NANOTECHNOLOGIES FOR THE EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

NanoDiaRA

NMP4-LA-2009-228929

Margarethe Hofmann-Amtenbrink
Scientific Coordination

Advanced Technologies for an Ageing Population
Glasgow, 23rd - 24th March, 2011

SEVENTH FRAMEWORK PROGRAMME

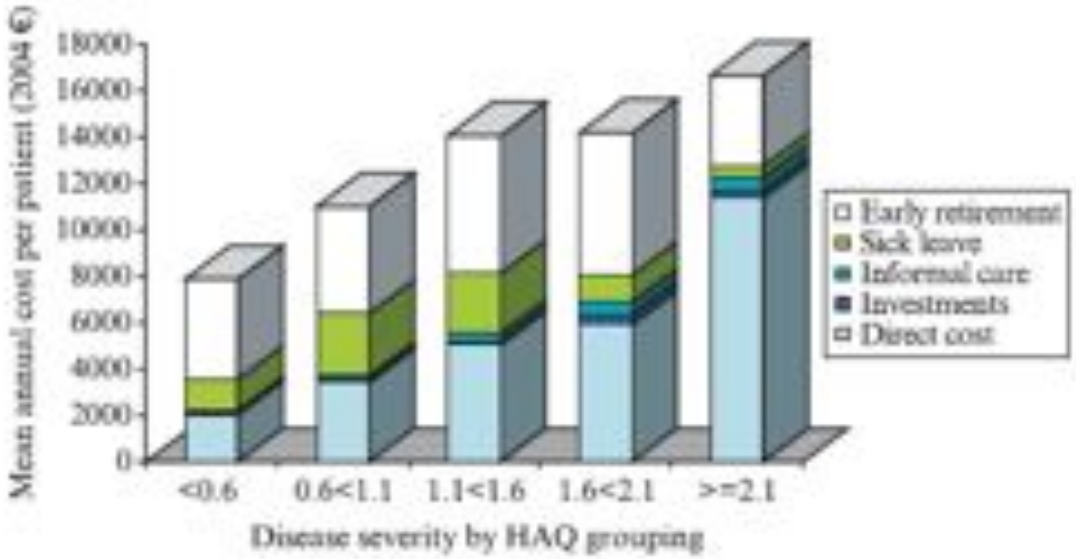
The aim of creating NanoDiaRA

- Unmet needs in arthritis
- Novel tools using nanotechnology approaches

Why Arthritis?

Studies* concluded that RA

- leads to substantially increased health care costs,
- severely limits patient involvement in the workforce,
- reduces the ability to perform normal activities and therefore reduce drastically the quality of life.



**HAQ=Health Assessment Questionnaire: 0 = without difficulty, 3=unable to perform

* G. Kobelt, „Health economic issues in rheumatoid arthritis", Scandinavian Journal of Rheumatology, 2006, 35 (6), pp 4125- 425
G. Kobelt et al, „Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study", Joint Bone Spine 2008, 75, pp 408-415

Rheumatoid Arthritis

mild **moderate** **severe.**

Rheumatoid Arthritis RA - the disease

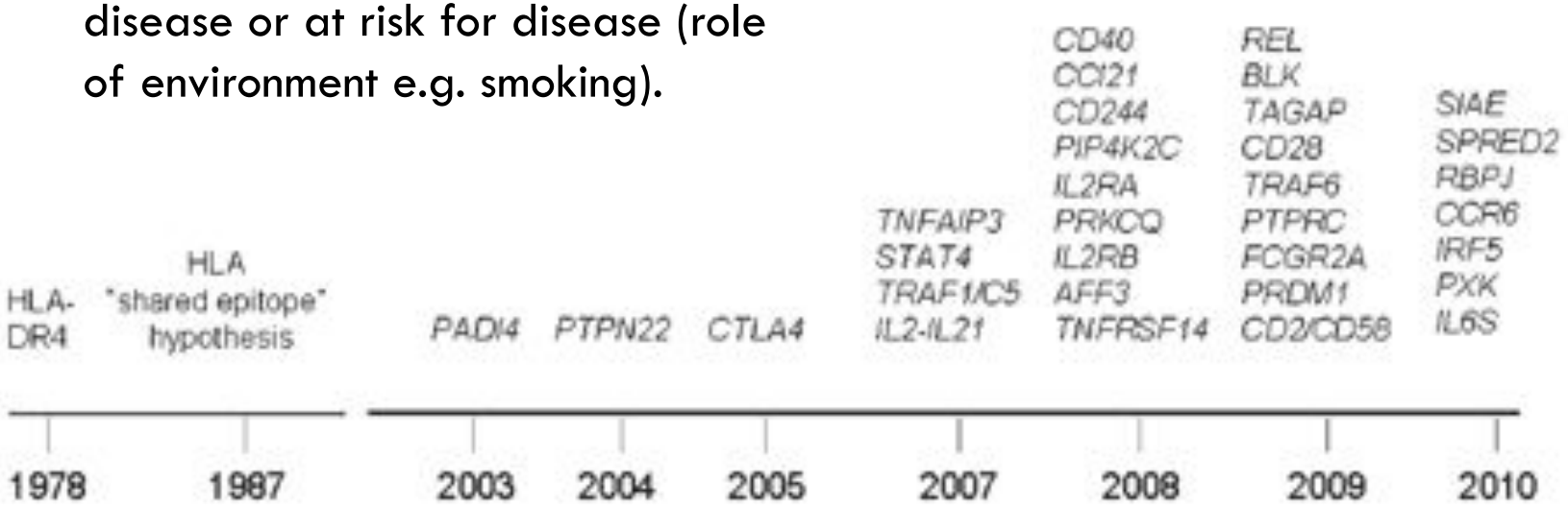
Rheumatoid arthritis (RA):

- Is a chronic systemic autoimmune inflammatory disease that is characterized by symmetrical synovitis, progressive joint damage, pain, fatigue, and disability[1].
- It may result from the interaction of many factors such as genetics, hormones, and the environment.

[1]T. Yoshino, Intern Med 50: 269-275, 2011

Genetic Involvement

- More than 35 genetic regions associated with RA but:
  - Gene action cannot be properly understood without examining a relevant phenotype: Implies more precise definition of the clinical disease phenotype, more research to characterize individuals as subphenotypes, persons with disease or at risk for disease (role of environment e.g. smoking).



A timeline of gene discovery in rheumatoid arthritis

Peter K. Gregersen, Bulletin of the NYU Hospital for Joint Diseases 2010;68(3):179-82

RA - the requirements

- RA criteria require the presence of established joint damage; thus, they are limited in their ability to identify patients with early disease
- Early aggressive therapy has the potential to minimize joint damage and significantly suppress disease progression
- There is a need for criteria that will facilitate early diagnosis.

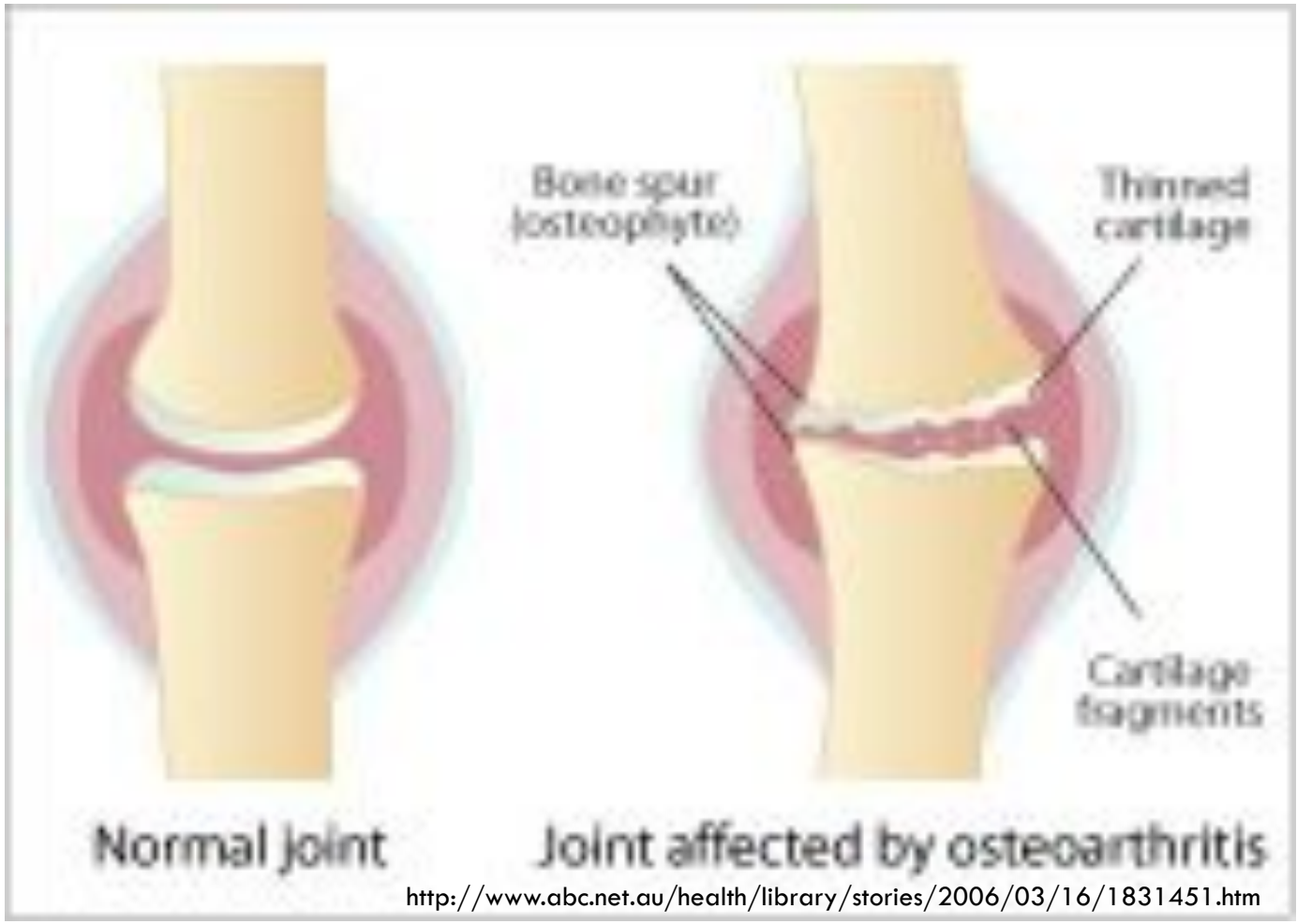
J. Sokolove, V. Strand, Bulletin of the NYU Hospital for Joint Diseases 2010;68(3):232-8

Social impact of Arthritis

- Work disability is a common and the most expensive consequence of rheumatoid arthritis (RA), resulting in lost income for the patient and less productivity for society[1].
- Ample evidence indicates that physically demanding jobs, lower educational level, older age, and longer duration plus severity of RA raise the risk of work disability[1].
- The global prevalence of RA based on literature data is at about 0.5-1.0%[2]. In Great Britain about12% of the population aged 65 years are affected with RA[2].
- In USA estimated 16% of the population had some form of arthritis in 1997[3]

[1]K. Puolakka et al., Ann Rheum Dis 2005, 64,130–133
[2]Laidmaë, V.I. and Tulva, T.: The Internet Journal of Rheumatology 4 (2008), Nr. 2
[3]J.Y. Reginster, Rheumatology (2002) 41 (suppl 1): 3-6.

Osteoarthritis



http://www.abc.net.au/health/library/stories/2006/03/16/1831451.htm

Osteoarthritis OA - the disease

Osteoarthritis (OA):

- Is an age-related degenerative disease of cartilaginous tissues[1]
- Is the most frequent chronic musculoskeletal disease and by far the most common cause limiting the daily activities of the elderly population[2]
- Usually develops without known cause but there is evidence of risk factors such as genetic predisposition, age, obesity, female sex, greater bone density, joint laxity, and excessive mechanical loading[2]

[1]X.Li et al, Mol Biol Rep 2011, Feb 16
[2]*L. Punzi et al.*, Swiss Med Wkly. 2010;140:w13098

Social impact of Osteoarthritis

- Osteoarthritis (OA) has a major impact on functioning and independence and ranks among the top ten causes of disability worldwide.
- Symptoms and disability increase in prevalence with increasing age and people with OA use health-care services at a higher rate than a representative group of all adults.
- Annual costs of end-stage knee and hip OA for at least 65 years old people were determined to be $3800 = 2x that of normal OA population[1]
- The annual cost to society in medical care and wage loss due to arthritis is expected to reach nearly $100 billion dollars by 2020, with consequent increased spending on diagnosis and therapy, side-effect prevention and lost earnings[2]

[1] R.D. Altmann, *Am J Manag Care. 2010;16:S41-S47*
[2] *L. Punzi et al.,* Swiss Med Wkly. 2010;140:w13098
Other info: S. Gupta, Rheumatology 2005;44:1531–1537

RA and OA – the treatment

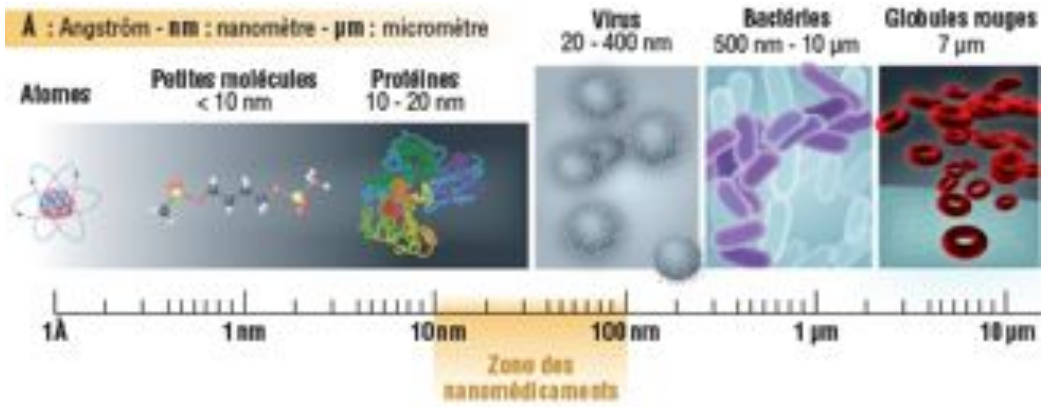
- Current therapeutic approaches for osteoarthritis (OA) are largely palliative dealing with symptoms[1]
- Modifying the structural progression of OA has become a focus of drug development[1]
- Very early use of effective DMARDs is a key-issue in the treatment of patients with the risk of developing persistent and erosive arthritis[2]
- Effective treatments in rheumatoid arthritis (RA) and osteoarthritis (OA) are therefore based on early detection of disease and monitoring treatment efficacy.

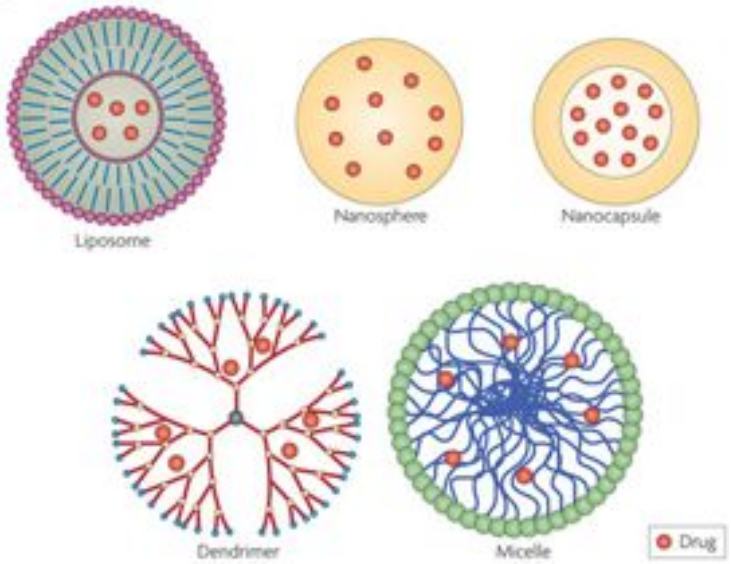
[1]D.J. Hunter, Nature Reviews Rheumatology 7, 13-22 (January 2011)
[2]L. M. da MotaRev. Assoc. Med. Bras. vol.56 no.3 São Paulo 2010

Nanotechnology in Medicine

- Pysico-chemical properties of drugs are not often favaorable to cross biologic/ enzyme barriers
- Leakage to other tissues

- Nanotransporters < μM
- ~70x smaller than red blood cells
- Targeting of drugs



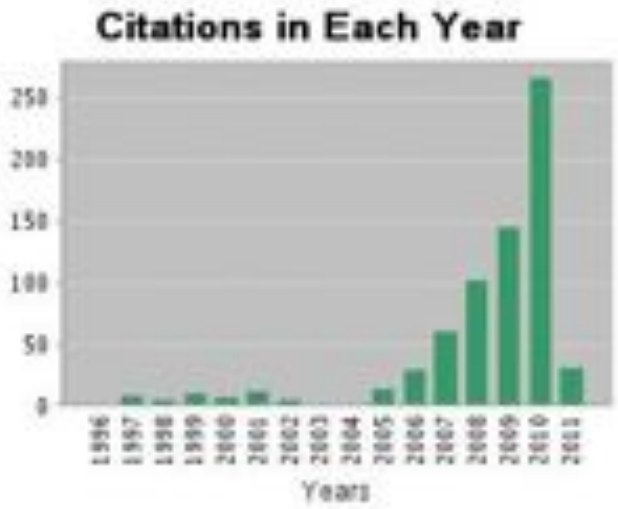


- New materials and new physical concepts
- Lipids, polymers: assemly of particular structures

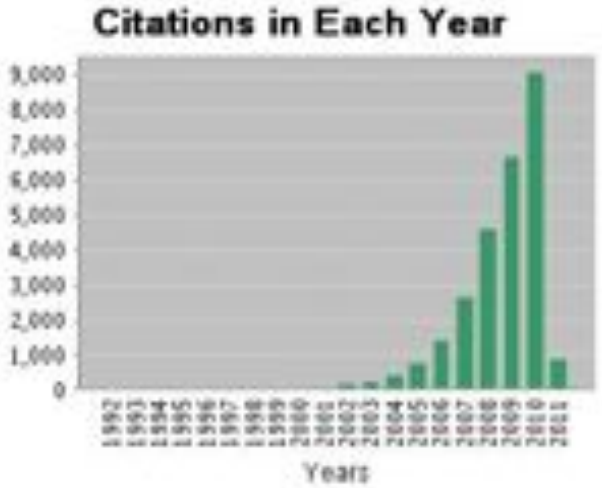
- Distribution related to the physical-chemical properties of the nanovectors
- Control of the distribution to tissues, cells and even subcellular compartments

Nature Reviews/Neurosciences, adapted by M. Dreano

Research Activities on Nanotechnology Based Diagnosis in Cancer and Arthritis



Topic=(**arthrit*** AND Diagno* AND Nano*) all year (total 37)



Topic = (**cancer*** AND Diagno* AND Nano*) all year (total 1399)

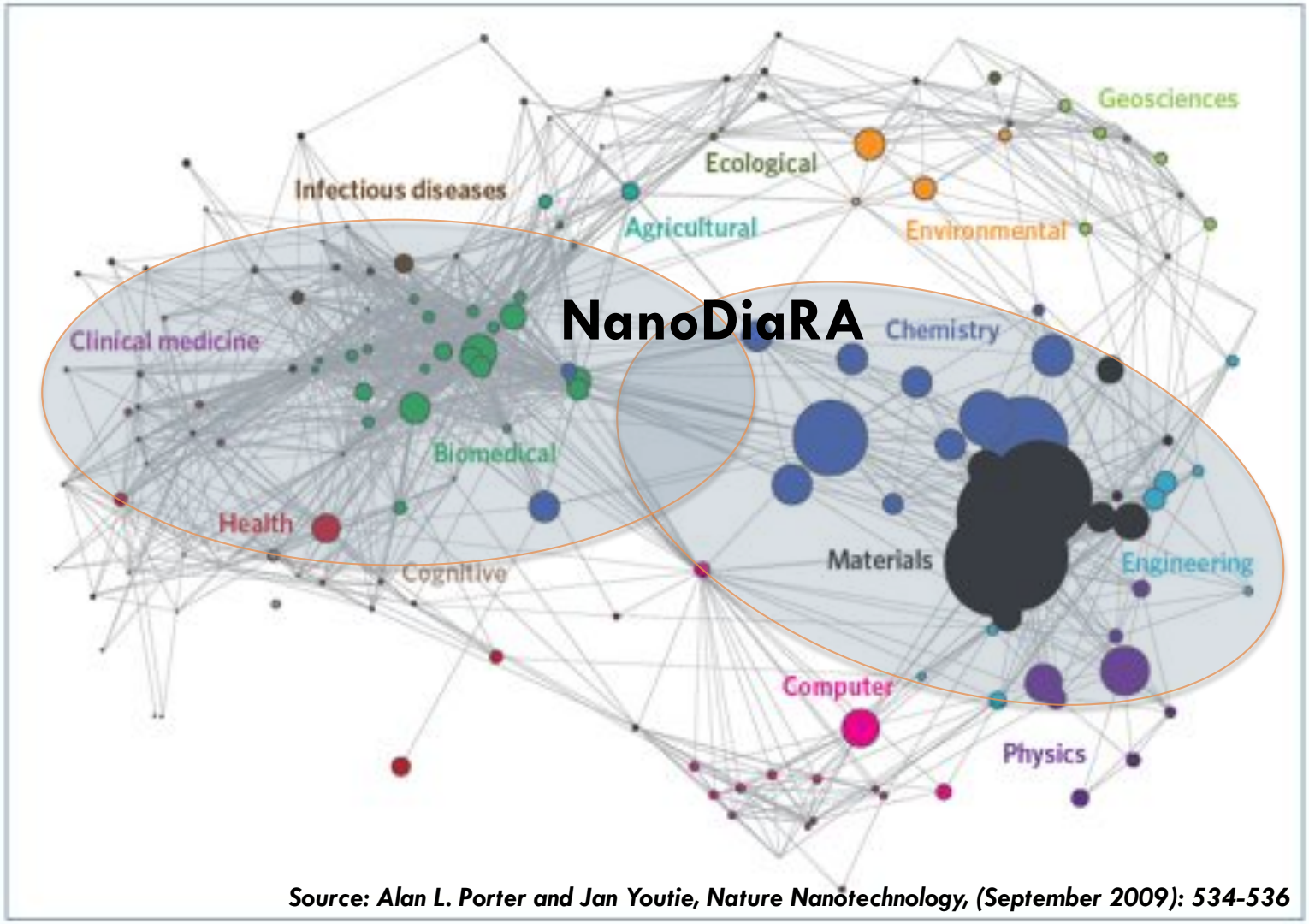
AIM of NanoDiaRA

- The EU funded project NanoDiaRA combines for the first time a nanoparticle based approach as a generic platform for the development of various novel diagnostic technologies

- This includes:
  - Microarray and imaging technologies allowing high detection sensitivity and specificity
  - Investigation of disease-related molecular and cellular processes rather than just outcomes

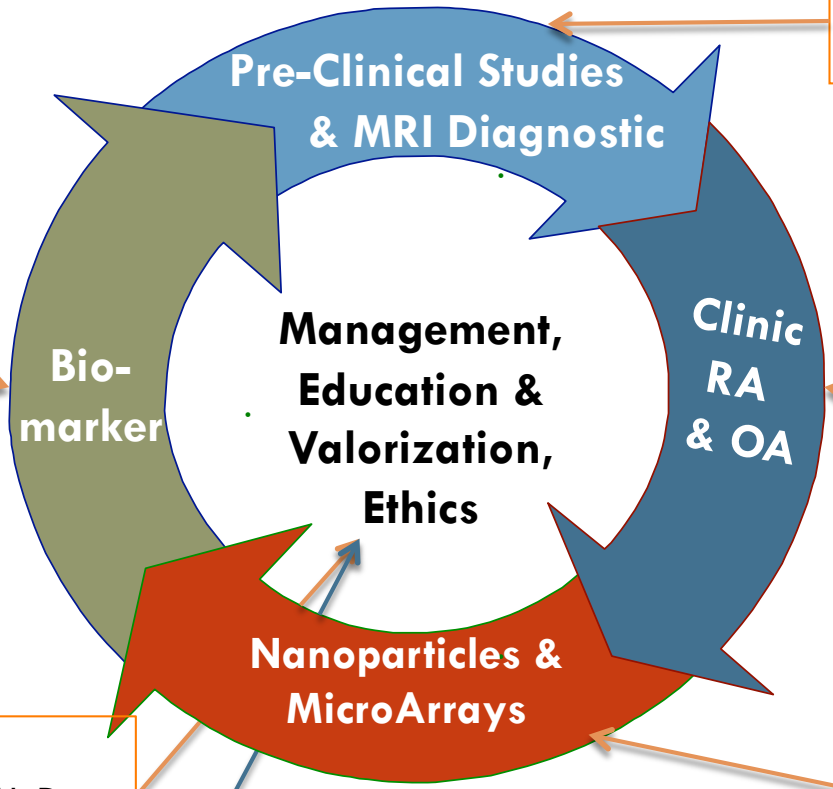
- Such a comprehensive approach addresses key requisites for modern therapy.

NanoDiaRA: Part of Global Nanoscience



Source: Alan L. Porter and Jan Youtie, Nature Nanotechnology, (September 2009): 534-536

Consortium Structure



Radboud University Nijmegen, NL
University Hospital Geneva, CH

Lund University, SE
AnaMar AB, SE

Charité Universitätsmedizin Berlin, D
Paracelsus Medical University, Salzburg, A
University of Tartu, EST
Merck Serono SA, CH

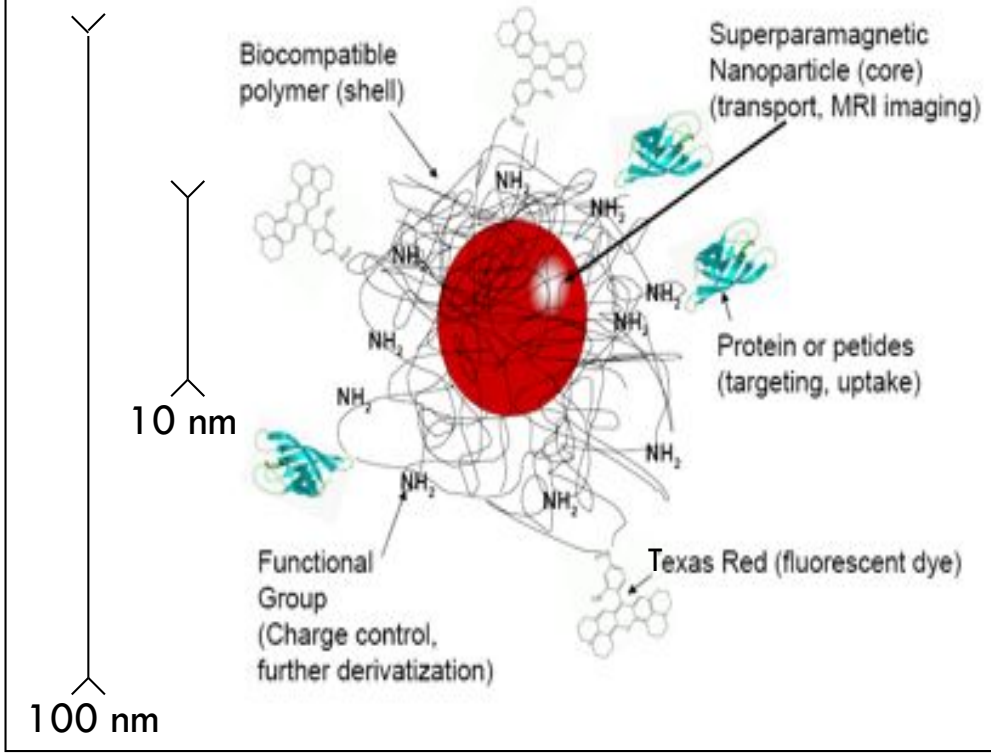
Europäische Akademie Bad Neuenahr-Ahrweiler GmbH, D
MatSearch Consulting Hofmann, CH

Dr. A. Robin Poole, Prof. Emeritus, McGill University (Consultant), CAN

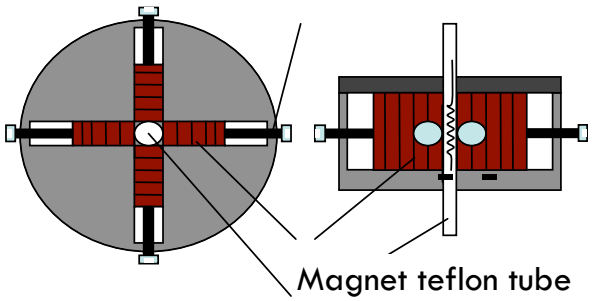
EPFL Ecole Polytechnique Fédérale de Lausanne, CH
University of Fribourg, CH
CSEM Centre Suisse d'Electronique et de Microtechnique SA, CH
Arrayon Biotechnology SA, CH
Merck Chimie SAS – Estapor Microspheres Division, F

Superparamagnetic Nanoparticles (SPION) Platform technology developed by EPFL

SPION



Magnetic Fixed-Bed Reactor



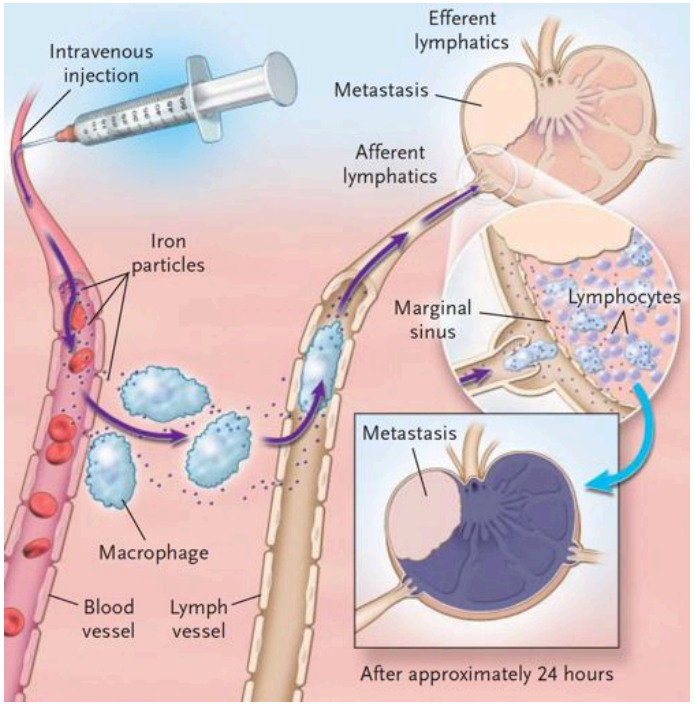
Coating and derivatization of nanoparticles to:

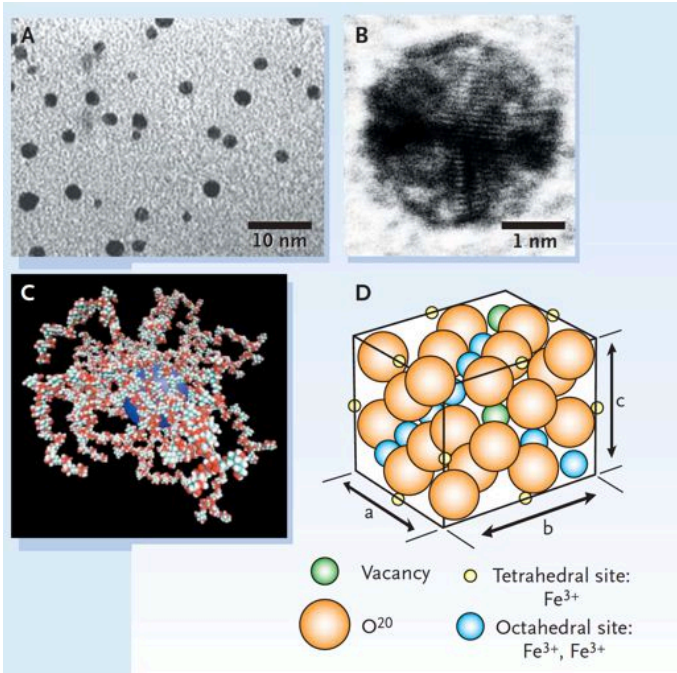
- Improve reproducibility
- Reduce size distribution
- Facilitate the up-scaling

Steitz et al., 2007, Bioconj. Chem. 18, 1684-1690

Nanotparticles for Imaging & Drug Delivery

- Coated and derivatized iron oxide particles are injected either intravenous or intraarticular



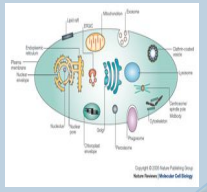


- They find their way to the targeted tissue either by blood or lymph vessels
- Macrophages are special transporter of nanoparticles to the inflamed tissue

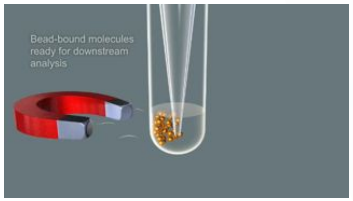
Mukesh G. Harisinghani, The new england journal of medicine 2003 vol. 348 no. 25, 2491

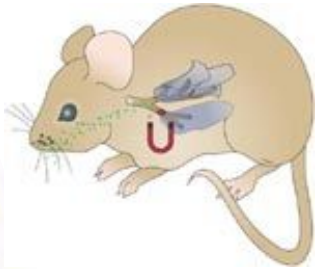
Fields of Interest

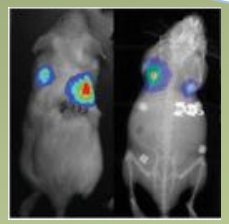
NanoDiaRA

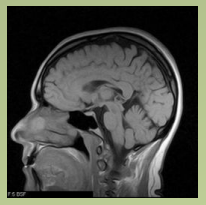


SPION –
Superparamagnetic
Iron **O**xide
Nanoparticles



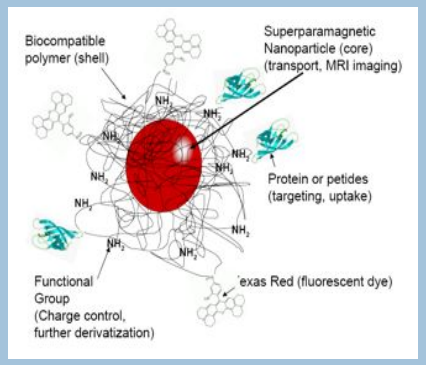






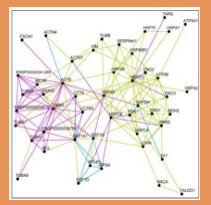
NanoDiaRA

Project Layout for Innovative Products

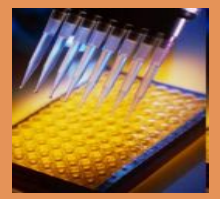


FP5, national research

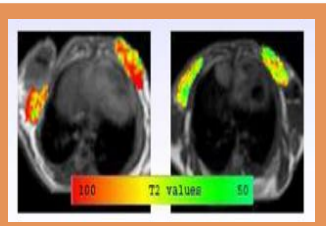
Early detection of biomarker through protein profiling



Early detection of low concentration bio-markers by special microarray technologies



Early detection and monitoring of disease by SPION contrast agents in MRI



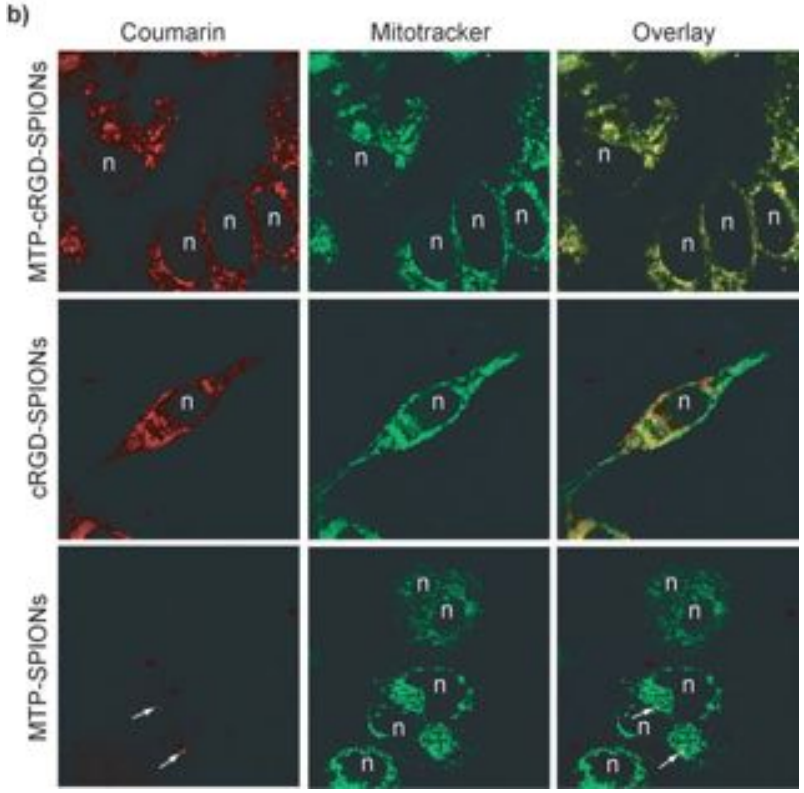
Pharmacogenetic analysis to easier subtype responders/non-responders

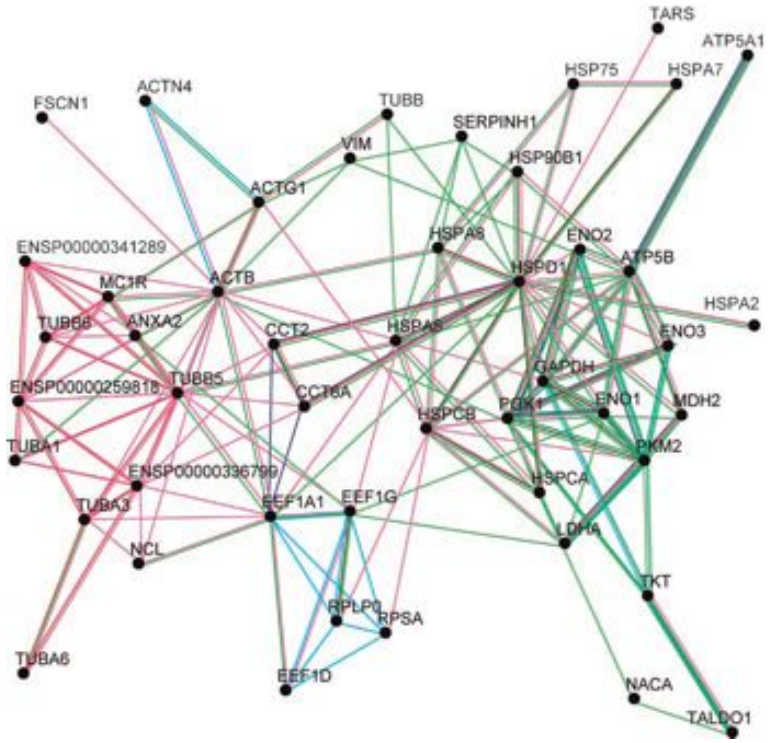
Biomarkers

- The development of biomarkers for autoimmunity is a major undertaking critical to elucidating disease pathogenesis and assessing disease activity in routine care as well as in clinical trials.
- In general, biomarkers represent products of cells (for example, cytokines) or phenotypic or functional changes in cells usually sampled from the blood. These changes include the expression of cell surface markers or patterns of gene expression.

D. S. Pisetsky, Arthritis Research & Therapy 2009, 11:135

Functionalized SPION to Exploring Cell Events

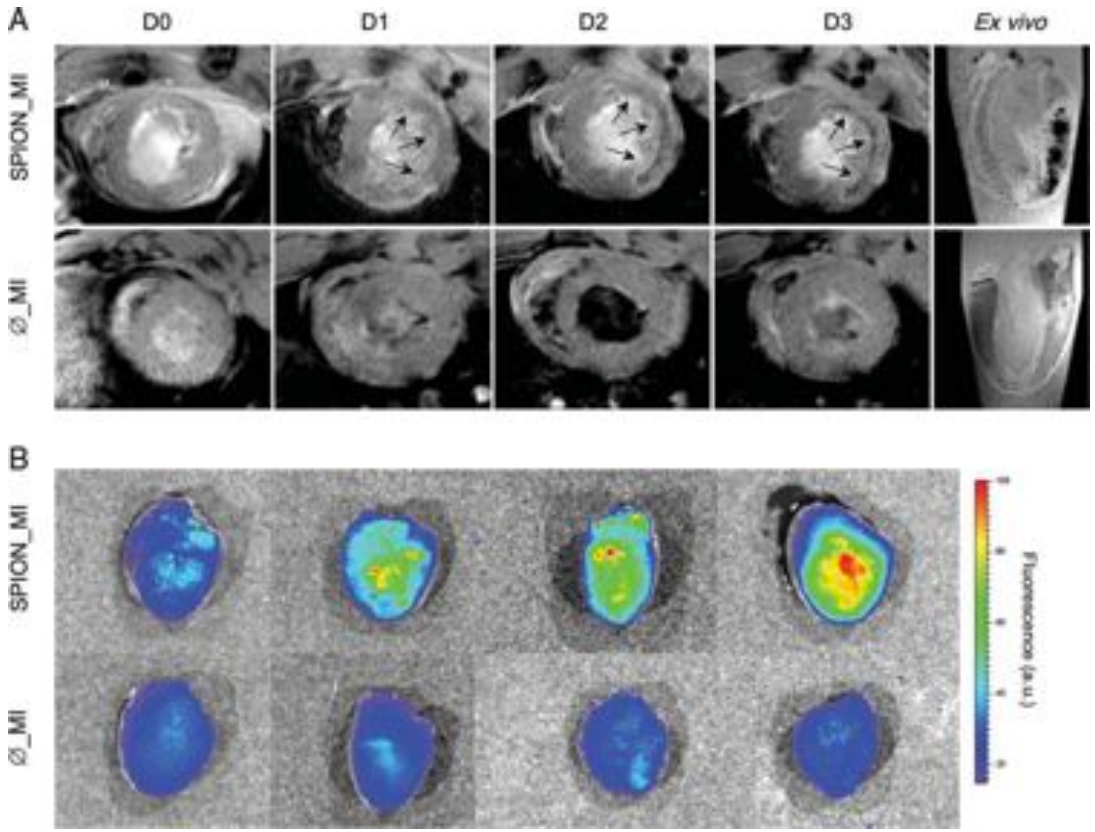




Functionalized SPIONs, their ability to be magnetically recovered from cells and to be analyzed by mass spectrometry allow to explore a complex intracellular pathway, helpful in intracellular drug delivery, or study of complex cellular signaling pathways.

Advanced Technologies for an Ageing Population, 23-24.3.2011

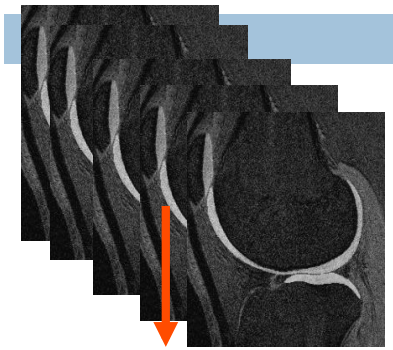
Functionalized SPION to Depict Inflammation

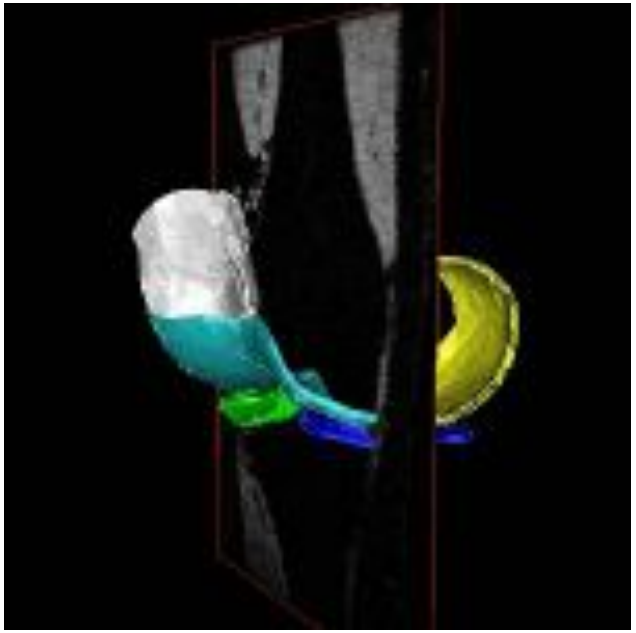


- In vivo MRI of the infarcted groups is presented in (A). The first line corresponds to a representative rat and clearly shows the appearance over time of a hypointense (black) signal in the myocardial infarction area (arrows) due to the SPION.
- The second line corresponds to a representative rat and does not show any hypointense signal.
- Ex vivo MRI (last column) and ex vivo reflectance fluorescence (B) confirms the in vivo results

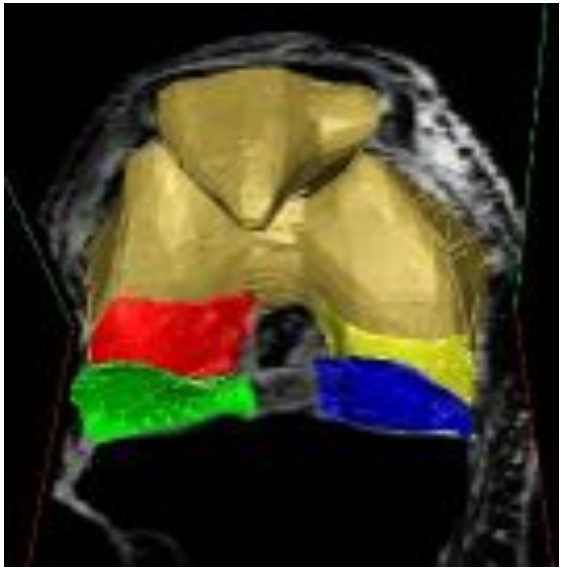
University Hospital Geneva: K. Montet-Abou et al., Eur Heart J (2010) 31 (11): 1410-1420

Quantitative Cartilage Analysis

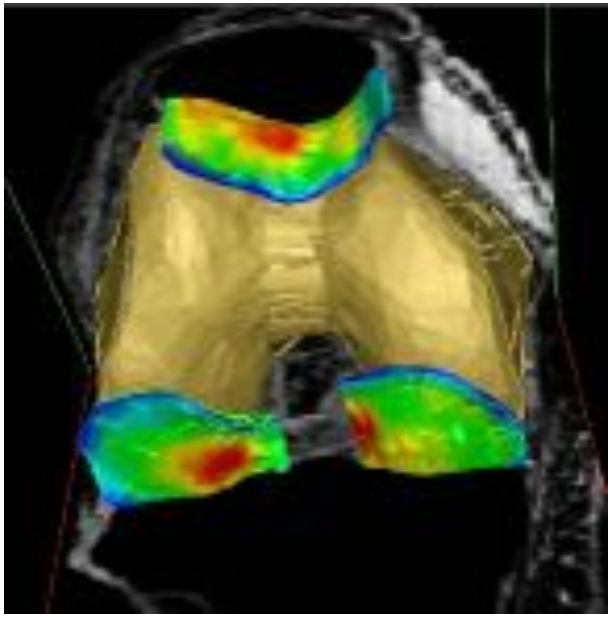




Volume

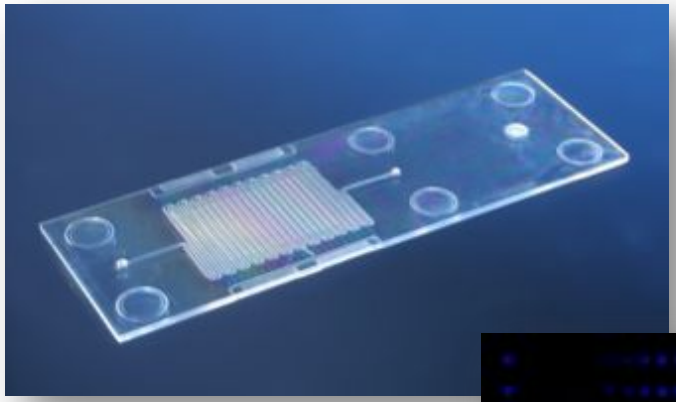


Joint Surface Area & Curv.

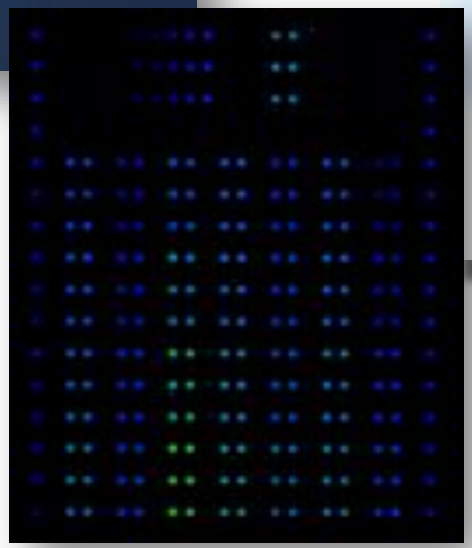


3D Thickness

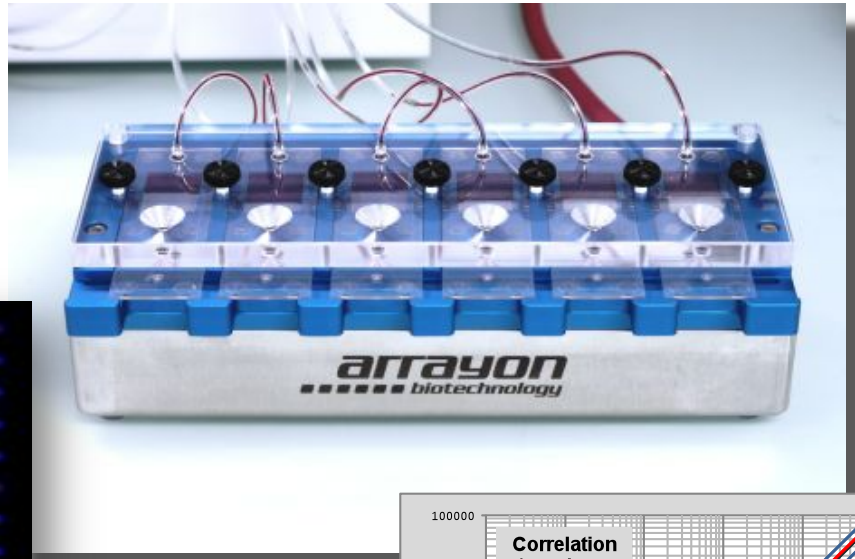
Microarray Technology



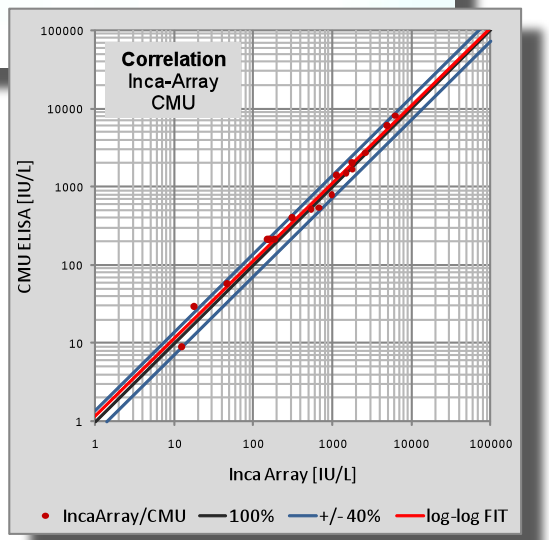
IncaSlide



Fluorescent Microspots



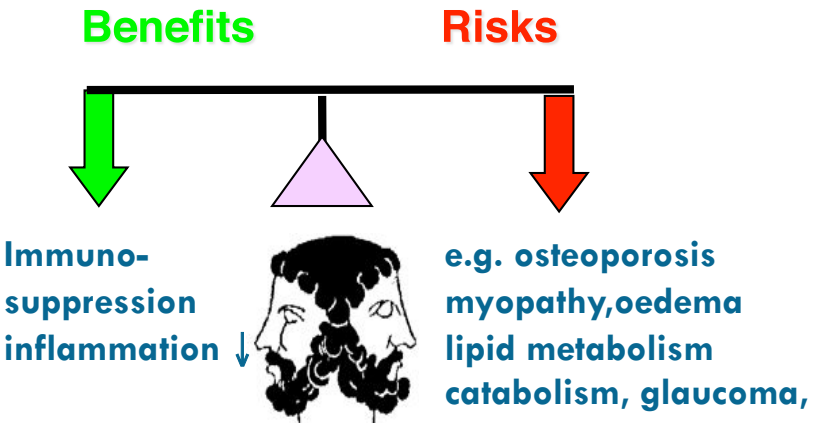
IncaTrace



- IncaArray Bioanalytics combines multiplex protein analytics and microfluidics

- **www.arrayon.com**

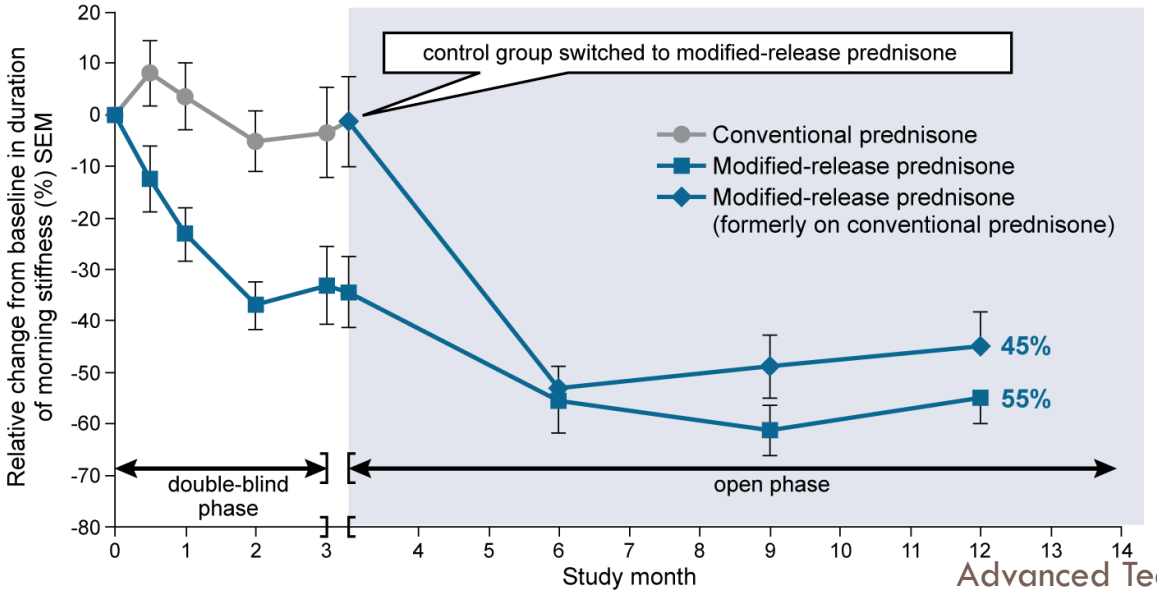
Glucocorticoid (GC) therapy in rheumatology



Requirements

- GCs with ↓ mineralocorticoid but ↑ anti-inflammatory active like prednisone/prednisolone.
- Delivered to the site of inflammation to optimise dosing regimens and to improve treatment with conventional GC
- **E.g. targeted delivery = a specific formulation to change the timing**

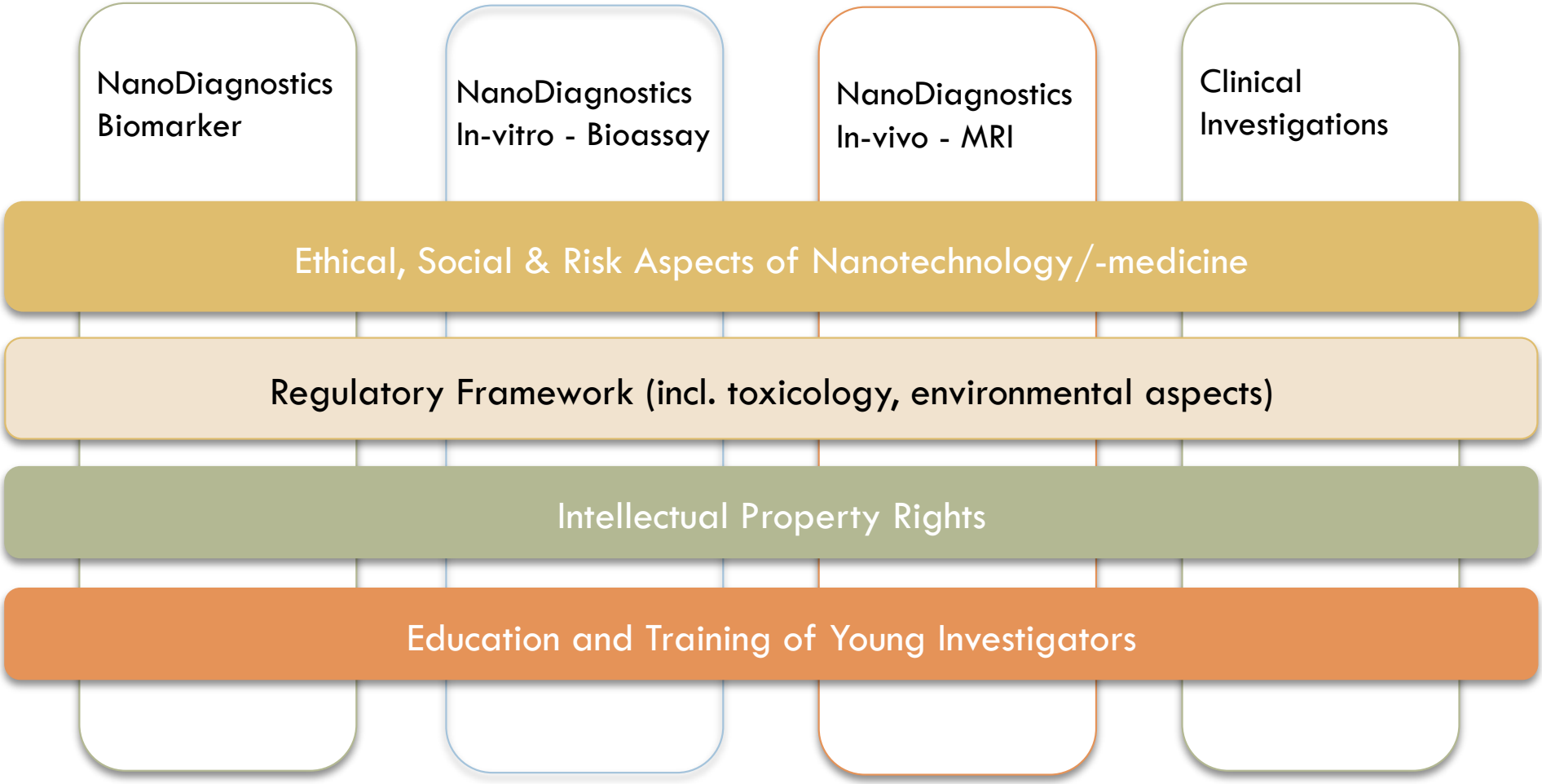
CHARITE: Buttgereit *et al. Lancet (2008)*, Buttgereit et al. *Ann Rheum Dis (2010)*



Active (red) within an inactive (white) coat: High-precision production for accurate and consistent central core positioning

Sustained reduction in duration of morning stiffness in patients taking modified-release prednisone in the evening for up to 12 months

Nanotechnology: combined with ethical & social issues

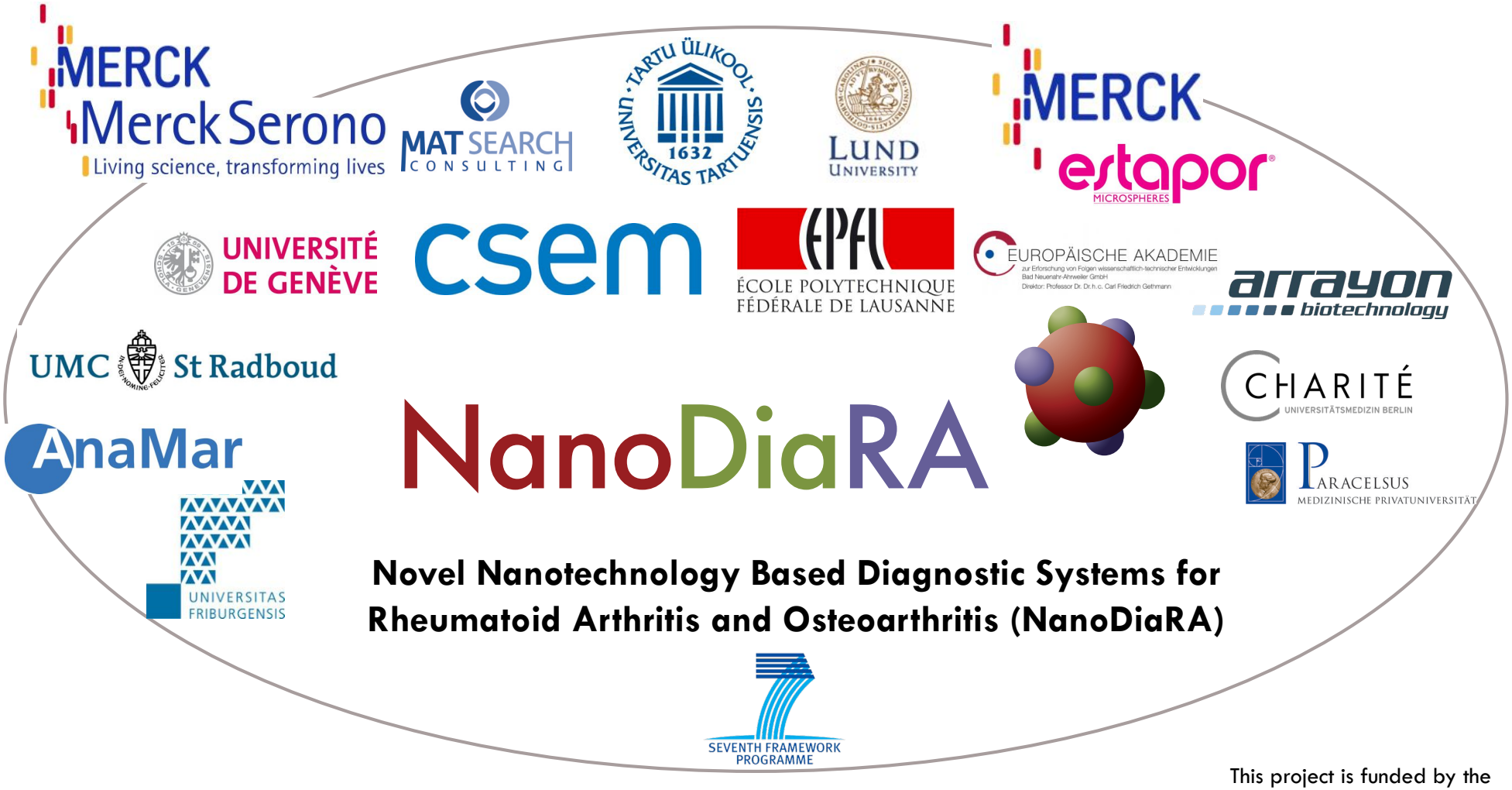


NanoDiaRA

Scope of the European research and NanoDiaRA:

- Developing nanotechnology-based systems for diagnosis and/or therapy for diabetes, ***muscolo-skeletal or inflammatory diseases***.
- Where meaningful, research should address the ***combination of diagnosis and therapy (theranostics) in multi purpose systems.***
- They should demonstrate ***high specificity, efficacy and where appropriate biocompatibility.***
- Linked animal testing should be kept to the minimum needed and should be replaced by in vitro testing wherever possible.
- ***Addresses only human healthcare***.

Thank you for your attention



This project is funded by the EU Framework 7 Programme, contract no NMP4-LA-2009-228929