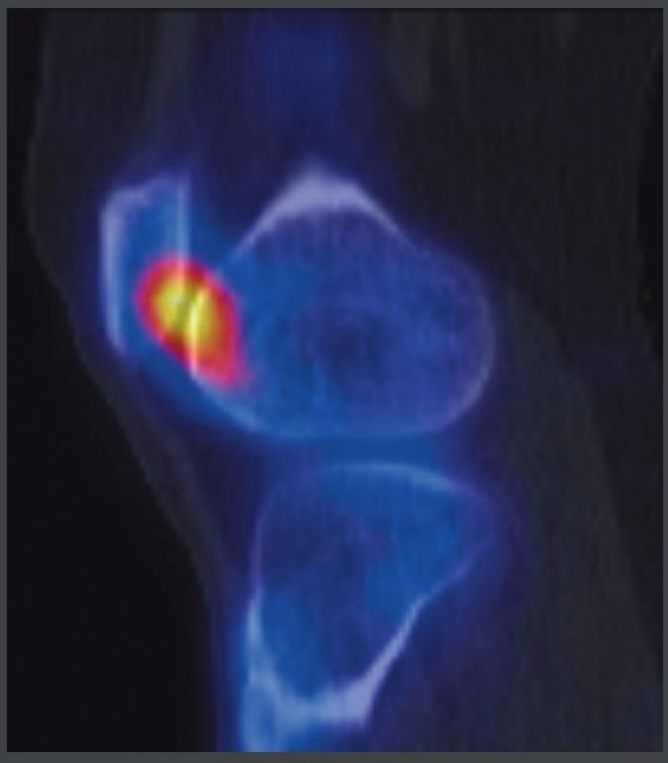
OSTEO ARTHRITIS RESEARCH CENTER BASEL

Universitätsspital Basel

November 16th 2012

# Interdisciplinary Conference On Early Osteoarthritis Basel

## Departments of Orthopaedic Surgery and Rheumatology University Hospital Basel



www.osteoarthritis.ch

# WELCOME TO BASEL

Dear colleagues,

It is with great pleasure that we welcome you to the 1st «**Interdisciplinary Conference On Early Osteoarthritis**» organised by the Departments of Orthopaedic Surgery and Rheumatology at the University Hospital of Basel.

Osteoarthritis is the most common form of joint disease and leading cause of disability among people aged over 65. However, patients may face this disease at any stage in their life, for instance after a serious sports or work injury. Regrettably, osteoarthritis is incurable and only symptoms can be treated. As a consequence, the management and care of osteoarthritis pose a large economic burden in the Western world.

Traditionally, osteoarthritis has been considered to be a simple degenerative disorder, caused by wear and tear of articular cartilage. More recently, it has been appreciated that a complex interaction between inflammatory processes and osteochondral tissue along with impaired biomechanics are crucially involved in onset and progression of osteoarthritis.

The early stage of disease is crucial in terms of both diagnosis and treatment. However, diagnosing early osteoarthritis has been difficult in the past due to a lack of appropriate biomarkers. The number of pharmacological treatment options, notably disease-modifying anti-osteoarthritis drugs, remains limited. To effectively address these issues, an interdisciplinary and translational research approach between orthopaedic clinicians, anatomists, radiologists and basic scientist is of utmost importance.

At this conference, we aim to provide a platform to review and discuss recent and future developments regarding diagnosis, pathogenesis and therapy for osteoarthritis. For this, we have brought together internationally renowned speakers from multiple disciplines operating at the forefront of early osteoarthritis research.

We hope you will enjoy a fruitful meeting and stay in Basel.

Thomas Hügle

Victor Valderrabano

Alan Tyndall

# PROGRAM

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|---|---|
| **9:00** | **Welcome**<br>Thomas Hügle, Victor Valderrabano, Alan Tyndall |
| **9:10** | **Early OA: Definition and differential diagnosis**<br>Alan Tyndall, Basel, Switzerland |
| **9:30** | **Early steps in OA pathogenesis**<br>Cy Frank, Calgary, Canada |
| **9:50** | **The role of inflammation in early OA**<br>Thomas Hügle, Basel, Switzerland |
| **10:10** | **What have early arthritis clinics taught us ?**<br>Jaap van Laar, Newcastle upon Tyne, United Kingdom |
| **10:30** | **Coffee** |
| **11:00** | **Ultrastructural cartilage damage in early OA**<br>Martin Stolz, Southamption, United Kingdom |
| **11:20** | **Subchondral bone pathology in OA**<br>Magdalena Müller-Gerbl, Basel, Switzerland |
| **11:40** | **The biomechanics of early OA**<br>Walter Herzog, Calgary, Canada |
| **12:00** | **Experiences from the Dutch early OA registry**<br>Floris Lafeber, Utrecht, Netherlands |
| **12:20** | **Lunch** |
| **13:30** | **Old and new imaging modalities for OA**<br>Ueli Studler, Basel, Switzerland |
| **13:50** | **Drug therapy for early OA – What´s the evidence ?**<br>Patrick Vavken, Basel, Switzerland |
| **14:10** | **Biologics in OA – Where do we stand ?**<br>Ulrich Walker, Basel, Switzerland |
| **14:30** | **Innovative surgical interventions**<br>Victor Valderrabano, Basel, Switzerland |
| **14:50** | **Coffee** |
| **15:20** | **ADIPOA project: Adipose derived stroma cells for OA**<br>Christian Jorgensen, Montpellier, France |
| **15:50** | **Management of early OA – Round table**<br>Thomas Hügle, Victor Valderrabano, Alan Tyndall |

# EARLY OA: DEFINITION AND DIFFERENTIAL DIAGNOSIS

**ALAN TYNDALL MD** – PROFESSOR OF RHEUMATOLOGY

Department of Rheumatology, University of Basel, Switzerland

**Definition**: Osteoarthritis diseases (OA) are: "The result of both mechanical and biological events that destabilise the normal coupling of degradation and synthesis of articular cartilage chondrocytes and extracellular matrix and subchondral bone. Although they may be initiated by multiple factors, OA diseases involve all the tissues of diarthrodial joints. Ultimately, OA diseases are manifested by morphological, biochemical, molecular and biomechanical changes of both cells and matrix which lead to softening of articular cartilage, sclerosis and eburnation of subchondral bone, osteophytes and subchondral cysts. When clinically evident, OA diseases are characterised by joint pain, tenderness, limitation of movement, crepitus, occasional effusion and variable degrees of inflammation without systemic effects. „

( Kuettner *et al* , OARSI, 1995)

**Differential diagnosis**: Pain +/- swelling in a joint plus radiological signs of OA are not necessarily linked, since not all radiological OA is symptomatic. An intraarticular local anaestheic may confirm that the pain is from the joint itself, and at the same time yield diagnostic fluid. All monoarticular effusions should be aspirated to exclude inflammatory diseases such as crystal arthropathy (CPPD often associates with OA) or infection. On the other hand early OA may be low grade inflammatory fluid („activated OA"), and not yet be visible on normal X-rays, but rather only on MRI or ultrasound. An MRI may also show a non-radiological visible osteonecrosis, stress fractures, internal derangement e.g. meniscus or cruciate rupture or other lesions such as tumour, regional osteoporosis (Sudeck atrophy) , infection etc. Periarticular lesions such as enthesopathy and bursitis are usually distinguishable through careful clinical examination.

# EARLY STEPS IN OA PATHOGENESIS: ACL INJURY & RECONSTRUCTION AS A MODEL

**CY FRANK MD** – PROFESSOR OF ORTHOPEDIC SURGERY

Division of Orthopedics, University of Calgary/Alberta Health Services, Canada

Anterior cruciate ligament (ACL) injury, with or without reconstruction, is known to be risk factor for osteoarthritis onset and progression. Our research group has been using a sheep model to study both isolated and combined ACL injuries and 'idealized' ACL reconstruction using the native ACL replaced immediately and anatomically against other states of quantified instability - to quantify and separate the biological and biomechanical changes that correlate with cartilage damage. Results in these models collectively suggest that synovial inflammation after intra-articular injury (including some effects of ACL surgery itself) amplifies cellular responses in the joint and it also appears to amplify biomechanically-induced articular cartilage damage in some, but not all individuals. The individual-specific nature of these effects remains to be elucidated.

# THE ROLE OF INFLAMMATION IN EARLY OA

**THOMAS HÜGLE MD, PHD** – HEAD OF ORTHOPEDIC RESEARCH

Departments of Orthopedic Surgery and Rheumatology, University of Basel, Switzerland

Dolor, rubor calor, and functiona laesa as the clinical hallmarks of inflammation are frequently encountered in patients with OA. Accordingly, synovitis either histologically or by MRI can be detected in the major part of patients, both in the early and late phase of OA. Other structures in the joint are affected by inflammation as well. Fat tissue or subchondral bone can be infiltrated by macrophages and lymphocytes and/or overexpress inflammatory cytokines such as interleukin-6. Intra-articular crystals such as hydroxyapatite or calciumpyrophosphate, which often occur in the course of osteoarthritis are no longer considered as mere bystanders but active triggers of osteoarthritis, e.g. by activation of the inflammasome leading to interleukin-1 production. Apart from localized inflammation, systemic inflammation e.g. occurring in obesity has also been identified as risk factor for osteoarthritis. The fact that inflammation already occurs in the early phase of osteoarthritis supports its active role in the pathogenesis of osteoarthritis and as target for therapy. In fact, some reports have shown higher degrees of inflammation in the early phase of OA, including expression of tumor necrosis factor or interleukin-1. This might partly explain the observed decreased bone density in early OA in animal models.

# WHAT HAVE EARLY ARTHRITIS CLINICS TAUGHT US?

**JAAP VAN LAAR MD, PHD** – PROFESSOR OF CLINICAL RHEUMATOLOGY

Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University, United Kingdom

Early arthritis clinics are now commonplace in secondary care. Their integration in routine Rheumatology practices followed seminal studies conducted from the '90-ies onwards which demonstrated that prompt diagnosis and treatment of patients presenting with early (rheumatoid) arthritis improved disease control and longterm outcomes with respect to joint damage, functional ability and quality of life. As a result complications such as spinal cord compression, rheumatoid vasculitis, melting cornea are rarely seen anymore. Rheumatology inpatient beds are relics of the past, and Rheumatology has become an office-based specialty where most patients are treated in outpatient clinics, day units or in the community. This transformation was driven by the implementation of new treatment paradigms, e.g. the use of combination therapy, and the advent of potent biologicals including monoclonal antibodies to neutralise the pro-inflammatory cytokines TNF-alpha and IL-6, or to deplete pathogenic B-cells. The identification and treatment-to-target of (rheumatoid) arthritis patients using protocolised disease assessment in a very early stage has changed the goalpost in that drug-free remission has become a reality.

Imaging techniques such as ultrasound and MRI are increasingly being used in the workup of patients with early arthritis, especially in the light of emerging data which show that joint damage may progress in some patients with clinically inactive disease.

The success of early arthritis clinics is contingent on the active participation of primary care doctors and education of patients to reduce patient's and doctor's delay in referral as there is a window of opportunity in early disease where active intervention fundamentally changes the disease course.

In many respects management of osteoarthritis patients is very similar to that of rheumatoid arthritis patients twenty years ago with a paucity of effective disease modifying osteoarthritis drugs (DMOADs) and validated disease activity instruments, and poor understanding of pathogenic pathways. Early osteoarthritis clinics may help change this.

# ULTRASTRUCTURAL CARTILAGE DAMAGE IN EARLY OA

**MARTIN STOLZ PHD** – LECTURER IN ORTHOPEDIC TRIBOLOGY

National Centre for Advanced Tribology at Southampton, University of Southampton, United Kingdom

Articular cartilage matrix is responsible for load bearing and facilitates a smooth articulation of the opposing joint surfaces. These functions are engendered by two main interpenetrating suprastructural compartments, the collagen-containing fibrillar meshwork and the highly hydrated extrafibrillar proteoglycan matrix that comprises the large, cartilage-specific proteoglycan aggrecan. Both aggrecan and the collagens aggregates are highly ordered structures that are processed in hierarchically self-assembly and allow the tissue to dynamically respond to altered environmental conditions. The chemical and physical states of the proteoglycans or collagens also play an important role in defining cartilage pathology. A loss of proteoglycans or collagens may change the water content and affect tissue functional properties, which over time can damage the tissue and ultimately turn healthy into osteoarthritic cartilage. Here, we aim to get insights into the series of steps involved in the degradation and disassembly of the hierarchical fibrillar architecture at high resolution, preferably at the authentic location within cartilage. Articular cartilages are permeated by small prototypic fibrils with a homogeneous diameter of 18.5 nm that can align their D-periodic register and merge into larger fibres by lateral association. Interestingly, these fibres have tissue-specific organizations. They are twisted ropes in superficial regions of knee-joints or assemble into parallel aligned cable-like structures in deeper regions of knee joint or throughout hip joints articular cartilage. These novel observations contribute to an improved understanding of fibre biogenesis, function, and homeostasis in hyaline cartilage.

# SUBCHONDRAL BONE PATHOLOGY IN OA

**MAGDALENA MÜLLER-GERBL MD** – PROFESSOR OF MACROSCOPIC ANATOMY

Department of Biomedicine, Institute of Anatomy Basel, University of Basel, Switzerland

Osteoarthritis is characterized by cartilage degradation, subchondral sclerosis and osteophytes. The subchondral bone plate, which adapts to mechanical loading, plays an active role in the development of osteoarthritis, e.g. by abnormal transmission of stress to the overlying cartilage. Osteoarthritis is not only characterized by hypo- respectively hypermineralization of the subchondral bone but also by topographical changes of bone density maxima. Interestingly, subchondral bone alterations are partly reversible after osteotomy. In the early phase of osteoarthritis, animal studies have demonstrated a biphasic course of subchondral bone mineralisation. Simultaneous to the occurrence of cartilage defects, bone mineral density decreased followed by alteration in the mineralization distribution of the subchondral bone plate, in later stages bone mineral density increased again.

# THE BIOMECHANICS OF EARLY OA

**WALTER HERZOG PHD** – PROFESSOR OF KINESIOLOGY, ENGINEERING AND MEDICINE

Faculties of Kinesiology, Engineering and Medicine, University of Calgary, Canada

Biomechanics is the study of forces on biological systems and the effects that these forces have on the system. In the context of osteoarthritis (OA), the forces acting in and on joints have been thought to be crucial, and the greatest forces are delivered to the joints by muscular contraction. For example, knee extensor forces in the cat reach 4-5 times body weight for slow walking and can reach 10 times body weight for a young, healthy person.

Muscles are critical in maintaining joint stability in healthy and diseased joints by providing shock absorption and ensuring good load transmission across joints through proper alignment of the articulating surfaces. Muscle weakness, and associated change in the biomechanics of joints, has been associated with onset and progression of OA and is one of the earliest and most frequent signs for OA onset, and has been argued to be a better predictor of OA than joint space narrowing or pain. Muscle weakness might be a unifying feature for other risk factors, since strength decreases with age, is smaller in women compared to men, is decreased relative to mass in obese individuals, and is reduced post joint injuries.

I will discuss selected examples of changes in muscle forces with the onset and progression of OA, provide evidence that muscle weakness is an independent risk factor for the onset of OA, and that altered coordination of the knee extensor muscles has surprising effects on the mechanics of the patello-femoral joint. Although muscles are probably the least studied of the tissues in OA onset and progression, and receive a fraction of the attention given to cartilage, bone and ligaments, muscles may end up being more important than all the other tissues in deciding the fate of aging, diseased and traumatized joints, and may offer unexplored opportunities for effective rehabilitation intervention.

# EXPERIENCES FROM THE DUTCH EARLY OA REGISTRY (CHECK)

**FLORIS LAFEBER PHD** – PROFESSOR OF EXPERIMENTAL RHEUMATOLOGY

Department of Rheumatology and Clinical Immunology, UMC Utrecht, Netherlands

## COHORT HIP & COHORT KNEE (CHECK)

**CHECK** (Cohort Hip & Cohort Knee) is a cohort of 1002 participants with pain and/or stiffness of hip and/or knee, age 45-65 years, and without a previous visit or with a first visit no longer than six months ago to the general practitioner for these complaints were included. At baseline 82% of the participants had knee complaints (18% had hip complaints only), and the radiographic knee damage of the entire cohort was limited with K&L grade in the knee of 0 in 81%, I in 16%, II in 3%, and III in 0.4%. Relevant characteristics of this prospective study are:

1) inception cohort - OA patients are followed from their first symptoms onwards
2) 10 year follow-up with annual assessments – this allows to pick up fluctuations over time
3) 3) annual assessments of etiological factors - biomechanical, metabolic, and psychological factors
4) annual assessment of disease outcome at various levels - joint tissue damage, pain, and disability. Most importantly, due to the robust infrastructure, at 8 years loss to follow-up is less than 10%.

**Goal of this cohort is to:**

To study the development and course of OA (pain, function, and joint damage)

To study the mechanisms (biomechanical, metabolic, and psychological) that relate to outcomes of OA (pain, function, and joint damage)

To identify markers for diagnosis and prognosis of outcomes of OA (pain, function, and joint damage)

The CHECK cohort offers the unique possibility to answer the research questions.

# OLD AND NEW IMAGING MODALITIES FOR OSTEOARTHRITS

**UELI STUDLER MD** – HEAD OF MUSCULOSKELETAL DIAGNOSTICS

Department of Radiology, University of Basel, Switzerland

Radiographs play still an important role to confirm the diagnosis and assess the severity of osteoarthritis (OA). Radiography can clearly show osseous changes, such as osteophytes, cysts and sclerosis. However, radiographs lack the ability to directly visualize cartilage loss or soft-tissue alterations. Radiographs are therefore insensitive for confirming early disease. Magnetic resonance imaging (MRI) is capable of delineating cartilage and other joint tissues directly. MRI allows detection of subtle morphologic damage and assessment of compositional changes. Investigational MRI techniques include T2 relaxation mapping, dGEMRIC, and diffusion weighted imaging of cartilage. First experiences indicate the potential of new hybrid technologies such as SPECT/CT or PET/MRI to provide both functional and anatomical information.

# DRUG THERAPY FOR EARLY OA WHAT'S THE EVIDENCE?

**PATRICK VAVKEN MD, MSC** – ORTHOPEDIC RESIDENT

Department of Orthopaedic Surgery, University of Basel, Switzerland

In accordance with recent evidence-based recommendations of the Osteoarthritis Research Society International (OARSI), the European League Against Rheumatism (EULAR), and the American College of Rheumatology, the mainstay of treatment in early OA is still non-surgical, i.e. a combination of non-pharmacological and pharmacological modalities.

Drug therapy can be grossly categorized by the route of administration into systemic, topical, and intra-articular therapies.

Systemic oral drug therapy includes analgesics (NSAIDs, acetaminophen/paracetamol, coxibs, opioids), SYSADOA (SYmptomatic Slow Acting Drugs for OA including avocado/soybean, unsaponifiables (ASU), chondroitin, diacerein and glucosamine) and others such as sex hormones and psychotropic drugs. The Levels of Evidence for analgesics are 1A (meta-analysis of RCTs) and 1B (at least one RCT), and these drugs are still the first line treatment with A and B level recommendation. SYSADOA receive a high level recommendation by the OARSI and EULAR, but not the ACR, most likely because of differences in the assessed products.

Topical drug therapy consists of NSAID and capsaicin application and receive a Level 1A recommendation, although with limited effect sizes.

Intra-articular drug therapy consists of corticosteroids, hyaluronic acid, and most recently autologous blood products. While no consensus exists for the latter, the former receive a Level C recommendation based on Level 1B evidence.

Based on these findings the OARSI, EULAR, and ACR recommend an initial drug treatment with paracetamol in combination with non-pharmacological modalities. Topical NSAID may be safely used as adjuncts. SYSADOA have symptomatic effects and may modify structure, but should be discontinued after 6 months if no benefit is seen. The ACR recommends that patients do not use SYSADOA. Patients unresponsive to paracetamol should be treated with NSAID and gastroprotective agents, or a coxib, with additional opioids as needed. Intra-articular injection should be reserved for flares of knee pain.

# BIOLOGICS IN OA – WHERE DO WE STAND?

**ULRICH WALKER MD, PHD** – PROFESSOR OF RHEUMATOLOGY

Department of Rheumatology, University of Basel, Switzerland

Biologics are medicinal products created by biologic processes, rather than chemistry and are composed of cells, tissues, or are produced by biotechnology and other technologies.

In osteoarthritis (OA), biologics are being designed to target a variety of biological processes that include pain, inflammation, or cartilage degeneration. Pro-inflammatory cytokines (IL-1 and TNF-alpha) and nerve growth factor (NGF) are upregulated in OA and promote joint pain. Tanezumab, a humanized monoclonal antibody directed against anti-NGF continues to be evaluated in clinical trials, as is botulinus toxin, a peptide that blocks neuromuscular transmission by impairing acetylcholine release, inhibits cytokines, neuropeptides and other inflammatory mediators in OA, and has an intrinsic anti-nociceptive mechanism.

IL-1 and TNF-alpha are catabolic cytokines that participate in the degradation of the hyaline cartilage. A variety of biologics either target IL-1 directly, or the IL-1 receptor which is present on chondrocytes. Anti-IL-2 strategies are currently being evaluated in several clinical OA trials. The available data of biologics that neutralize TNF-alpha do not support short term efficacy in OA.

Recombinant fibroblast growth factor promotes anabolic processes in the articular cartilage of adult animals and stimulates proteoglycan synthesis. A phase II study in knee OA is ongoing.

Platelet rich plasma may provide platelet cytokines that regulate cell migration, cell proliferation, angiogenesis, inflammation mediation, and collagen synthesis. Intra-articular injections of platelet rich plasma are being evaluated in clinical trials but there is no consensus concerning the minimum biochemical activity, dosing or dose schedule.

# EARLY OA: INNOVATIVE SURGICAL INTERVENTIONS

**VICTOR VALDERRABANO MD, PHD** – PROFESSOR OF ORTHOPAEDIC SURGERY

Department of Orthopaedic Surgery, University of Basel, Switzerland

Young patients with early osteoarthritis may become a challenge for the treating orthopaedic surgeon due to high expectation, high functional demands, and limited treatment options. The treatment option include conservative measures and surgical procedures, which may be divided into two main groups: procedures that preserve the joint and those that do not. Joint sacrificing procedures such as joint arthrodesis or total or partial joint replacement are controversial in younger patients, who are usually less satisfied and experience higher failure rate. Furthermore, arthrodesis of an joint may result in functional restriction, gait abnormalities, and development of secondary degenerative changes in the adjacent joints. Conservative measures such as joint injections, physical therapy, weight loss etc. may provide short-term pain relief and regain functional activities. However, conservative measures are usually only palliative in nature and most patients need further treatment in the long-term. In the last decades cartilage repair procedures are gaining more interest due to their potential to provide the postoperative pain relief and to stop or to decrease the progression of degenerative changes. Cartilage repair procedures include osteochondral autograft transfer (OAT)/mosaicplasty, bulk allograft transplantation, autologous chondrocyte implantation, and autologous matrix-induced chondrocytogenesis (AMIC). We successfully perform AMIC procedure in patients with early osteoarthritis of the knee or ankle joint, as this procedures provide following advantages: significant pain relief, excellent clinical and radiological results, single step procedure, no harvesting morbidity. Joint distraction is an another promising treatment approach, especially in patients with posttraumatic osteoarthritis. Adding motion to distraction may have an early and sustained beneficial effect in this patient group. In patients with concomitant substantial deformities, such as valgus or varus deformity in the coronal plane a realignment surgery may improve biomechanics of osteoarthritic joint resulting in significant pain relief, improved function, and decreasing radiological signs of arthritis.

The planning of treatment of young patients with early osteoarthritis is not simple and is in most cases highly individual. Preoperative planning include meticulous analysis and understanding of osteoarthritis aetiology, careful physical examination, and comprehensive radiologic assessment.

# ADIPOA PROJECT : ADIPOSE DERIVED STROMA CELLS FOR OSTEOARTHRITIS

**CHRISTIAN JORGENSEN MD, PHD** – PROFESSOR OF IMMUNOLOGY AND RHEUMATOLOGY (ON BEHALF OF THE ADIPOA CONSORTIUM)

INSERM U 844 and Montpellier University Hospital, France

Osteoarthritis (OA) is a degenerative joint disease, with loss of matrix, fibrillation, formation of fissures, and ultimately complete loss of the cartilage surface, for which no efficient therapy is available. OA is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life, with strong impact on quality of life of healthy aging population in European countries. Cartilage is known to be populated by chondrocytes but also in a limited number of cells with characteristics of mesenchymal stromal cells and side population. Culture expanded adipose derived stromal cells CD73/CD90/CD105 triple positive subpopulation had multipotency for chondrogenic, osteogenic and adipogenic differentiation. We have shown that stromal cells, in particular adipose derived stromal cells have an immuno-modulatory and anti-fibrotic activity, protect cells for oxidative stress through secreted growth factors. We have shown that Intra-articular injections of mesenchymal stromal cells prevent the development of osteoarthritis in two large animal models, but the mechanism are unknown, and the role of endogenous stem cells present in the cartilage is elusive.

The objectives of this collaborative FP7 project are to establish stem cell based regenerative medicine in Rheumatology. For this, we have performed preclinical experiments and toxicology studies using increasing dose of adipose-derived stem cells (ASC) and we propose to validate new concepts for OA therapy in open phase 1 dose-escalating clinical trials using autologous ASC focusing on symptomatic OA according to EMEA guidelines. We demonstrate that autologous ASC are optimal candidates to stimulate the regeneration of injured cartilage.

# NOTES

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