NANOPARTICLE APPROACHES FOR DIAGNOSTIC AND THERAPY: SCIENTIFIC PROMISES AND INDUSTRIAL EXPECTATION EXAMPLE RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

NanoDiaRA

NMP4-LA-2009-228929

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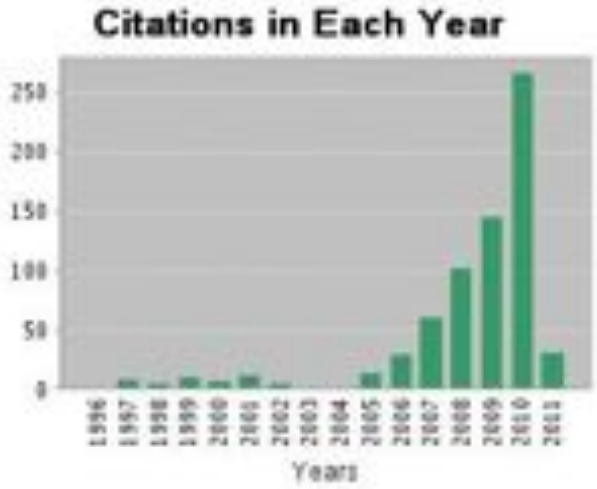
Scientific Coordination

SEVENTH FRAMEWORK PROGRAMME

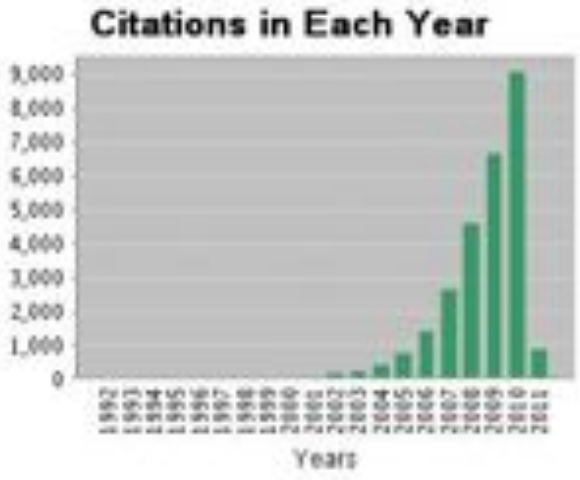
Why using nanotechnology in arthritis?

- Arthritis is a diasease with high impact on the workforce and the quality of life of patients
- Unmet diagnostic & therapeutic needs in arthritis
- Nanotechnology has a potential to increase specificity and sensitivity in diagnostics and therapy

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)

Rheumatoid Arthritis (RA)

- RA is a chronic systemic autoimmune inflammatory disease that is characterized by symmetrical synovitis, progressive joint damage, pain, fatigue, and disability.[1]
- RA criteria require the presence of established joint damage; thus, they are limited in their ability to identify patients with early disease

mild **moderate** **severe**

http://nihseniorhealth.gov/rheumatoidarthritis/whatisrheumatoidarthritis/stages_ra_popup.html

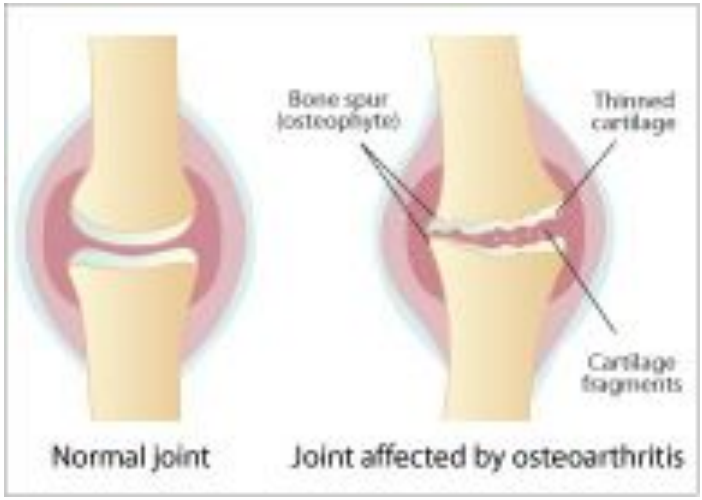
- Early aggressive therapy has the potential to minimize joint damage and significantly suppress disease progression
- There is a need for criteria that will facilitate early diagnosis.[2]

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

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

Osteoarthritis (OA)

- 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 and usually develops without known cause.[2]



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

- Osteoarthritis (OA) has a major impact on functioning and independence and ranks among the top ten causes of disability worldwide.
- 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.[3]
- 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.[3]

[1]X.Li et al, Mol Biol Rep 2011, Feb 16. [2]*L. Punzi et al.,* Swiss Med Wkly. 2010;140:w13098.
[3]R.D. Altmann, *Am J Manag Care. 2010;16:41-47*. 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

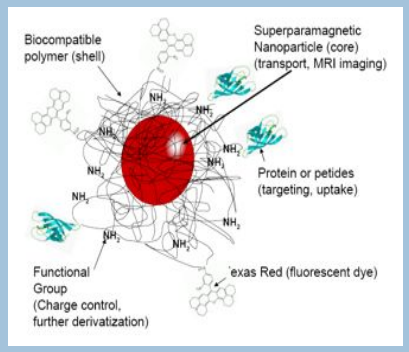
AIM of NanoDiaRA

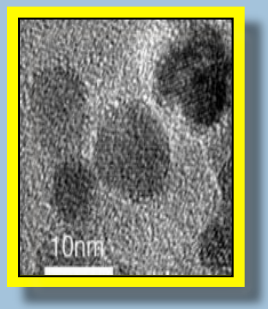
- The FP7 project NanoDiaRA combines for the first time a nanoparticle based approach as a generic platform for the development of various novel diagnostic technologies.

- 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.

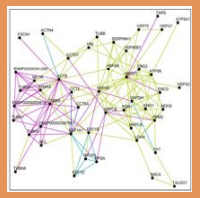
NanoDiaRA R&D Approaches



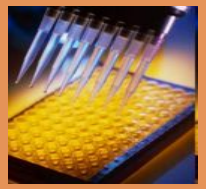


FP5, national research

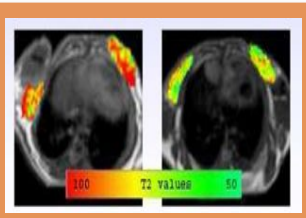
Early detection of biomarker through protein profiling



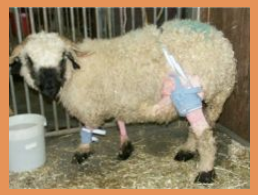
Early detection of low concentration bio-markers by special microarray technologies



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

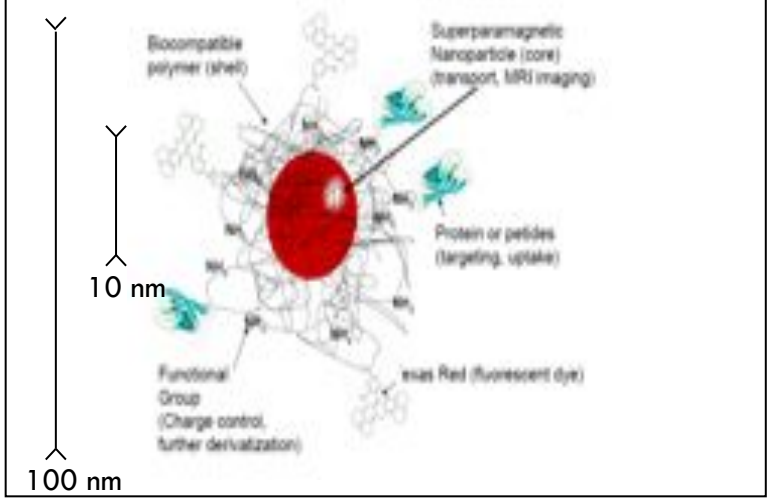


Pharmacogenetic analysis to easier subtype responders/non-responders



Development of Superparamagnetic Iron Oxide Nanoparticles (SPION)

SPION



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

Magnetic Fixed-Bed Reactor

Processing SPION for medical use need„Standard Operating Procedures“ (SOP) for

- Synthesis of SPION
- Coating and functionalization of SPION with specific biomolecules/biomarkers
- Characterization of SPION and their properties

The goal of such procedures

- Improve reproducibility and reliability of the processes
- Facilitate the up-scaling to industrial standards
- Minimize risks for working people and endusers

Biomarkers

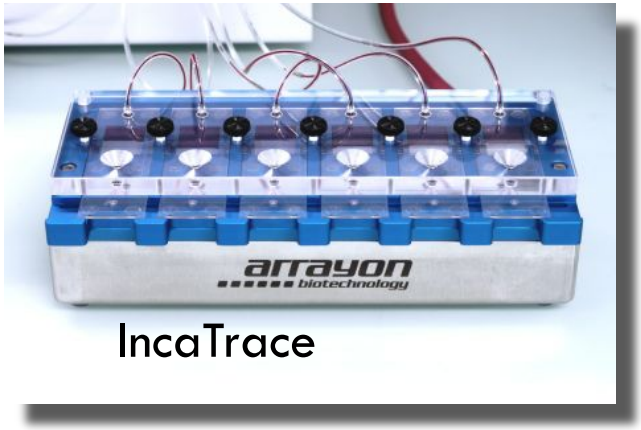
- As noted in a recent FDA guidance document, the use of biomarkers in drug discovery, development and post-approval has the potential to facilitate development of safer and more effective medicine.
- Biochemical markers in blood and urine provide information on systemic skeletal tissue turnover and are not necessarily specific for the alterations occurring in the signal joint.
- The utilization of more sensitive imaging methods such as MRI, in future clinical trials, …. provide a way forward for biomarkers qualification.[1]

[1] Osteoarthritis and Cartilage 19 (2011) 515 - 542

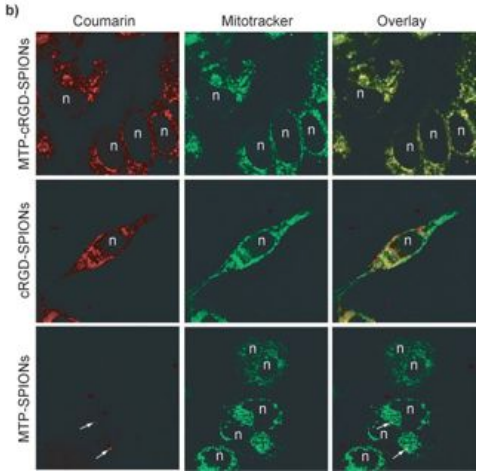
Microarray Technology

Functionalized SPIONs are able

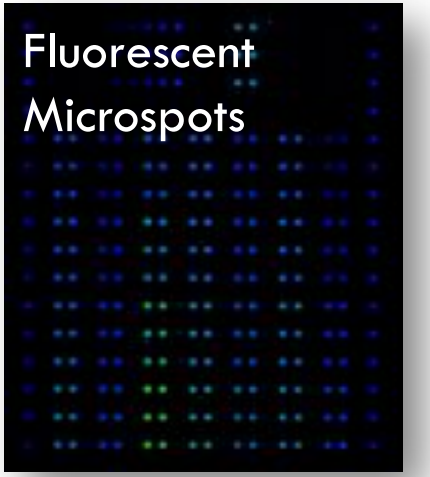
- to separate biomarkers from biosamples like urine, serum etc. and by this increase the sensitivity of array technologies.
- to be recovered from biosamples and cells anylyzing their protein corona by mass spectrometry and hopefully explore new biomarkers.



IncaTrace



The strong collaboration with clinics is essential to achieve the right answers.



Sensitive Imaging methods

- In vivo imaging by using contrast agents like e.g. SPIONs will serve for detecting inflammation in RA and OA patients at earlier time-points and will facilitate monitoring of disease detection and progression as well as verification of targeted drug delivery and biosensing.
- Necessary developments:
  - *New developments and improvements of more sensitive and specific MRI imaging based on the SPION technology.*
  - *Establishing of animal models representing the onset and progression of a disease.*
  - *Adapt segmentation technologies to the new requirements.*
  - *Translate findings to human applications.*

Toxicity Tests

- The development of functionalized SPIONs for in vivo application must focus on a specific nanoparticle preparation for the preclinical use, requiring very detailed toxicity tests including among others
  - Acute toxicity
  - Genotoxic potential
  - Pharmacokinetic (PK) and biodistribution studies
  - Single dose and repeat-dose iv toxicity studies in rats and further mammalian species

Challenges

Developing nanoparticle-based diagnostic in vitro and in vivo tools require standardized methods for

- particle characterization
- particle – cell/tissue/organ and particle - biofluid characterization including the protein corona of particles and their influence on the biological environment
- toxicology tests adapted to nanoparticle requirements

AND

- appropriate animal models reflecting the human disease

At this timepoint many of the methods are either not yet developed in a standardized manner or have to be adapted to nanoparticle requirements

Thank you for your attention

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