NANOTECHNOLOGIES FOR THE EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

NanoDiaRA

NMP4-LA-2009-228929
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 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

Stages of RA

Early RA  Intermediate RA  Late RA

mild  moderate  severe.

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

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.\(^1\)

\(^1\)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 about 12\(^\%\) 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\(^3\)

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\(^1\)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

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\(^2\)

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\(^1\) 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\(^2\)

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\(^2\) L. Punzi et al., *Swiss Med Wkly.* 2010;140:w13098


RA and OA – the treatment

- Current therapeutic approaches for osteoarthritis (OA) are largely palliative dealing with symptoms

- Modifying the structural progression of OA has become a focus of drug development

- Very early use of effective DMARDs is a key-issue in the treatment of patients with the risk of developing persistent and erosive arthritis

- Effective treatments in rheumatoid arthritis (RA) and osteoarthritis (OA) are therefore based on early detection of disease and monitoring treatment efficacy.

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

Nanotechnology in Medicine

- New materials and new physical concepts
- Lipids, polymers: assembly of particular structures
- Distribution related to the physical-chemical properties of the nanovectors
- Control of the distribution to tissues, cells and even subcellular compartments

- Physico-chemical properties of drugs are not often favorable to cross biologic/ enzyme barriers
- Leakage to other tissues
- Nanotransporters < µM
- ~70x smaller than red blood cells
- Targeting of drugs

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)

Max 8

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

Max 340

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


Consortium Structure

Pre-Clinical Studies & MRI Diagnostic

Management, Education & Valorization, Ethics

Nanoparticles & MicroArrays

Clinic RA & OA

Bio-marker

Superparamagnetic Nanoparticles (SPION) Platform technology developed by EPFL

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

Coating and derivatization of nanoparticles to:
- Improve reproducibility
- Reduce size distribution
- Facilitate the up-scaling
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 Oxide
Nanoparticles
Project Layout for Innovative Products

Early detection of biomarker through protein profiling

Early detection of low concentration biomarkers by special microarray technologies

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

Pharmacogenetic analysis to easier subtype responders/non-responders

FP5, national research
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 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.
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.


Quantitative Cartilage Analysis

Volume

Joint Surface Area & Curv.

3D Thickness

Paracelsus Medical University, Salzburg, A
Microarray Technology

- IncaArray Bioanalytics combines multiplex protein analytics and microfluidics


www.arrayon.com
Glucocorticoid (GC) therapy in rheumatology

Benefits

- Immunosuppression
- e.g. osteoporosis
- Myopathy, oedema
- Lipid metabolism
- Catabolism, glaucoma

Risks

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

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


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

Nanotechnology: combined with ethical & social issues

- NanoDiagnostics Biomarker
- NanoDiagnostics In-vitro - Bioassay
- NanoDiagnostics In-vivo - MRI
- Clinical Investigations

Ethical, Social & Risk Aspects of Nanotechnology/-medicine

Regulatory Framework (incl. toxicology, environmental aspects)

Intellectual Property Rights

Education and Training of Young Investigators

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

**NanoDiaRA**

Novel Nanotechnology Based Diagnostic Systems for Rheumatoid Arthritis and Osteoarthritis (NanoDiaRA)


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