the domains of the care, teaching and research, and to improve the attractiveness of HUGO's hospitalo-university sites in the field of the musculoskeletal diseases.

**The reserved general principles** are **regional level, homogeneity** of the coverage in the domains of the care, teaching and research, **interface and complementarity**.

## III- **Methodology to reach the goal**

### 1- General principle

**In terms of improvement brought in patients care**, we wish:

- To set up and support networks, troops and registers, so that a patient in any western hospital department has the same clinical observation, the same care, the same chances to be included in protocols of research.
- The connection between the various clinical units and research will be remitted to a network and a staff who will organize collection and management of samples and clinical data.
- Thanks to the city-hospital cooperation, the impact of the network will extend with the Societies of western rheumatology (SRO), orthopaedics Western (SOO) and their grouping with the western radiologists (SORRO).

**In terms of policy of education and research, we wish:**

- **To harmonize** the programs of education of all teachers of the region.
- **To develop** the clinical research at the regional level, so that the members know protocols of research of all other centres and can help them in the recruitment and to improve protocols.
- **To favour** the interface between the research units and the various clinical departments and the access to the clinical, biological data banks

### 2- Coherence with the policy of the partners of the CHU, University, Research

The themes are centred on the recognized units of research of the CHU to favour the development of the centres of excellence of the inter-region.

### 3- Privileged partnerships

- Cooperation will be developed with other specialities studying the analysis of the movement, reference laboratories in autoimmunity, with Society of rheumatology, orthopaedics, infectious

disease, colleges of education (Rheumatology, Orthopaedics, Infectious diseases, Microbiology), research units

- The national and international links will be strengthened by the increase of the critical mass of the network.
- The associations of patients will be invited to participate.

### 4- Operational mode

The links between clinical units and research units will be obtained using

- A dedicated site
- A network and a staff dedicated to the clinical research
- Biannual meetings of members.

We thus plan

- to create a dedicated web site which will allow
  - to collect and download forms validated by the network concerning "patient's education", " patients advices", "forms of informed consent for data collection", "algorythm for the residents of the network ", " forms for patients examination ".
  - to collect a common learning material in every CHU (slide library, movies).
  - to list the current available material (equipment) for ancillary studies.
  - to put on-line the on-going PHRC and other studies for which the ancillary studies are possible.
  - to discuss the creation of a musculoskeletal Master's degree
- To obtain a minimal staff dedicated to musculoskeletal research and to create a link between the staffs of clinical research for the various hospitals through the above-named site. This staff will have responsibility to make the bench to beside connection. It can be financed in proportion to the MERRI obtained.
- Decide within the network that all theses of medicine are in form of submitted articles written in English.
- To organize the biannual meetings of sub-units of the network.

## IV- <u>Critères of evaluation of the success of the Network</u>

The evaluation of the success will be made on the following items:

- In two years
  - Have been able to create a web site welcoming elements necessary for the functioning of the network for care, education and research.
  - Have been able to harmonize the collect of patients characteristics as well as patients care.
  - Have been able to obtain a dedicated staff making the link between the units and creating a real bench to beside connection.
  - Have been able to conduct regional works.
- In 5 years
  - Number of current studies at the regional level in the musculoskeletal domain.
  - Publications of the members.
  - Percentage of theses of medicine drafted in form of submitted articles written in English
  - Number of student doing a musculoskeletal Master's degree.
  - Number of pathologies having a standardized examination in the inter-region.

## V- Description of the governance

The governance is managed by

- **The scientific council**
  - is consisted of the coordinator, representatives of each CH, and office-based rheumatologists.
  - Defines a general policy of research allowing a bench to beside connection. The scientific council fixes the objectives and assures their follow-up.
  - Sets up an approach of evaluation.
  - Participate in the elaboration of the annual report of activity.

- **The council of management**
  - is consisted of a healthcare professional representing each of the CH and office-based rheumatologists.
  - Assures the administrative and financial management, the distribution of funds.
  - Develops a guideline and a calendar.
  - Organize the obtaining of the financing necessary for the fixed objectives (biological collections, web site, technicians for the collection and data capture, secretarial help).

- Estimates annually the progress of the project.

**Any publications** and presentations concerning the data of the group have to mention it with the rules of usual publications:

- The first author: responsible for the project (or the nominee by him).
- The other places (in particular the second and the last author) are determined according to the investment in the study, the active rows followed by "Victor Hugo".
- Each of the establishments has the freedom to publish its own data.