- **Title of the proposed project**

Subchondral bone markers as predictors of knee osteoarthritis progression and treatment response - **the BiOA Project.**

- **Collaborating partners**
  - Portuguese Society of Rheumatology (SPR), Lisbon, Portugal
  - CEDOC, NOVA Medical School / Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Portugal.
  - Rheumatology Research Unit (RRU). Instituto de Medicina Molecular (IMM/FM/UL), Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal.
  - Imagerie Multimodale, Multiéchelles et Modélisation du Tissu Osseux et articulaire (I3MTO), Université d'Orléans, Orléans, France.
  - Bone and Mineral Metabolism Unit, Department of Internal Medicine, University of Florence Medical School, Florence, Italy.
  - Bone and Joint Research Unit, Service of Rheumatology, IIS Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain.
- **Short description of the project**

1. <u>Research idea</u>

   Increasing experimental and clinical data suggest that alterations in subchondral bone are a crucial aspect of the joint damage that characterizes the development and progression of OA and eventually might constitute a disease therapeutic target. Our goal is to examine the contribution of subchondral bone components as predictors of knee osteoarthritis progression and treatment response to apply in trials for Disease Modifying Osteoarthritis Drugs (DMOAD). Using a prospective observational cohort of 800 knee osteoarthritis patients we will test radiographic texture analysis (RTA) a new technique which measures subchondral structural changes, using high resolution digital x-ray (BMA^{tm} D3A Medical Systems). Three of the collaborating partners own this device (SPR and French and Spanish teams). In addition, in an intervention trial with hyaluronic acid, we will test if subchondral bone microanalysis with RTA is a predictor of treatment response. We will also look whether bone biochemical biomarkers are predictors of knee osteoarthritis progression in the context of the prospective observational cohort or of treatment response in the intervention trial.

   In OA animal models, findings from clinical studies will be further tested to precisely analyze the complex molecular pathways and structural changes associated with disease progression and response to treatment. This will enable a mechanistic approach by linking local biochemical markers expression and structural modification to the specific drug effect. By understanding the role of subchondral bone on knee osteoarthritis and its relationship and cross-talk with cartilage structure and mediators, this study might discover new surrogate markers with application in DMOAD trials.

2. <u>Unmet need that will be addressed</u>

   A major goal for osteoarthritis (OA) research is to identify a disease modifying intervention which can slow, halt, or reverse OA progression. Despite its clinical and social relevance, to date no drug has achieved a meaningful disease modifying effect. Moreover, it is widely accepted that the use of insensitive tools for assessment of diagnosis and response to treatment have been hampering progress in this area. In a coordinated multidisciplinary and international effort, this innovative project will assess novel and established biochemical and imaging OA markers. In the process, a comprehensive biomarker assessment will enable the identification and characterization of OA patient subsets based on specific disease drivers and progression criteria thereby contributing to validation of surrogate endpoints to use in DMOAD development.

3. <u>Core methodologies / technologies to be employed</u>

   The proposed study will have the duration of 3 years, starting May 2014 and finishing April 2017, and will encompass 4 major aims.

Aim 1:

Hypothesis generate – To explore associations between subchondral bone changes and disease severity (time frame: 6 months)

Cross-sectional evaluation of the baseline data from EpiReumaPt, a large Portuguese population-based epidemiologic study which gathered 800 knee OA patients. We will investigate in this large cross-sectional study the association between radiological and clinical indices of disease severity with bone texture parameters evaluated by high resolution digital x-ray (Bone MicroAnalysis – BMA). Promptly available blood samples will be used to explore associations between biochemical biomarkers of bone (P1NP, CTX-I, osteocalcin, cathepsin K, sRANKL, OPG, PTHi, DKK1, DKK2, sclerostin and R-spondin) and cartilage (COMP, PIIANP, MMP-3) remodeling and inflammation (IL1, IL6, TNF and TGF-β). We will investigate their association with disease severity BMA and clinical covariates (BMI, age, gender, pain, function, stiffness, QoL).

With this cross-sectional study we will be able to select serological markers associated with more severe structural changes that might constitute potential surrogate markers of severity and response to treatment that will be validated in large prospective clinical studies.

Aim 2:

Prospective Cohort study – To identify whether subchondral texture measures and bone biochemical biomarkers are predictors of knee OA progression. (time frame: 3 years).

A prospective cohort will be annually followed, to assess symptoms (KOOS), QoL (SF-36) and structural (RTA) outcomes. Blood samples will also be collected every 12 months to assess the above mentioned biochemical biomarkers of canonical Wnt signaling pathway modulators and cartilage and bone remodelling.

Aim 3:

Randomized clinical trial (time frame: 2 years) – To test whether the new predictors of disease progression (RTA and bone biochemical biomarkers) are also predictors of treatment response.

An RCT with intra-articular hyaluronic acid will be performed to evaluate if the above mentioned structural and biochemical biomarkers serve as surrogate biomarkers for delay of structural progression (joint space narrowing), reduction of symptoms (KOOS) and improvement in QoL (SF-36).

Aim 4:

Preclinical studies - (time frame: 1.5 year) – To assess predictors of progression and treatment response markers (subchondral bone structure and bone biomarkers) in animal models of early and late knee OA

- **Progression predictors**

A rabbit model of early and late OA will be used to study bone remodeling and the Wnt signaling pathway in the progression of OA. Cross-talk between subchondral bone and cartilage will be assessed by analyzing local expression of the above mentioned biochemical markers. Additionally, cartilage histology, dynamic histomorphometry and micro-CT assessments will provide further insight into bone and cartilage microstructure.

- **Response to treatment**

From the above mentioned animal models we will test the effect of new (eg. anti-DKK1, anti-SOST, anti-CTSK) and established drugs (hyaluronic acid, strontium ranelate) on structural and biochemical markers eventually validating them as the new surrogate markers of treatment response.

4. <u>Relevance to ERRF call for proposals</u>

   This proposal addresses three of the major goals of *the ERRF Call for Research Proposals in the Area of Osteoarthritis*: Predictors of progression of OA, cartilage-bone interactions and treatment strategies in OA. Our collaborative research project relies on distinct teams (from six different institutions) from four EULAR country members with different backgrounds and skills, joined together in a collaborative effort to achieve the aims of the study. Using rigorous methodology we expect to validate predictors for OA progression and define distinct phenotypes of the disease based on a translational mechanistic approach. This knowledge will ultimately lead to a more methodologically robust and reasoned DMOAD trial greatly increasing the possibility of success.

- **Indicative budget**

  The budget needed for the project is approximately 450.000 Euros to be distributed across the 3 years. A detailed budget for each one of the consortium partners will be assigned according to the tasks and workpackages planned.