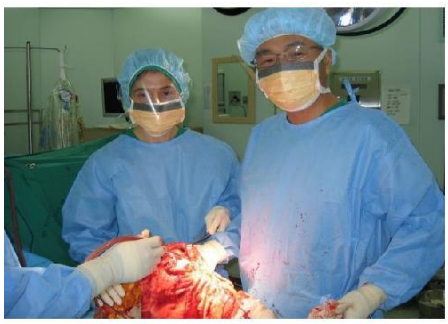
Research history and declaration of interest

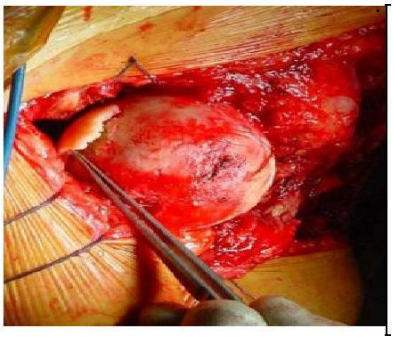
My ultimate goal is to facilitate the design, translation and implementation of relevant solutions for disease prevention and health care that enable regenerating damaged or lost connective tissues. Efficient methods for substituting lost or damaged cartilage, bone, adipose tissue and skin as well as non-invasive therapies for musculoskeletal diseases are long sought after however, to date incompletely addressed. It is my opinion that clinically oriented research, interdisciplinary as well as training and education are crucial requirements for fast forwarding development application of regenerative medicine principles and technologies.

Trained as an orthopedist I was committed to applying the advanced most techniques and concepts available at the time. I was enrolled in several fellowships granted by international professional boards in different international settings in order to acquire expertize in modern technology at to be exposed to clinical research;

Topic &Sponsor	Place & Mentor	Duration	Research & training
Knee Surgery, Sports Traumatology, Arthroscopy Association (ESSKA	University Hospital Ghent, , Ghent, Belgium *prof*. R.*Verdonk* Md PhD	Feb 2006 – March 2006	clinical evaluation of meniscal grafts (cryopreserved allogenic graft) methods of harvesting, preservation and re-implantation
Knee, arthroscopy and hip surgery (clinical and research fellow)	Gyeong Sang National University College of Medicine, Jinju, South Korea Prof. Se Hyun Cho Md PhD,	Feb 2004 – Oct 2004	Clinical and radiological evaluation of total knee arthroplasty (TKA) prevention of sepsis and septic prosthesis management, implementing a novel method of bone substitution after resection of the infected implant.
Knee arthroscopic surgery and replacement – Zimmer	Seoul National University Hospital Bundang, Seoul, South Korea Prof. Kim Tae Kyun Md PhD	July 2004	Clinical, radiological and MRI evaluation of TKA, implementation of OATS (osseocartilaginous autologous grafts) for cartilage repair procedure in the clinical settings and instrumentation development. Evaluation of the implanted knees. Implementation of computer assisted surgery (CAS) for TKR clinical study and Zimmer product development

The experience of advanced operative and clinical research for total joint replacement procedures I was acquiring was great, still images of huge joint sacrifice stood in my mind.





I wondered if we could have an easy to use, injectable solution to prevent or completelly restore degraded joints. Embracing the fascinating principles of Regenerative medicine, I became involved in clinical trials dedicated to investigate bone substitutes and several biologic injectables (platelet rich plasma and a modified form of autologus concentrated serum) attempting regeneration/replacement/healing of missing bone parts and atrhritic joints.

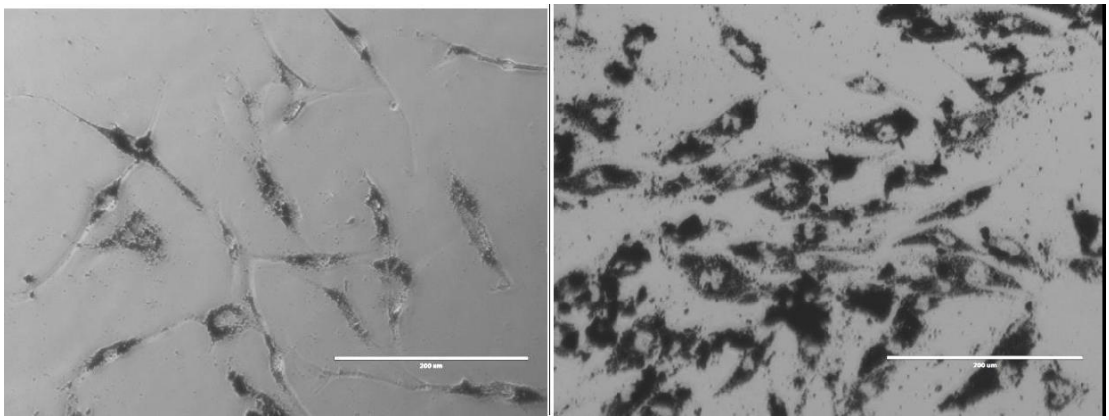
The use of synthetic bone substitutes Ceraform Teknimed	University of Medicine and Pharmacy Iasi Romania Prof Dr Paul Botez Md PhD	July 2006-October 2009	Clinical, radiological and histological evaluation of CERAFORM ® as a modality of biological bone substitution- a study on 44 cases with 2 years follow up
Goldic® as a modality of treating knee arthritis	University Hospital Iasi	June 2012-July 2014	Clinical, radiological and MRI evaluation of knee osteoarthritic patients treated with PRP versus Goldic ☺

Scientific curiosity ignited, I further enrolled in a PhD and looked for training and guidance from the experts in the field of medical regeneration, particularly aiming joint biologic resurfacing. In parallel I initiated a RM foundation in my home country dedicated to facilitating research, enable interdisciplinary collaboration and provide specific education

Topic &Sponsor	**Place & Mentor**	**Duration**	**Research & training**
Mesenchymal Stem Cells culture and differentiation techniques Osteoarthritis Research Society International (OARSI)-	Institute for Regenerative Medicine (REMEDI), National University of Ireland, Galway Prof. Frank Barry	April 2010-April 2011	Cell sources for cartilage regeneration. Identification of adult stem mesenchymal stem cell sources in trabecular bone, synovial tissue, periarticular adipose tissue, comparison of expansion, differentiation, capability to populate a nanostructured scaffold, survival and efficiency of colonisation. cell culture, assessment of differentiation, life cell imaging technology, cell scaffold interaction
Cartilage progenitors in OA- University of Medicine and Pharmacy Iasi Romania	University of Medicine and Pharmacy Iasi Romania Prof Dr Florin Zugun Eloae	May 2011-May 2012	Detection of osteoarthritic cartilage progenitor populations (presence of MSC like population in OA cartilage explants), isolation, phenotypic characterization.
EU Project StemMad	**University of Copenhagen Denmark Prod Dr Poul Hyttel**	August 2014-April 2015	**development of cellular based** models for study of Alzheimer, frontotemporal degeneration (FTD) neuropathic pain ectodermal differentiation of mesenchymal cells and adipose derived stem cells, cell culture, spontaneous three dimensional cell culture, fluorescence microscopy immunocytochemistry, qPCR .

Currently, at National institute of Advanced Physics Iasi I have contributed to putting together a stem cell lab. We test proprietary magnetic nanoparticles (MNPs) aiming to make possible

a (stem) cell tracking method that could be applied potentially for any form of cell therapy. Bone marrow, trabecular bone and adipose derived stem cells (ADSCs) are tested for their capability to uptake MNPs while retaining main phenotypic features (proliferative, differentiation and migratory capability) using 2D and 3D systems. MNP loaded cells targeting capabilities are tested under magnetic field for potential application in hyperthermia (HT) treatment of solid tumors and/or HT based controlled release of drugs and/or bioactive molecules. This is a fascinating opportunity to intersect RM and nanomedicine taking advantage of recent developments in both field to advance clinical – prone applications.



Adipose derived stem cells loaded with Fe-Cr-Nb-B nanoparticles (day 5 and 10 incubation)

Any sound and feasible solution to prevent and treat musculoskeletal tissues degenerative disease due to aging, overuse, mechanical misbalance, that could be rapid applicable from efficiency and regulatory perspectives have to start from the clinic in the form of well-defined unmet need and to go back to the clinic as a competitive product. I find that only reasonable modality to overcome the rocky road in between the two landmarks is to deepen knowledge about the (stem cell based) regenerative process itself. For many reasons of which I will only mention biomechanical context and timing, tissues that function as supporting and/or barrier structures (such as those pertaining to musculoskeletal system – bone, cartilage, tendons, muscle) do not allow in situ regeneration by recapitulating development. Bio mimicry and/or modulation of existent regeneration capability are promising in that they could actually burn the stages of tissue formation with the use of technology.

Aim is therefore, to pursue several research tracks, focusing on adipose stem cells and adipose derived MUSE cells as therapeutic agents, on stem cell derivatives, - exosomes as injectable cell free formulation for tissue regeneration and on additive manufacturing of cartilage, tendon and skin for in situ bio printing.

AMUSE -Adipose derived **multilineage differentiating stress enduring MUSE (cells** and stem cells) for the prevention and treatment of posttraumatic arthritis

Development of a strategy for prevention and treatment of posttraumatic arthritis (PTA)) using adipose tissue derived MUSE cells in combination with adipose derived stem cells (ADSCs) as therapeutic agent.

Expected results and impact

A combination of autologous adipose tissue derived MUSE and ADSCS has the potential in modifying PTA natural history by means of structural as well as paracrine effect. Due to their superior survival and rapid differentiation potential MUSE cell could engraft and participate to restoring the cellular content of degenerated cartilage. In the initial stages after cell administration, ADSCs could serve as cell shuttles for delivery of biologically active modulating the pro inflammatory milieu. By profiling both cells types transcriptome using NGS and bioinformatics analysis of possible pathways a better understanding of potential mechanism of action as well as cell based product characterization will be possible.

Adipose derived stem cells exosomes for the treatment of osteoarthritis.

ADSCs derived exosomes as therapeutic agents for the treatment of OA, as a form of non-invasive, on the shelf cell free therapy.

Expected results and Impact

Delivery of a patentable method for ADSCs collection, minimal manipulation, exosome extraction in order to offer the basis for point of care therapies. Here the interest goes to chondrocyte biology and anti-inflammatory modulation aiming OA therapies however, similar approaches can be expanded in order to compose relevant interventions for other musculoskeletal and potentially non musculoskeletal degenerative diseases. As such, tendinosis, bone non unions or avascular necrosis as well as peripheral arterial disease and neuropathies could be further investigated as therapeutic end points following similar strategies. By this, a method for treating degenerative diseases could be established that could be of and economic importance, significantly reducing costs related to disease treatment, nursing and disabilities. The outcome in provision of an efficient health care intervention would benefit the individual quality of life, the society at a general level. The approach has the potential in generating patentable interventions that could result in creation of SME(s) involved in product development and commercialization.

Additive manufacturing for cartilage and skin engineering

The use of a hydrogel (collagen/PCL and collagen/fibrinogen respectively) and cells (chondrocyte progenitors and dermal fibroblasts, keratinocytes respectively) for in situ bio printing of de novo tissue in animal model of cartilage and skin defects

Expected results and impact

Bio printing is capable of delivering a combination of scaffold and cells in a layer by layer manner. Suspended cells (or spheroids) come in close –hydrogel mediated contact within the bio ink droplets. Bio printing as a modality of directed self-assembly where separate elements deposited are allowed to fuse together during the maturation process allow for post printing cell cohesion similar to developmental stages. Tissue fusion represents the process by which isolated cell population come in contact and adhere by means of cell -cell interaction, cell matrix interaction and ECM remodeling.. By mimicking developmental stages, tissues of a cellular heterogeneity, topography and ECM proteins organization that mimic natural tissue,

can be obtain. Adapting existing equipment to operating room conditions in order to allow direct deposit of de novo tissues will facilitate graft integration and improve postsurgical recovery by minimalizing risk for immediate and delayed complications.

Another obligatory requirement for successful conceiving, designing and applying regenerative principles is to update educational principles.

Deep knowledge and expertise in life science, engineering or artificial intelligence disciplines (or a combination) is not only highly desirable but obligatory for any RM member team. However, becoming a true RM professional is simply more than being an well-educated expert. Improved humanistic and humanitarian values need to be acquired in order to enable true multidisciplinarity, to develop build in ethical perspectives on aspects such as research design and dissemination of results, intellectual property, and product commercialization.

Therefore updated educational goals that deliver in the same time scientific knowledge as well as ethical principles, methods for emotional self-control and a meta analytic approach for personal and group development and goal achievement.

Alongside with other advanced technologies prone to impact human life in a significant manner, RM needs to be generated and pursued from the perspective of „ collective intelligence" generated by individuals but overcoming single individual capability. Dealing with generated IP, result dissemination and productization in this context, require a next level in human consciousness, to be actively developed by nowadays educators.