



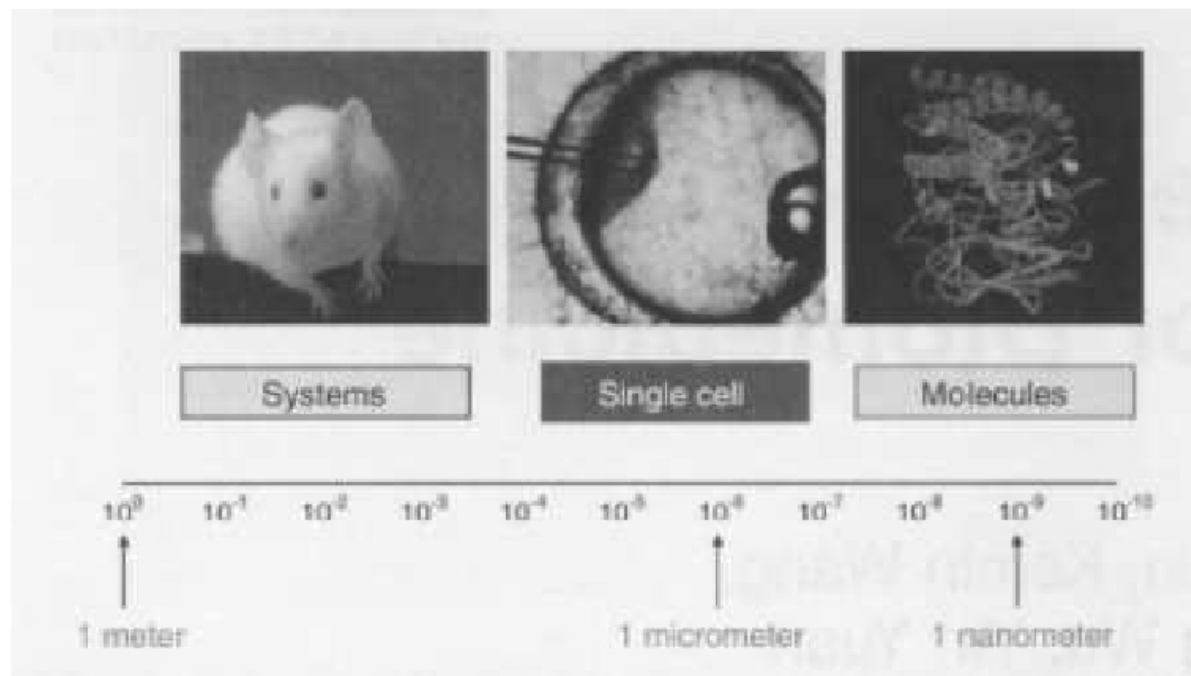
UNIVERSITY OF ROME "LA SAPIENZA"
NANOTECHNOLOGIES ENGINEERING

NANOPARTICLES IN BIOMEDICINE

CHALLENGES

The challenges are: in-situ analysis and in vivo at micro level, recognize biomolecules and their function in order to permit targeted manipulation to increase health.

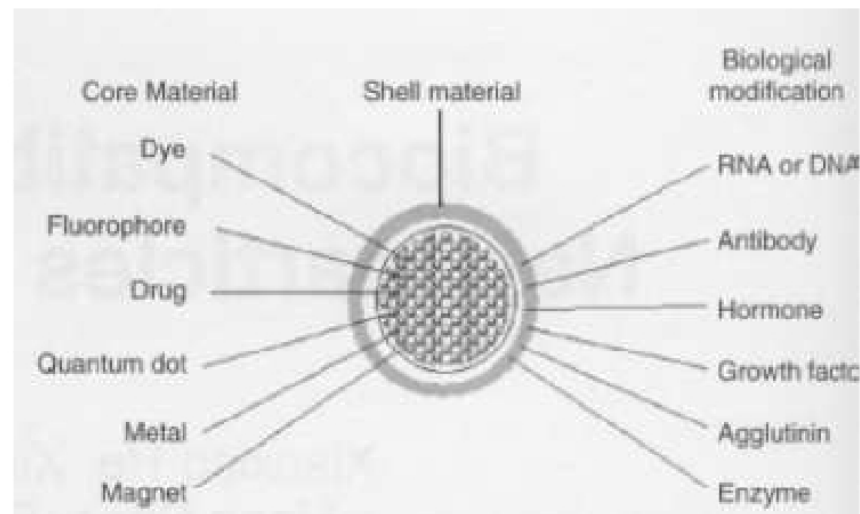
The used nanoparticles have size similar to those of biomolecules, therefore capable to interact locally with them. This may be of great importance to seek a cure to cancer.



CORE-SHELL NANOPARTICLES

May have a size between 1nm and 100nm, exhibits a core (at the center) of a specific material and a shell closing the core of a different material (such as biocompatible ones).

These particles are not rejected by the body and can be used for analysis and cure.



CORE

Generally can be of different materials such as:

- Luminescent, to permit tracking in the body
- Magnetic, for their transportation in and their recovery from the body
- Quantum dots
- Thermal, to allow local heating by microwaves

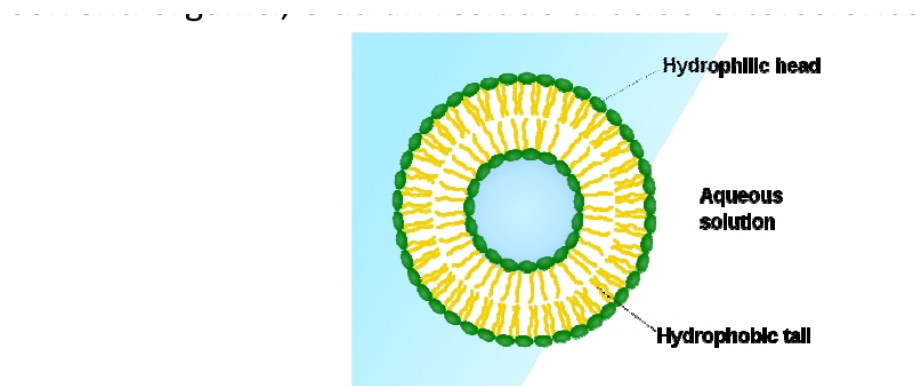
SHELL

Generally polymers or ceramic, the shell may be:

Of silicon oxide: soluble in the aqueous liquids, but not soluble by the acid solutions found in the human body.

Of Chitosan: very biocompatible and that is not rejected by human body

Of liposome: not soluble in water but in organic solvents.



FUNCTIONALITY

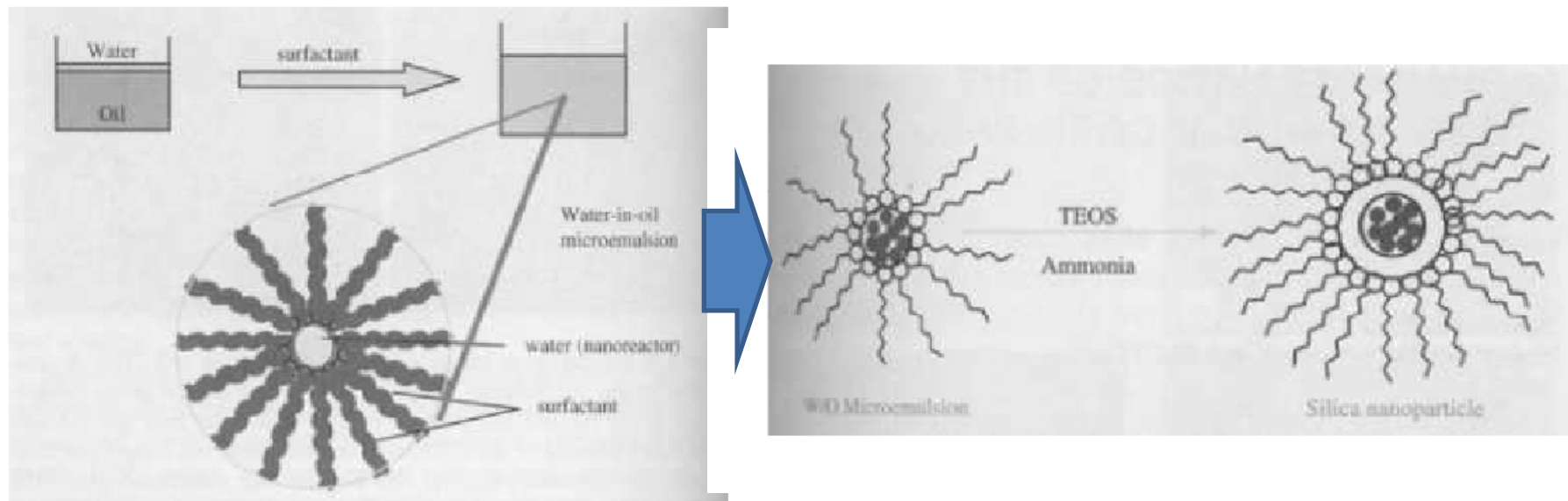
Functionality is achieved by adsorbing on the surface of the core-shell nanoparticles particular compounds, capable to interact with antigens, pathogens, DNA, RNA, cancer cells, etc.

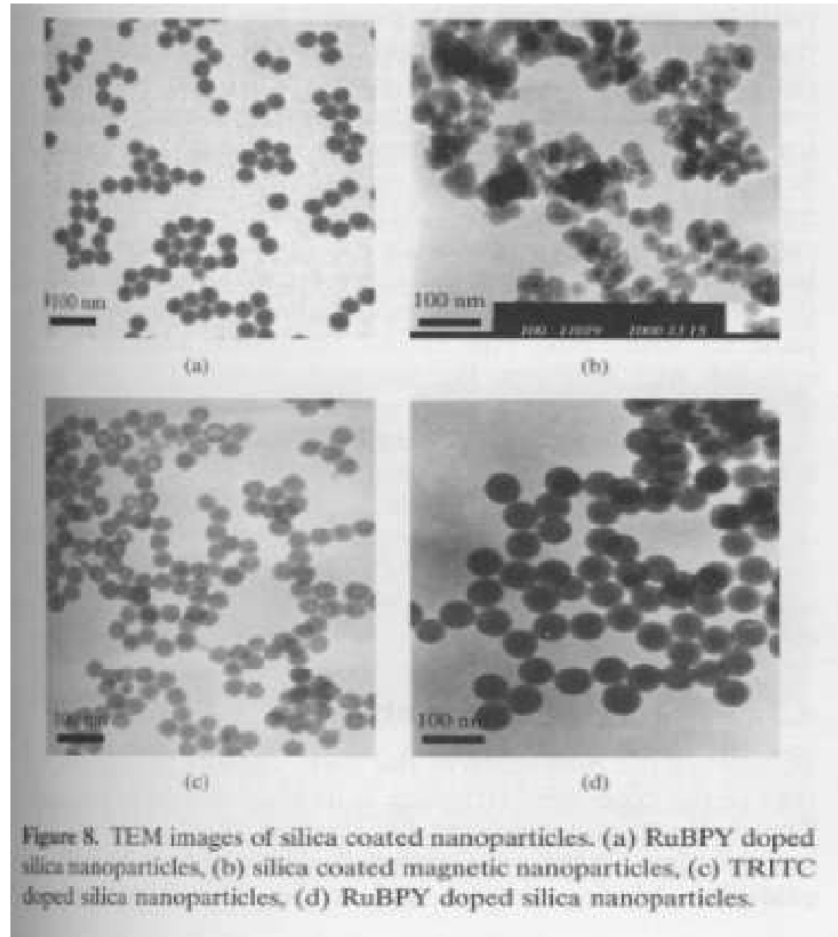
The nanoparticle will travel guided or unguided in the human body, seeking specific target biomolecules and may interact with them (attachment). After this step, the properties of the connected core may be used for analysis or treatment.

SINTHESYS

1. Generation of the core nanoparticles
2. Coating of the nanoparticles
3. Surface modification of the shell

Microemulsion (or inversed emulsion) techniques are widely used for the core. The shell is given by coating.

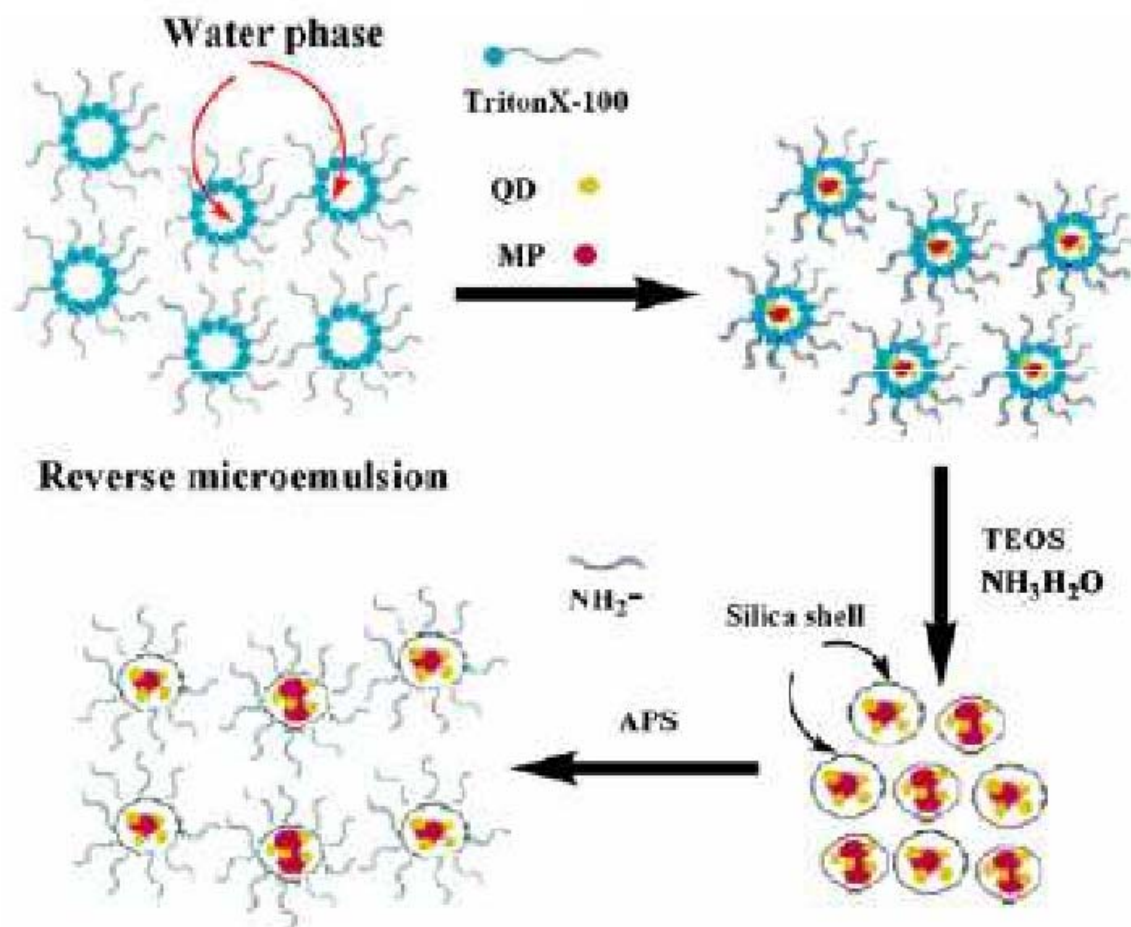




Surface modification (doping) is performed as a last production stage (adsorption) or during the coating by addition of functionalizing compounds. The first method is easy to carry out, but functionality may be lost due to detachment. The latter one requires higher amount of material to ensure surface functionality (embedding).

Here left:

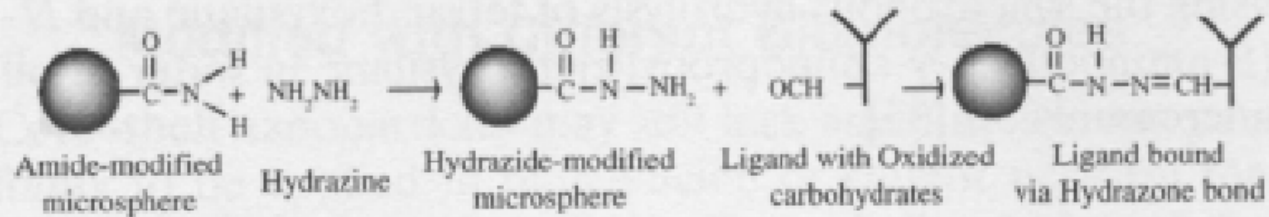
Different florescent molecules for diagnostics



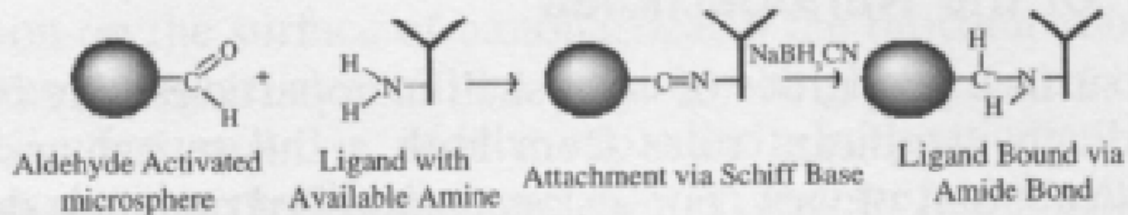
QD quantum dots, MP magnetic particles

CHEMICAL BONDS

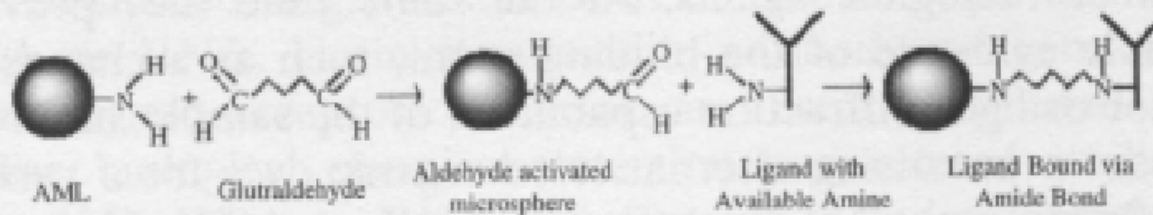
Amide-modified Microsphere,



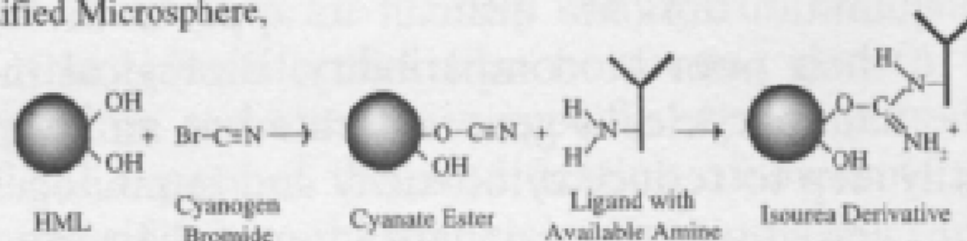
Aldehyde-modified Microsphere,



Amino-modified Microsphere,



Hydroxyl-modified Microsphere,



APPLICATION - ADVANTAGES

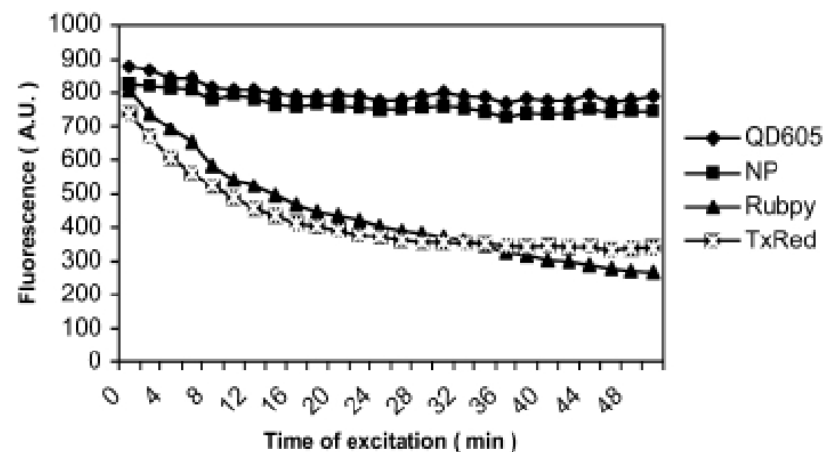
DRUG DELIVERY: some drugs are harmful to health or specific cells in the human body. Driving and releasing drugs only locally to the right spot is possible by nanotechnologies.

ANALYSIS: since fluorescent compounds for analytical purposes are toxic for human body at high concentrations (and this may vary as a function of the sensitivity of the patient), measurements may be performed only once for a long period of time. Nanotechnologies allows to reduce the required quantity to perform the same measurement.

BIOMARKER

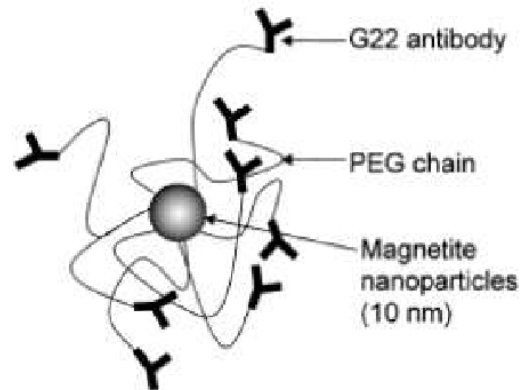
Fluorescent nanoparticles may be used. By UV irradiation, the luminescence is activated before injection and intensity can be measured. This gives an indication of the position of specific target cells in the human body as well as their density.

Moreover, once activated, their luminescence lasts longer, thus allowing longer analysis.



DIAGNOSTICS

In order to permit the nanoparticles to bond the target cells, the nanoparticles may carry on their surface different compounds capable to interact with different biomolecules.



DRUG DELIVERY SYSTEM (DDS)

Coated magnetic nanoparticles can be used to deliver included drugs in the core to specific regions of the body by external magnetic transportation. By microwaves the core can be heated (metal) destroying the shell and drugs may be released.

If the particle is less than 100nm, it will not be blocked by the liver and may thus travel around the body.

Particular applications involve certain surface characteristics that may bond to specific cells rather than others, therefore treatment may be driven locally to target cells.

HYPERTHERMAL CANCER CURE

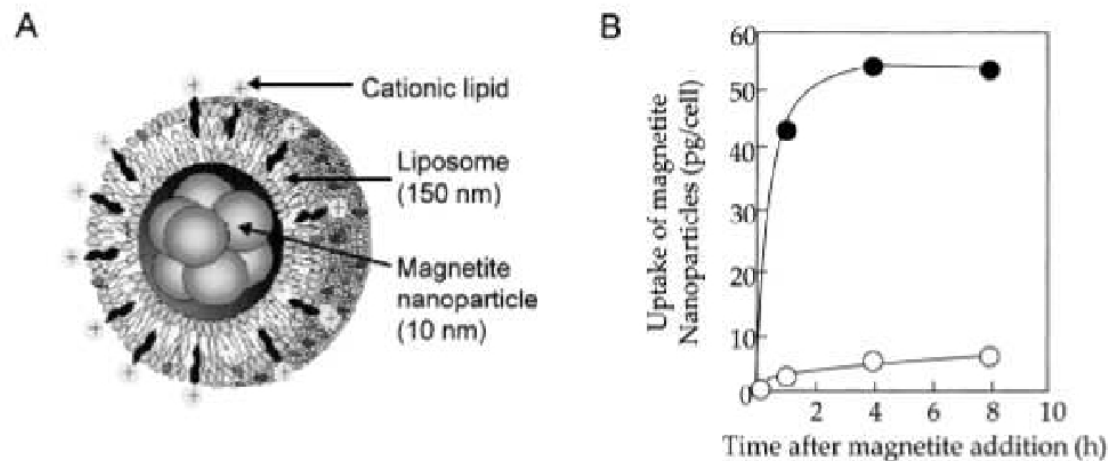
Hyperthermal treatments are based on local heating of tissues, well above physiological ones. The heating is given by EM fields (microwaves to short waves), depending on intensity and penetration depth. Nowadays, frequencies around 13,56 Mhz are the most used ones.

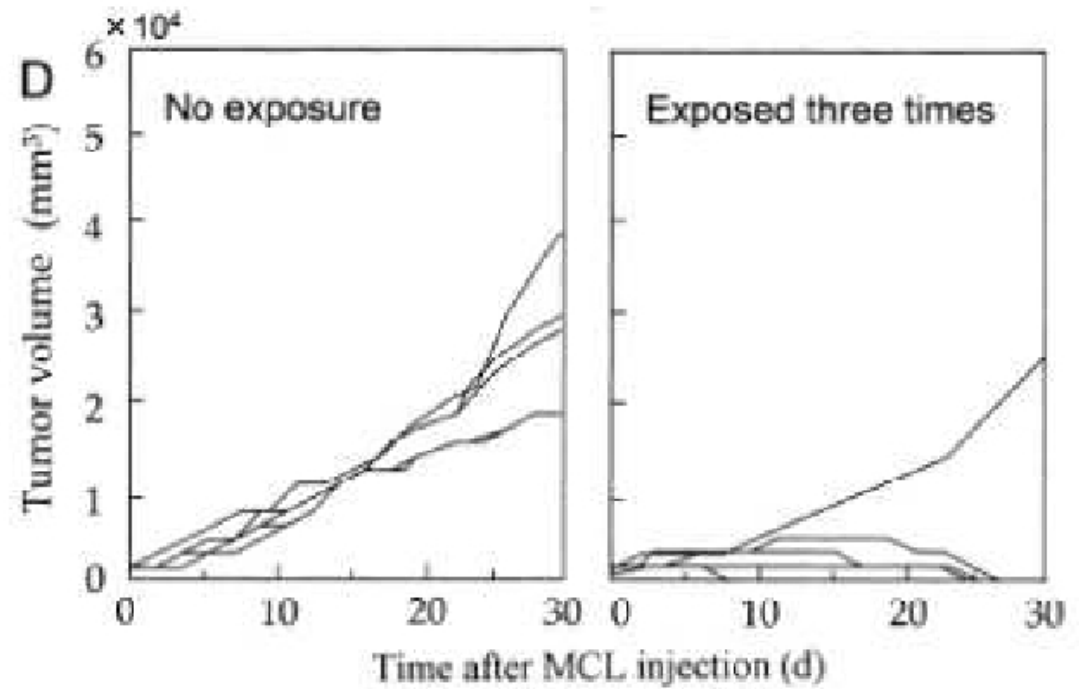
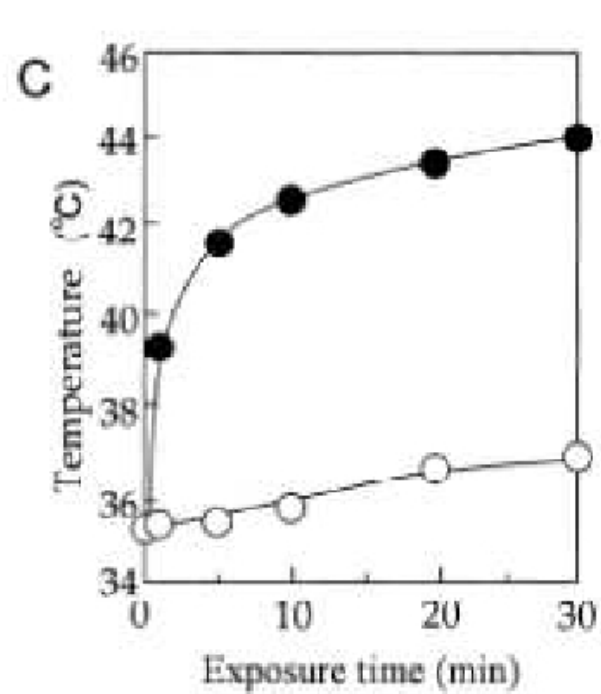
The heating may reach temperatures up to 43°C for 60 minutes. After this time, cells are destroyed.

Radio- and Chemiotherapy may be assisted by hyperthermal treatment in order to reduce their application time and intensity and permit to obtain the same success rate of cure.

The problem is to locally heat the target cells without heating a coarse region of health cells. Magnetic core nanoparticles may attach to the target cell thus allowing a biomolecular heating of single cells.

A coating of cationic lipids (black dots) were more efficient in bonding to cancer cells if compared to neutral lipids (white dots).





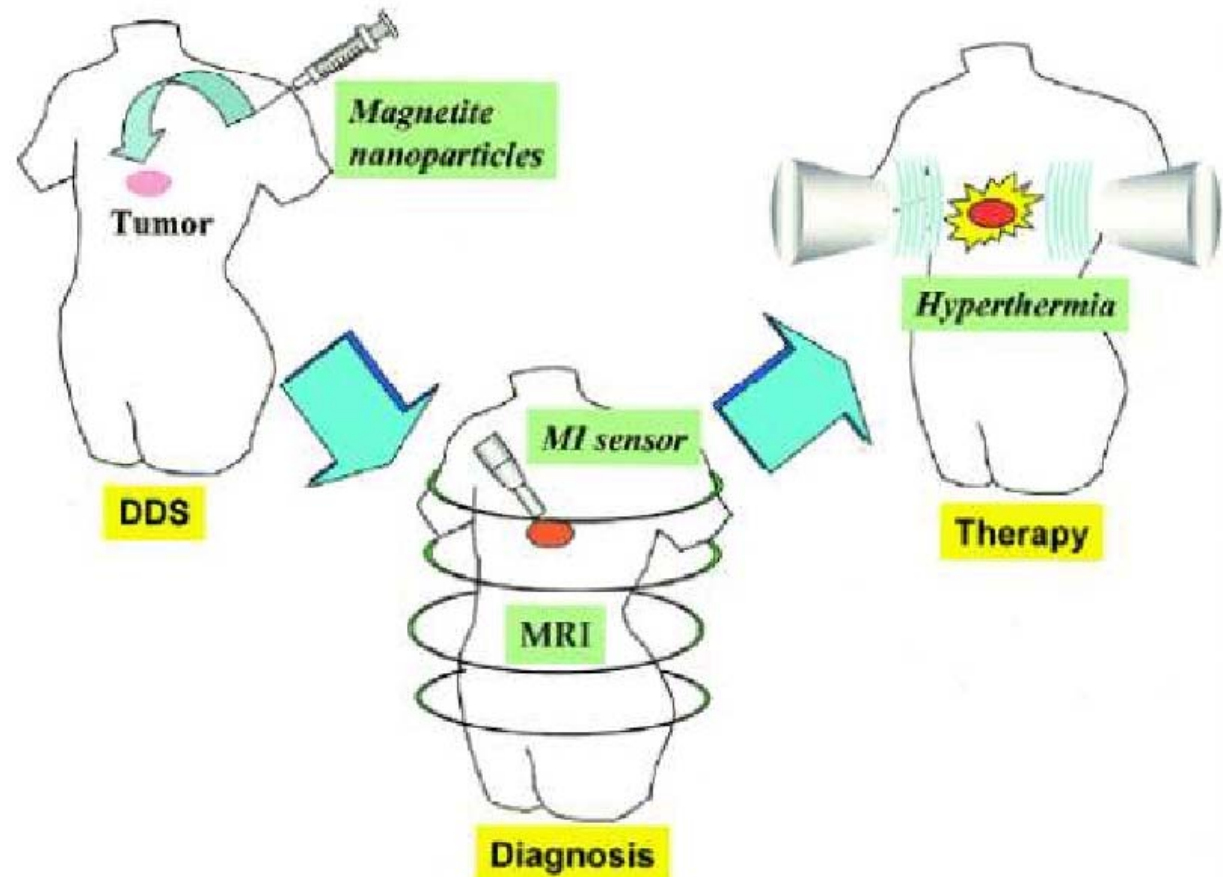
Chemiotherapy

not combined to

combined to

Hyperthermal treatments

1. Magnetic nanoparticles are functionalized by antibody.
2. Injection (0,4ml containing 3mg of nanoparticles)
3. After 48h, the analysis is performed to confirm attachment to the cancer cells and hyperthermal treatment may start.



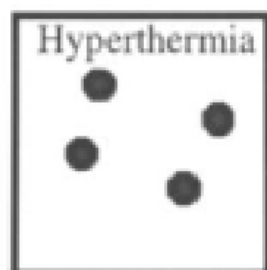
MEDICAL DIAGNOSTICS

The particles may be used for different applications on biomolecular level.

Magnetic nanoparticles are widely used. Bio-interaction is improved and a separation from the body is always possible.

Therefore magnetic nanoparticles are covered by polymers in order to have the desired properties of agglomeration and dispersion at given ambient conditions such as T, pH, EC, etc.

The most used polymer is “Therma-MAX” (patent) which exhibits different properties at different temperatures.

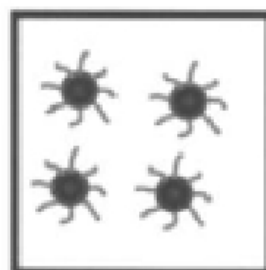


Conventional magnetic nanoparticles

The smaller particle size is desirable because of its larger surface area. However, overly compact particles cannot be separated magnetically.

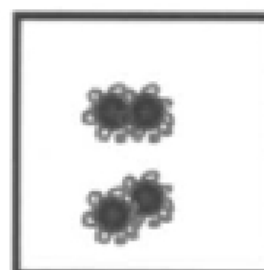


Modification by thermoresponsive polymers

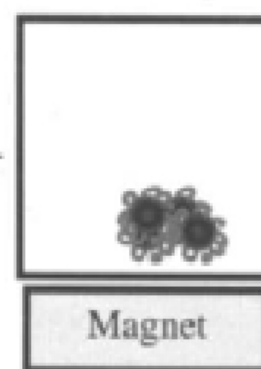


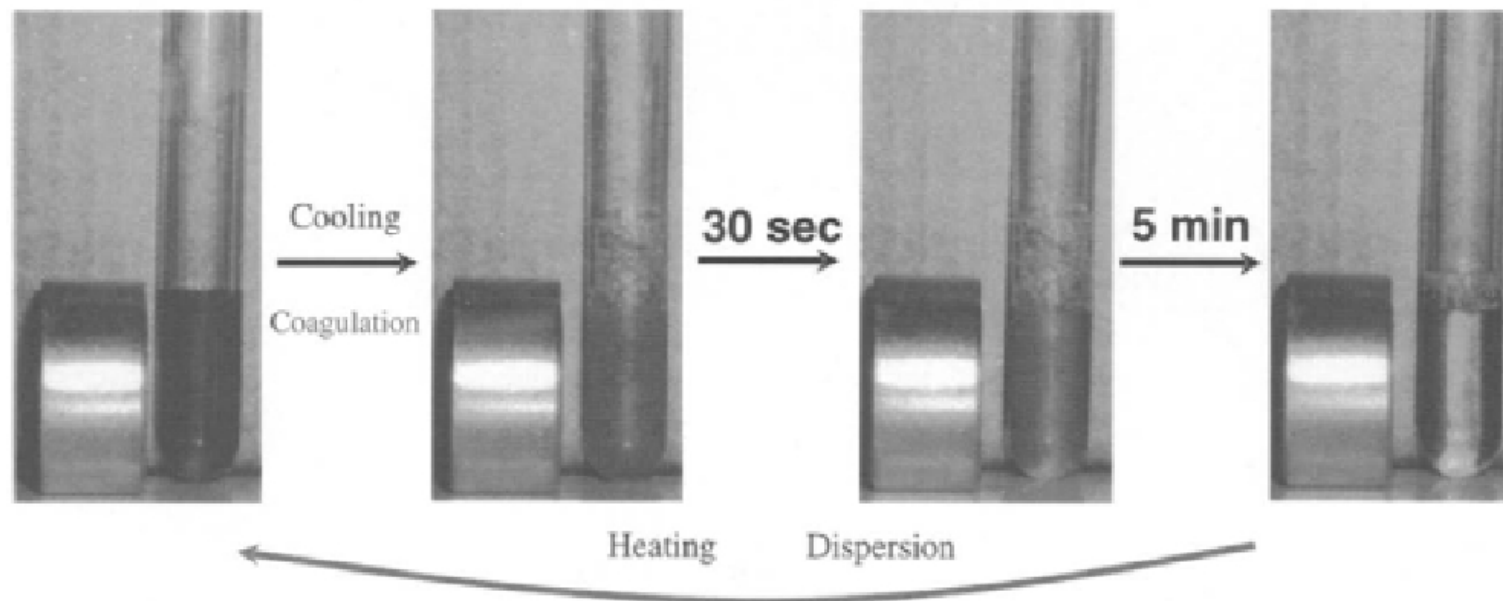
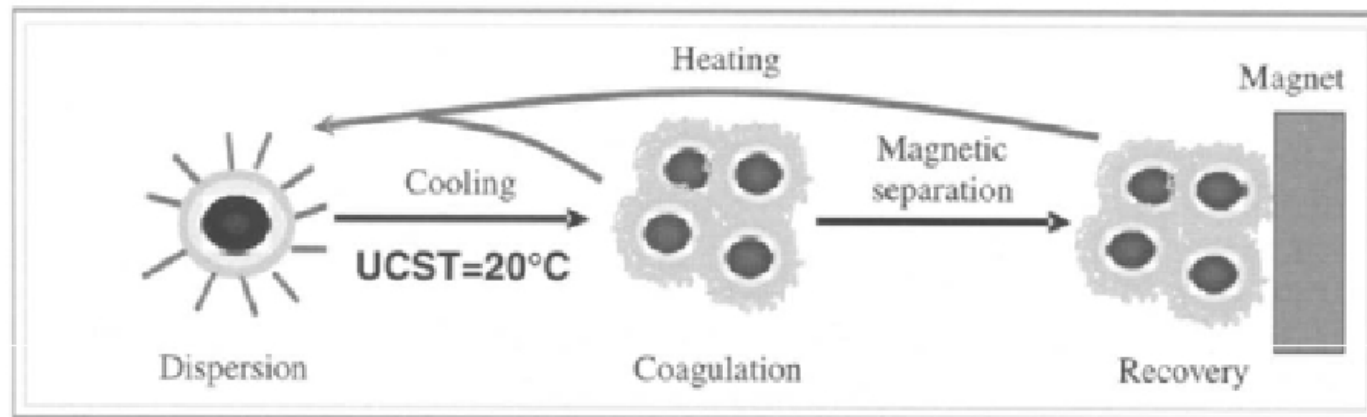
Thermoresponsive magnetic nanoparticles

Temperature change

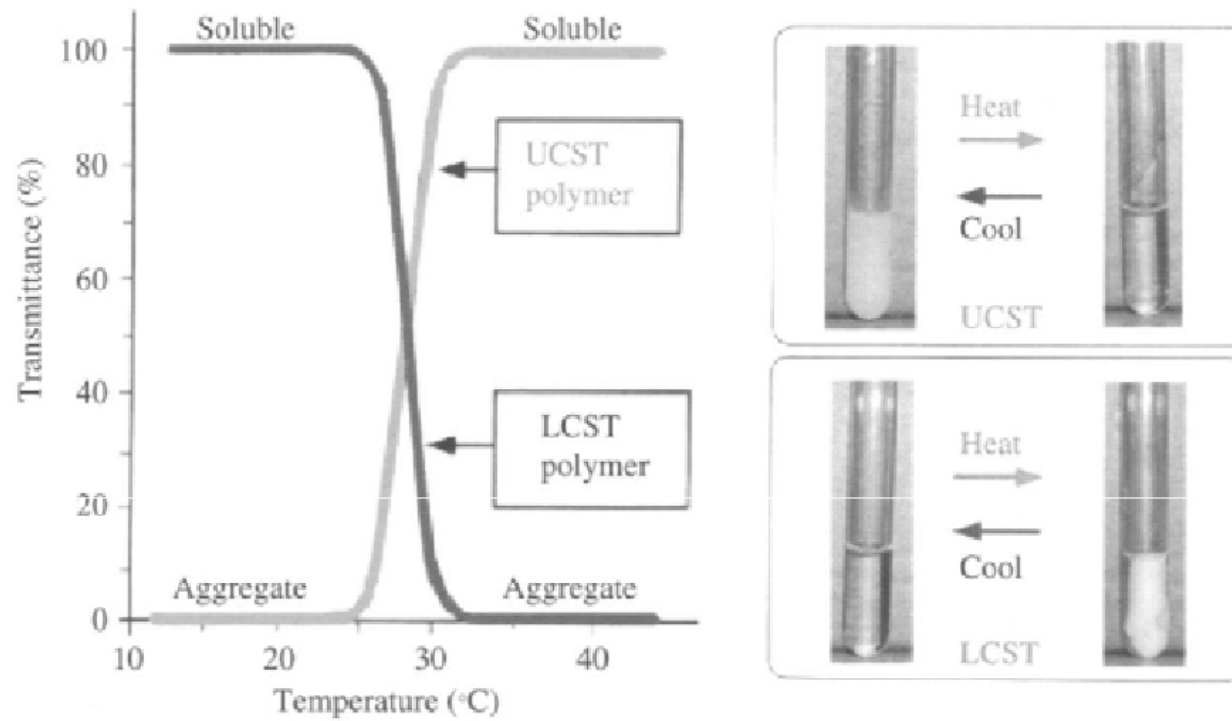


Magnetic separation





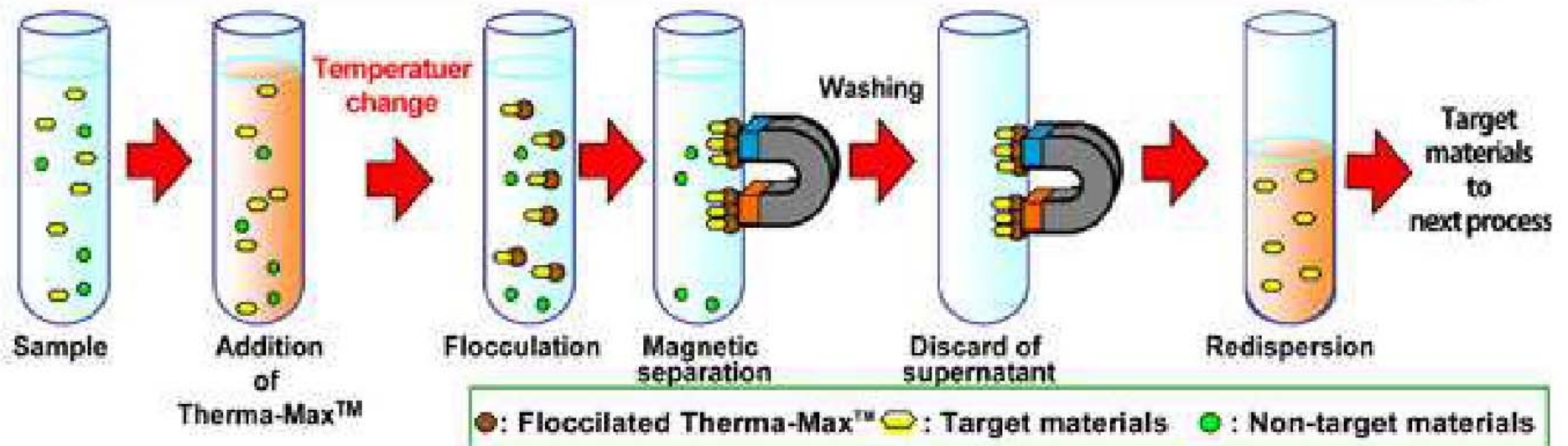
POLYMERS PROPERTIES CHANGES AS A FUNCTION OF T



Lower Critical Solution Temperature – **LCST**

Upper Critical Solution Temperature – **UCST**

Separation/Purification Protocol with *Therma-Max*TM

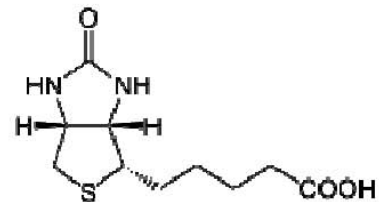
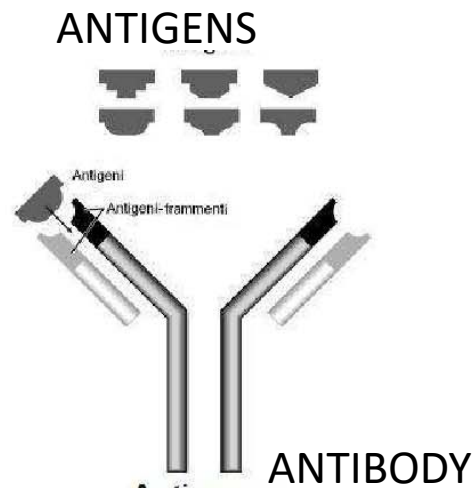


COOLING

HEATING

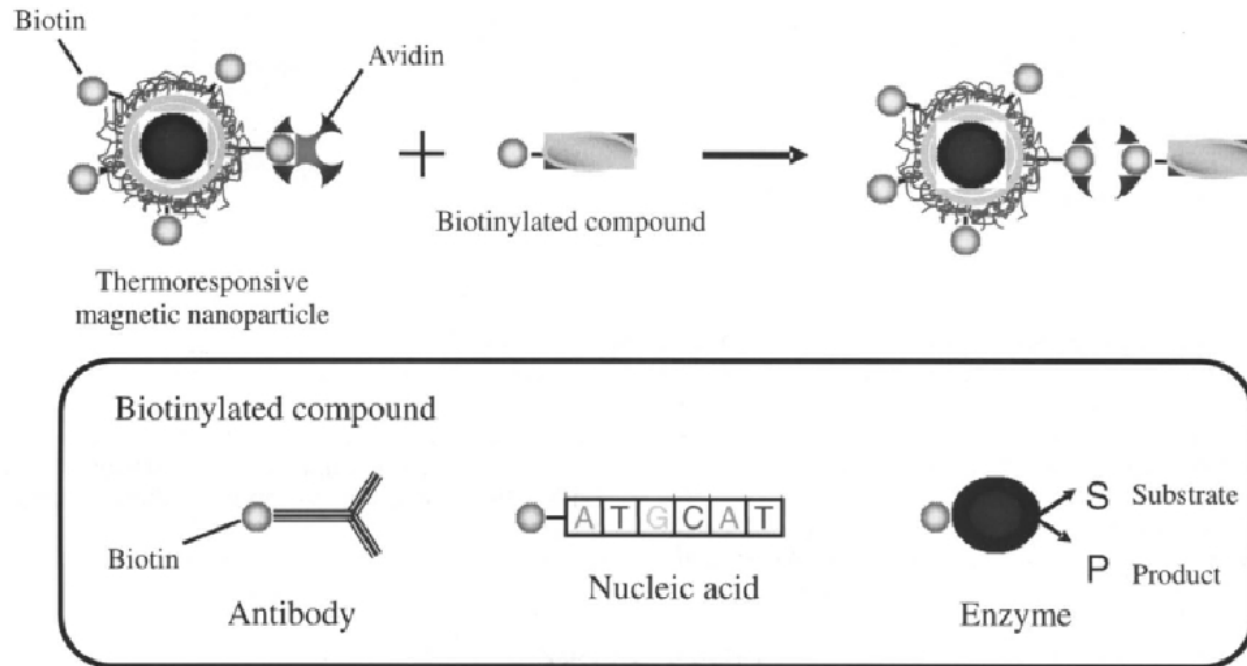
ANTIBODIES

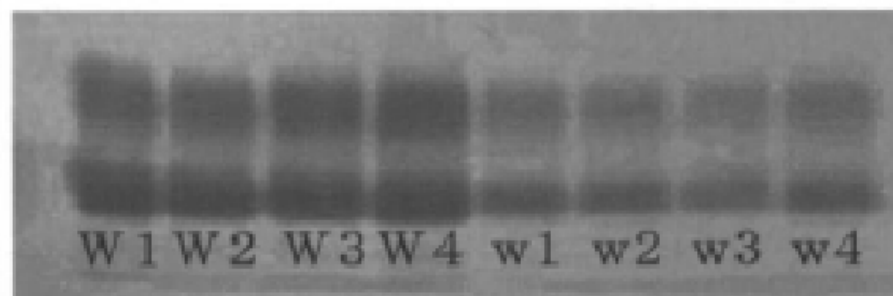
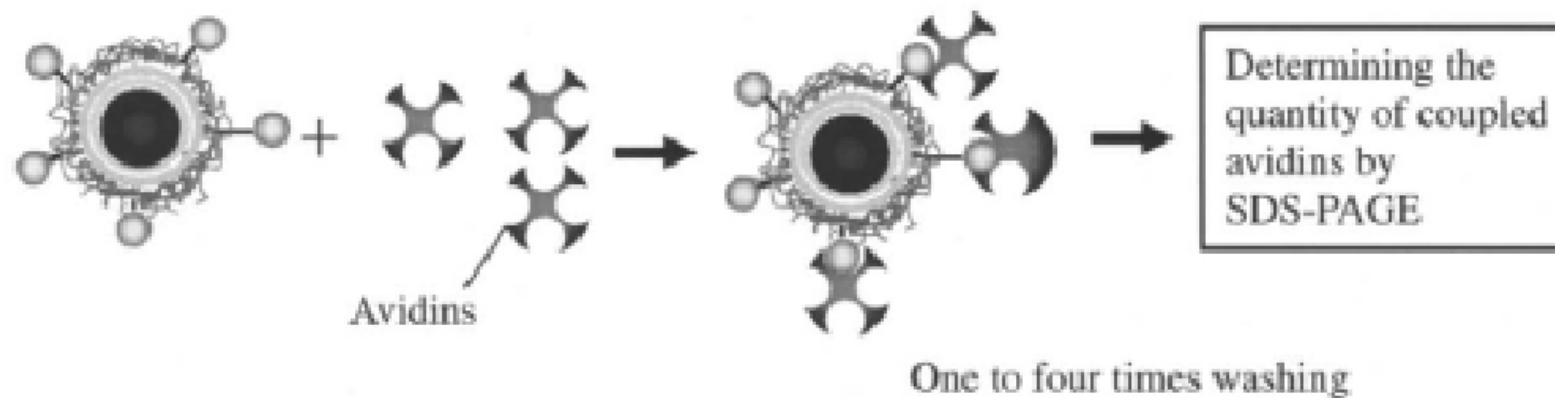
These structures (immunoglobulin) are formed by “Y” shaped mix of proteins. These structures are capable to capture most antigens by recognizing specific antigen terminals. On the terminal of the “Y” legs there are structures capable to close as soon as the correct antigen (key) is connected to the terminal (biotin). This leads to the connection of pairs pathogens and to agglomerate them, leading to their easy deactivation and elimination.



NANOPARTICLES FOR MEDICAL ANALYSIS

Magnetic core nanoparticles coated by a polyalcohol and the synthesis of the co-polymer with UCTS properties leads to composite nanoparticles with biotin terminals. The biotin terminal can connect other structures to the particle that can interact with many radicals such as antigens (virus, bacteria), DNA and proteins.





Avidins

W1 - W4: Washing times
Quantity of added avidins
(1 mg/ml) 50 μ l

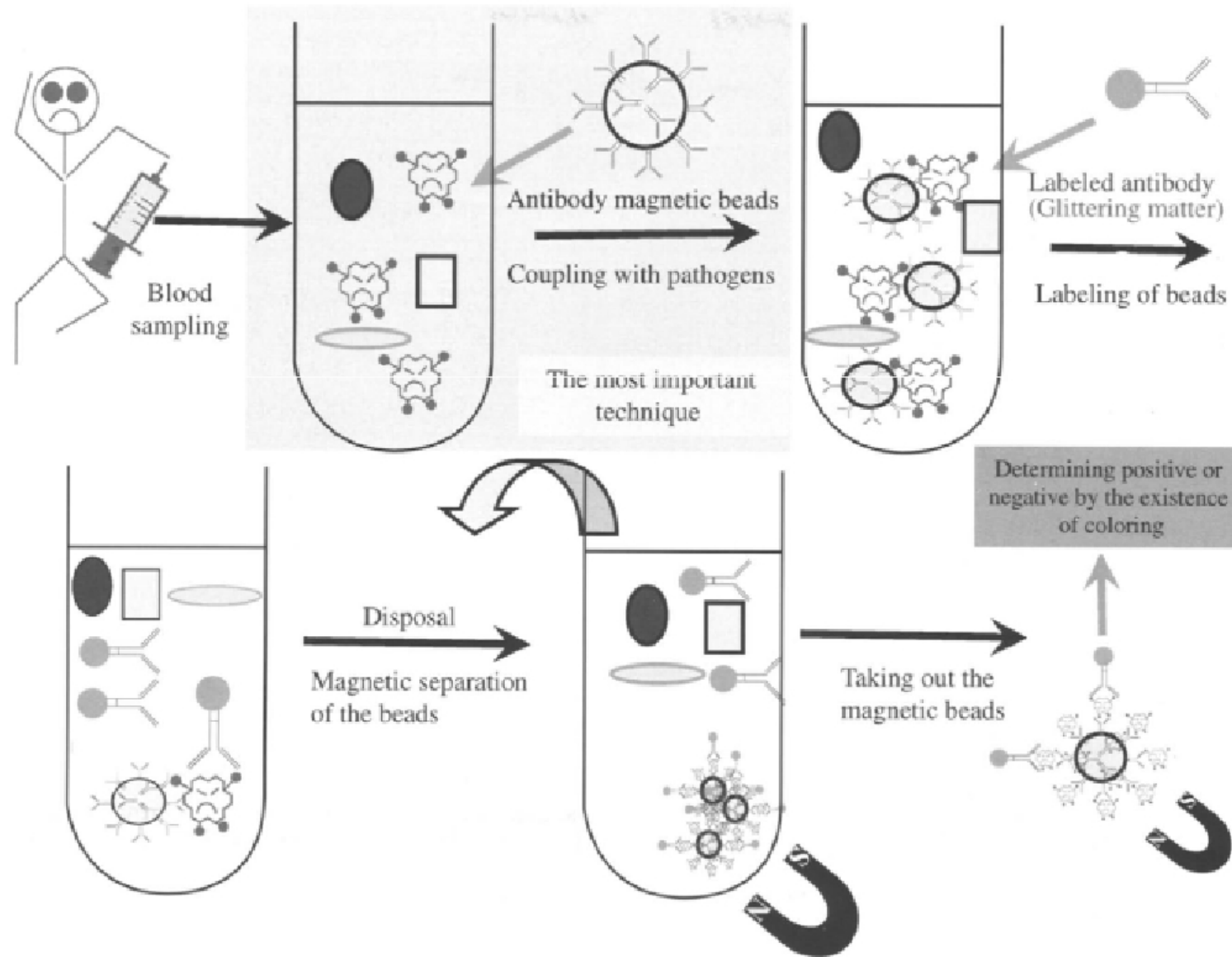
W1 - W4: Washing times
Quantity of added avidins
(1 mg/ml) 5 μ l

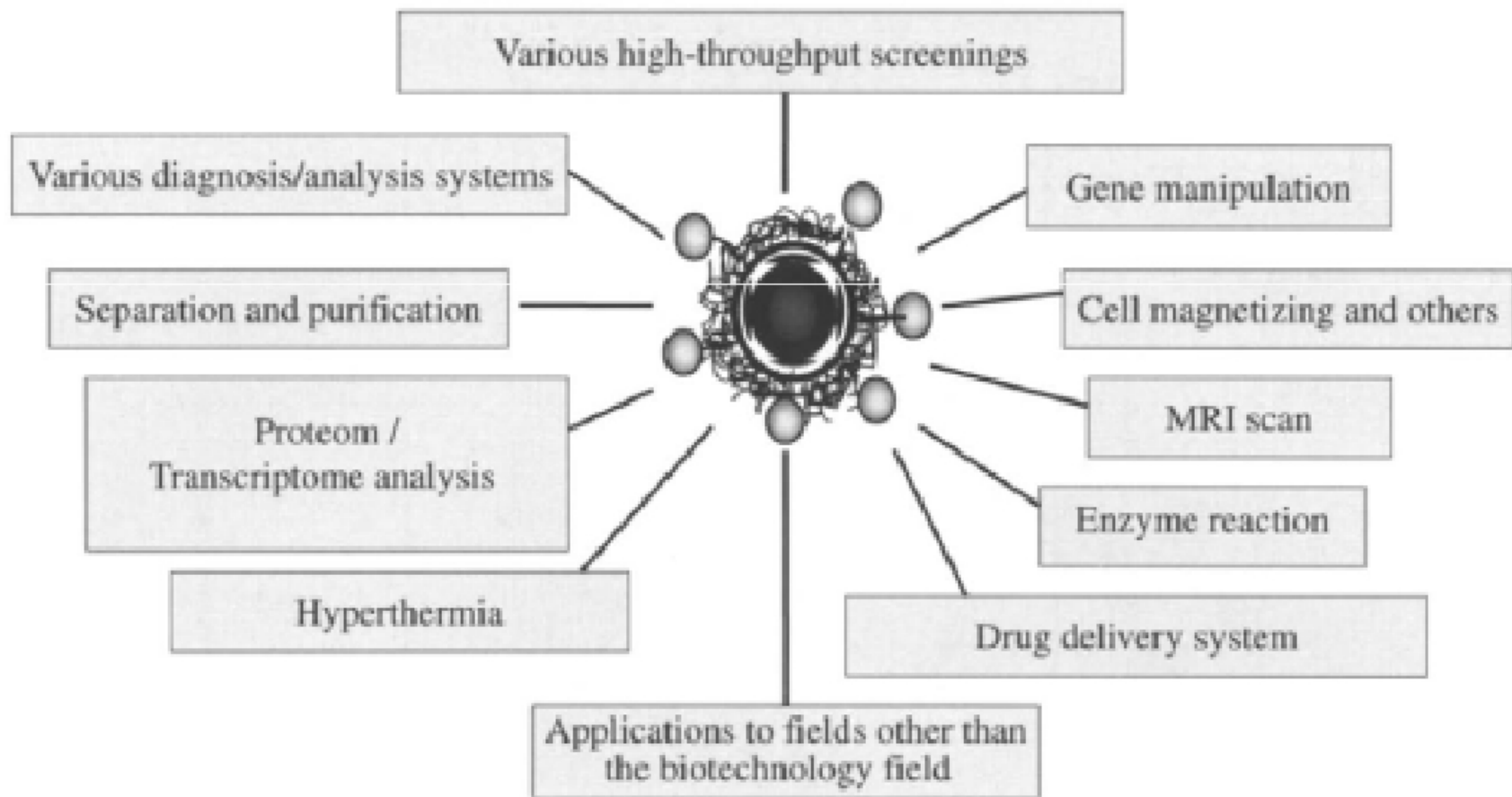
DIAGNOSTICS

Thermosensible coated magnetic nanoparticles can be used to indentify antigens in the blood streams. These particles may capture the antigen and successively a antibody connected to molecular sensors can be adsorbed. After recovery, analysis may be performed.

Example:

the sensor connected to the antibody may be a luminescent protein under certain radiation.





FIELDS OF APPLICATION