Nanotechnology in diagnostic and treatment Rheumatoid arthritis and osteoarthritis

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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.

\(^1\)T. Yoshino, Intern Med 50: 269-275, 2011
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-
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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\(^1\) Li X. et al., Mol Biol Rep 2011, Feb 16

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

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 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 20

\(^2\)L. M. da MotaRev. Assoc. Med. Bras. vol.56 no.3 São Paulo 2010
Nanotechnology for biomedical applications

**Diagnosis**
- Superparamagnetic Iron Oxide
- Quantum dots
- Vesicles
- Biosensors (cantilever)
- GMR- effects

**Therapy**
- Vessicles
- SPION
- Hyperthermia
- Quantum dots
- Theragnostic devices

Nanoparticle for medical applications

Fig. 5. Applications of quantum dots or multimodal contrast agents in biosensing.
Magnetic properties

- Single domain
- Multi domain
- Super Paramagnetic
- \( H_c = 0 \)
- \( H_c >> 0 \)

Magnetic field sensor

Spin valve

Pinning layer
- FeMn
- NiFe/Co
- Cu
- NiFe

Spin valve
- sensing current
- recorded bits

10nm
Pros and Cons

- MRI application for liver diagnostic is FDA approved and in clinical use
- Applications in imaging, drug delivery, hyperthermia are in pre-clinical and clinical tests
- Biocompatibility approved
- Multifunctional particles allowing active diagnosis and therapeutic applications
- Methods for synthesis, surface modification established in industrial scale
- Toolbox for Theragnostics

- Behaviour of particles in the different organs not known in detail
- Particle-protein interaction still under investigation
- Clearing mechanism?
- Combination of diagnosis and therapy useful?
- Acceptance of nanotechnology based treatments by patients?
- Added value? Risk-Benefit balance not yet established.
- Economics, market, health assurances?
Superparamagnetic Iron Oxide Particles

Research

Particle library

Spec. adsorption
at cell surfaces
organelles, ECM proteins

SDS-PAGE

Mag separation
and concentration

Particle derivatized
with specific antibodies

Diagnosis

Quantitative detection
Magnetic, ELISA

Protein identification
nanoESI-MS/MS

Particle derivatized
with specific antibodies

Mag separation
and concentration

Applied magnetic field

Magnetic bead coated with label antibodies

Sandwiched assay

Magnetic superparamagnetic
detector region coated with capture antibodies

Stray magnetic field

13
Targeting of organelles

Mitochondria Targeting
SPION with Coumarin and Mitochondria targeting peptide

Nucleus Targeting
SPION with ALEXA and NTP QPSPSPTGC
48 out of 58 proteins could be related to: Up-take mechanism, transport to mitochondria, mitochondria membrane, including energy related processes. Evidence view of the protein interaction network in STRING.
Multifunctional Core-shell Nanoparticles

Highly complex compounds:

- Core: magnetic and/or fluorescent materials
- Shell I: inorganic materials (SiO₂..)
- Shell II: functionalizable layer (COOH, SH, NH₂..)
- Therapeutic and/or imaging payload
- "Stabilizer"
- Targeting moieties

APS-SPIONs
(~25-35 nm; + 33 mV)

PEG-APS-SPIONs
1 hr recirculation
(~70 nm & -20 mV)

FL-protein-PEG-APS-SPIONs

cysteine-protein-FL-PEG-APS-SPIONs
(~80 nm & -13 mV)

APS: aminopropyltriethoxysilane

APS-SPIONs

PEG-APS-SPIONs

FL-protein-PEG-APS-SPIONs

cysteine-protein-FL-PEG-APS-SPIONs
Protein separation in-vitro, now also in-vivo

1. Particle incubation

Polyvinyl alcohol (PVA) coated SPION + 10% serum supplemented DMEM

2. Magnetic separation

Frit

3. SDS-PAGE
(Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis)

- Control volume and flow rate of elution step
- Reduce solution contamination during the process

Jatuporn Salaklang (2008), EPFL
Molecular Imaging

In vivo labelling of resting monocytes in the reticuloendothelial system with fluorescent iron oxide nanoparticles prior to injury reveals that they are mobilized to infarcted myocardium.

K. Montet-Abou et al
Uni Geneva and EPFL
Protein adsorption (PVA-coated SPION)

Lane 1: Marker (kDa)
Lane 2: Washing
Lane 3: 0.2 M KCl
Lane 4: 0.5 M KCl
Lane 5: 1.0 M KCl
Lane 6: 2.0 M KCl
Lane 7: Tightly bound protein on nanoparticles

Incubation of particles with serum. The serum to particle surface ratio was fixed at 2.8 ml per m² of particle.
HeLa cells after incubation with SPION

naked SPIONs

Negatively charged

Neutral charged

Positively charged
Proteins identified at the surface of positive, neutral and negative charged SPIONs

Table 1: MS analysis of proteins bound on different surface charged polymer coated nanoparticles

<table>
<thead>
<tr>
<th>Gel band Mw (Da)</th>
<th>Protein identity</th>
<th>Amount NspC</th>
<th>Particle charge</th>
<th>IEP of Proteins</th>
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Gene and Drug delivery

Magnet

NanoDiaRA: Part of Global Nanoscience

Acknowledgement


SNF, CTI, EU FP5, ESM, ANTIA Therapeutics
SNF-NFP 62, EU-FP7 NANODIARA

Thanks for your attention