



NanoAthero

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# **NanoAthero project:**

A new way to fight  
cardiovascular diseases

Nanomedicines are already on the market and the new ones turn on cardiovascular pathologies

INSERM coordinates the European NanoAthero program.

NanoAthero FP7 NMP program with €9.8m over 5 years, is intended for the diagnosis of atherosclerotic plaque to prevent cardiovascular diseases including stroke. It also relates to therapeutic uses for delivering drugs in target tissues.

NanoAthero project gathers 16 partners from 10 countries including France with INSERM, AP-HP, Inserm-Transfert and CEA (Grenoble and Saclay), Austria (Medical University of Graz), Denmark (University of Southern Denmark), Italy with a European industrial leader Bracco, Germany with the University of Erlangen, the Max Planck Institute and nanoPET Pharma, Hungary (Semmelweis University), England with Edinethics for ethics, Switzerland with Clinam (Association for nanomedicine), and Israel with the company Wizsoft. The Netherlands will coordinate two clinical trials with Amsterdam Medical Center and the University of Utrecht; France will be responsible for the third clinical trial to be conducted at Cardiology and Nuclear Medicine of APHP, Bichat hospital.

Because of their size, making them comparable to a DNA molecule or a protein, one hundred to one thousand times smaller than a cell, the nanoparticles have different physical properties from those of common objects. Evolving to the same scale as the biological mechanisms of the body, they are able to cross natural barriers and enter cells. Their main therapeutic application, currently, is to ensure the transport of drugs into the interior of the cell by wrapping in tiny structures, and to protect them from

interactions with the surrounding environment. The hope is to bring more of the active ingredient to its molecular target, avoiding its degradation or distribution in healthy tissues. Experiments abound in this area. Search with nanoparticle and drug as keywords gives more than 25,000 references on Medline search. Nearly 20 years after the arrival of the first Nanomedicine (Doxil, a doxorubicin nanoliposome, approved by the FDA in 1995) their promise in medicine are still awaited if you take into account the relatively small number of nanomedicine on the market. However, it is truly innovative drugs generally providing benefit over existing treatments. "49 health nanoproducts are currently on the market in the world," said Laurent Lévy, Vice-President of the European Technology Platform Nanomedicine (ETPN) and cofounder of Nanobiotix, on the occasion of World Cancer Day 2014. In 2008, there were 36. These figures come from a study by Bionest for LEEM. Of the 49 nanoproducts marketed, 7 are veterinary products and 42 are intended for human medicine: 35 medicines and 7 medical devices.

In France, nearly twenty nanomedicines are on the market, most of which relate to cancer. For example Abraxane is a nanoparticle formulation of paclitaxel-albumin approved for the treatment of metastatic breast and pancreas. Cancer cells interacted with albumin, which will allow concentrate paclitaxel in tumor. The Transparency Commission ruled that Abraxane provides a minor improvement in actual benefit (IBA) compared to taxol in the treatment of breast cancer (median Progression-free survival extended by one month and overall survival of two months, but more side effects).

Many nanoproducts involve liposomes, which also have the interest to concentrate in cancer cells. Injected into the bloodstream, they cannot pass through a normal vascular

endothelium. However they pass through the endothelium of tumor vessels – the cells are less tightly joined – and into the malignant cells. The Daunoxome is a liposomal dispersion of daunorubicin for the treatment of Kaposi's sarcoma in patients with AIDS. Myocet citrate liposome-encapsulated doxorubicin is indicated for the treatment of metastatic breast cancer. It has less cardiac toxicity compared with doxorubicin, but the IBA was considered modest.

These nanodrugs of first generation are subject to the phenomenon of opsonization that leads to their rapid uptake by the liver and their degradation. The hepatic uptake is an asset when it comes to treating liver cancer. However, it decreases the amount of drugs that happens to other target organs, since the plasma half-life is reduced. To avoid opsonization, the second generation of nanocarriers have been developed that

are covered with polyethylene glycol (PEG). These nanoproducts, called "stealth" escape uptake by liver macrophages. They stay longer in the bloodstream and reach more of their extra-hepatic targets. Caelyx, consisting of doxorubicin hydrochloride encapsulated in pegylated liposomes, is available in France since 1996, especially for women with metastatic breast cancer with increased cardiac risk. In this indication, it provides moderate therapeutic benefit in terms of cardiac safety as compared to free drug.

Nanocarriers of third generation are still in an experimental phase. They involve, in addition to pegylation, a targeting molecule, which can be the ligand of a receptor or an antibody directed against a protein overexpressed in the target tissue antibodies. These vectors are used to address the drug directly to the target, which gives hope for improved efficiency, reduced toxicity and lower doses.

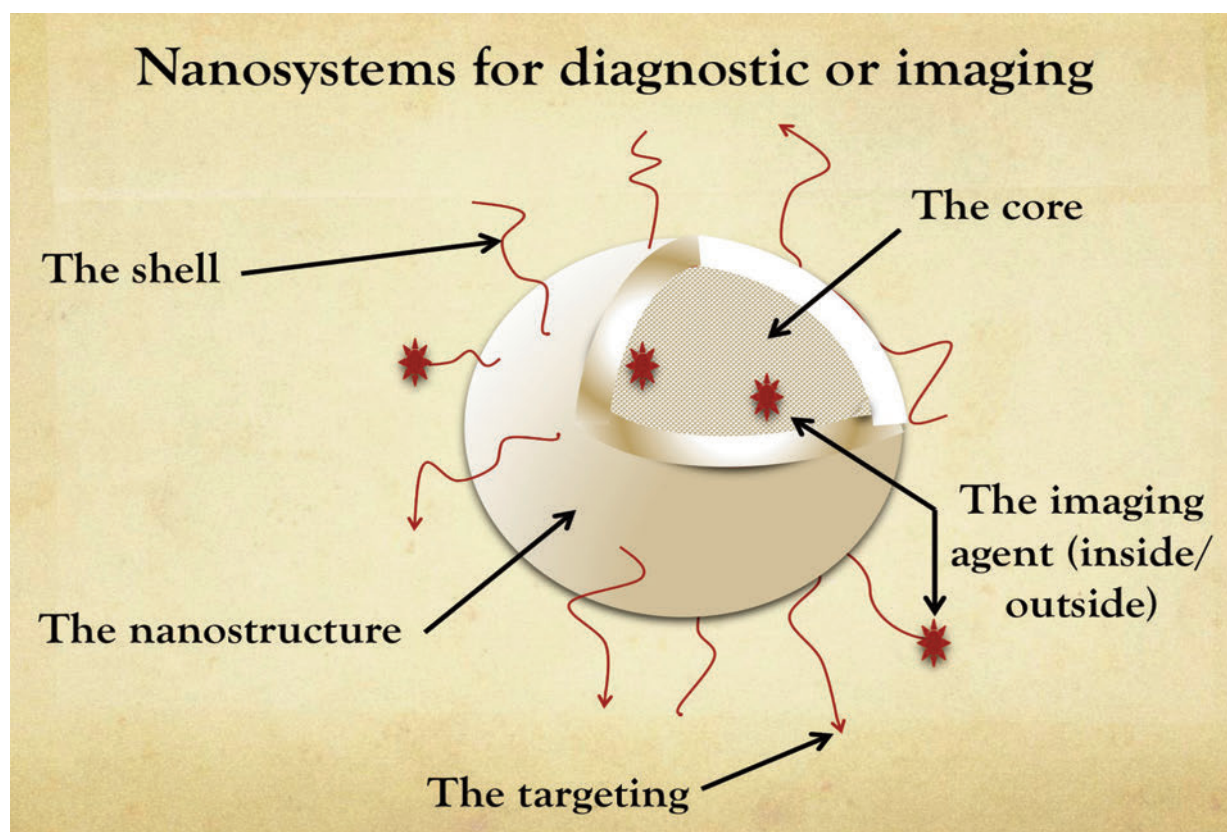


Figure 1. Nanosystems for diagnostic or imaging

However, few products reached the testing phase I/II trials. The Bionest study identified 122 nanomedicines in clinical development in the world, but among them, only 17 are in clinical phase II/III or III. Among them, oncology represents the main part (70 products), far ahead of infectious diseases (19 products) and cardiovascular disease (7 products). The potential toxicity of nanoparticles helps to explain why the research is primarily focused on oncology. It is very difficult to make an effective nanoparticle totally devoid of toxicity to the cells. In the case of cancer, this toxicity is less troublesome since, once reached its target, the nanoparticle should destroy malignant cells. In total, taking into account the 49 nanoproducs already on the market, there are 230 health nanoproducs marketed or in clinical development, including 222 for human medicine: 157 drugs and 65 medical devices.

Europe is very competitive in this area, with 1000 research groups and 500 SMEs. Various initiatives have been taken at European level to stimulate translational research in nanotechnology (see for instance: <http://www.etp-nanomedicine.eu>). NanoAthero project, funded by the European Commission and coordinated by Didier Letourneur Inserm U1148, includes the construction of several nanosystems, their evaluation, and clinical trials to evaluate the contribution of nanosystems in the diagnosis and treatment of atherosclerotic plaques and ischemic stroke. The first trial began in the Netherlands, including patients with carotid atheroma, to test the efficacy of a steroid (prednisolone) encapsulated in pegylated liposomes. The objective is to stabilize the plaque against local inflammation. This nanomedicine administered intravenously has proved efficacy in preclinical models of

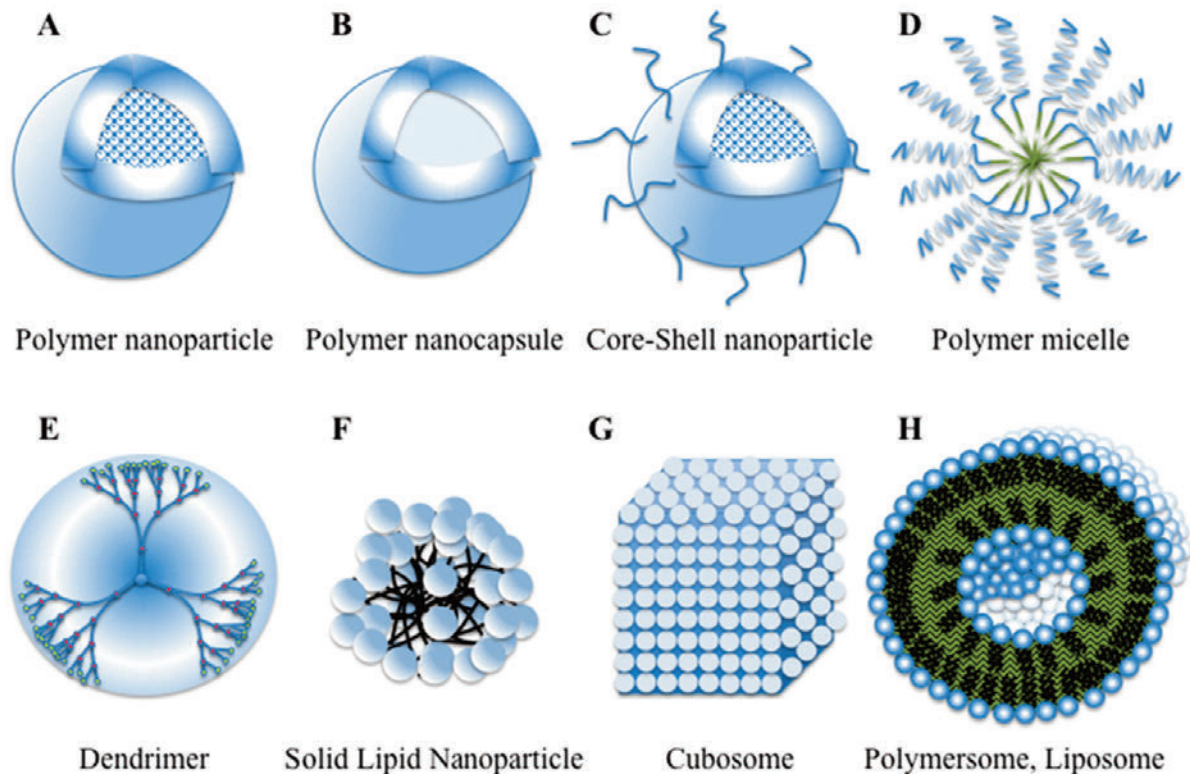


Figure 2. Different types of polymer-based nanocarriers



Figure 3. Different types of imaging modalities for preclinical evaluation of nanosystems. From left to right : MRI, Ultrasounds, SPECT, PET (SFR X. Bichat, Paris Diderot-Inserm U1148)

atherosclerosis. Other systems are being studied to optimize these nanosystems, possibly with targeting agents or other drugs.

A clinical trial should start at Bichat hospital (Dr Dominique Le Guludec) by 2016, to evaluate a new imaging technique for ischemic stroke. It uses a system developed from a polysaccharide extracted from brown seaweed (fucoidan), which specifically binds to P-selectin, a protein expressed on the surface of platelets and endothelial cells when they are activated. Associated with  $^{99m}\text{Tc}$ , this structure can visualize thrombi in preclinical imaging by SPECT scintigraphy. The idea is to detect early thrombotic events.

Didier Letourneur team also conducts works in the hope of improving thrombolytic therapy for ischemic stroke. Moreover, the incidence of stroke is increasing, especially among young people and women. The tissue plasminogen activator (tPA), a protein involved in the breakdown of blood clots is used in human (actilyse®) but has a short therapeutic window. The goal is to improve the treatment by combining a nanosystem that would set specifically at the thrombus to release the active ingredient without leaving the vascular compartment. We must find a safe nanoparticle platform that may combine enough rtPA without be metabolized. This is very complex because it is an enzyme that degrades very quickly.

In this new field of nanomedicine, there is a lot of research, but very few products arrived yet at the bedside. We have to ensure the safety of components, to successfully put enough active products in a nanosystem, and to produce according to safety standards GLP (Good Laboratory Practice). As for conventional medicines, this is a long way from the design of a nanosystem to the clinical application.

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# Eradicating cardiovascular diseases for good

Professor Joep Perk of Linnaeus University, and a member of the European Society of Cardiology, speaks to Editor Laura Evans about the importance of reducing cardiovascular diseases in Europe and how this can be achieved...

In Europe, cardiovascular diseases cause over 4 million deaths and over 1.9 million deaths in the European Union, which equates to 47% of all deaths in Europe and 40% in the EU. According to the European Heart Network,<sup>1</sup> death rates from cardiovascular heart disease (CHD) are generally higher in Central Europe, whereas death rates from stroke are much higher in Central and Eastern Europe. Overall CVD is estimated to cost the European Union economy €196bn a year.

Cardiovascular diseases are all the diseases of the heart and circulation, including coronary heart disease (angina and heart attack), heart failure, congenital heart disease and stroke. There are many factors that increase the risk of developing a cardiovascular disease including; smoking, weight gain, diet, and lack of exercise.

Member of the European Society of Cardiology, and Clinical cardiologist and Professor of Health Sciences at Linnaeus University, Professor Joep Perk speaks to Laura Evans about the problems cardiovascular diseases can cause throughout Europe, and what more could be done to decrease fatalities.

"If we go back some way in time, cardiovascular diseases were fairly uncommon in the beginning of the past century," Professor Perk begins.

"In Western Europe they started to show up in the 1930s and 40s and culminate around 1970 and 1980. In Western European countries there

has been a steady decrease over the past 20-30 years. Research has shown that, of the 6-year increase in life expectancy between 1970 and 2000, 65% of the increase – or almost 4 full years – is due to reductions in CVD mortality alone. As positive as this scenario is, heart disease remains the leading cause of death and the new epidemic has the potential to threaten the advances made to date. Europe is currently facing a series of emerging trends, such as the growing ageing population, that could create new challenges for healthcare systems."

"In Sweden, premature and early mortality in heart diseases has reduced to a third of what we had in the 1980s, which is a tremendous difference. At the same time as we see this lowering in Western Europe, we see some parts of Eastern Europe still experiencing problems."

Professor Perk explains there are some areas of Europe where cardiovascular disease is still rife. For example in Eastern Europe, the problem seems to be bigger than Western Europe, which Perk believes is due to lifestyle differences.

"Cardiovascular diseases are becoming a problem in middle and low income countries like India, Pakistan and Brazil, with 80% more early cardiovascular deaths being recorded.

"It is very much to do with public health; smoking, physical activity, what you eat, stress and our sleeping habits. In several Western European countries we have seen two thirds of a drop in

mortality over the past 25 years, which is due to the fact that people are smoking less, and are slightly more physically active.

“A country like Bulgaria for example has a huge problem. People are getting fatter, they are smoking more, move around less, and have more stressful lives which leads to a direct increase in mortality.”

The difference in mortality rates has a lot to do with developed countries having more effective treatment to hand. For underdeveloped nations, mortality rates are higher due to effective treatments or quality of care not being available, as Professor Perk explains.

“If you look at the risk factors, the number of people overweight and smoking is a bigger problem in richer countries. In poor countries, the quality of care, especially the follow up, is still undeveloped. For example, if you have a heart attack in Bangladesh, the survival rate is far worse than if you had one in the UK. If you look at the risk level for the average British citizen who is overweight and less active, when they have a heart attack they still have a better chance of surviving than the lean non-smoker in Bangladesh.”

Cardiovascular diseases remain the prime cause of premature deaths under the age of 75, and Professor Perk believes if we can tackle the problem head on, 80% of all cardiovascular diseases could be eradicated which is a huge achievement in itself.

Perk believes that education and legislation could play a key part in eradication. If people had the correct information and knowledge about these diseases, mortality rates could be a lot less.

“On a political level – more legislation on smoking, the amount of salt in food, access to fresh fruit and vegetables and physical activity is needed,” said Professor Perk. The EACPR issued an interesting paper about this.<sup>2</sup>

“People need to be informed that heart attacks

are something that at least 80% of people can influence through their own behaviour. We recently conducted a study and discovered the basic knowledge on how people could prevent this disease is lacking. There is a need for good public knowledge so people can take responsibility for their own health.

“On these 2 levels (public and personal) we can further eradicate cardiovascular disease. We know there is a significant difference of cardiovascular disease between the higher and lower income countries. If you make fruit and vegetables a lot cheaper, you give people with less resources a better chance of getting antioxidants into their diet, which can help to keep you healthy.”

Perk believes it is important to try and eradicate cardiovascular problems now, in order to prevent the next generation from developing the diseases.

“The main aim is to help the next generation who I would like to see active in sports. They have a body that has a reasonable guarantee to get to 90 years old. We have lots of children that are failing at school, they don’t sleep enough, and they don’t eat the right foods, and that is one of the main challenges in Europe.

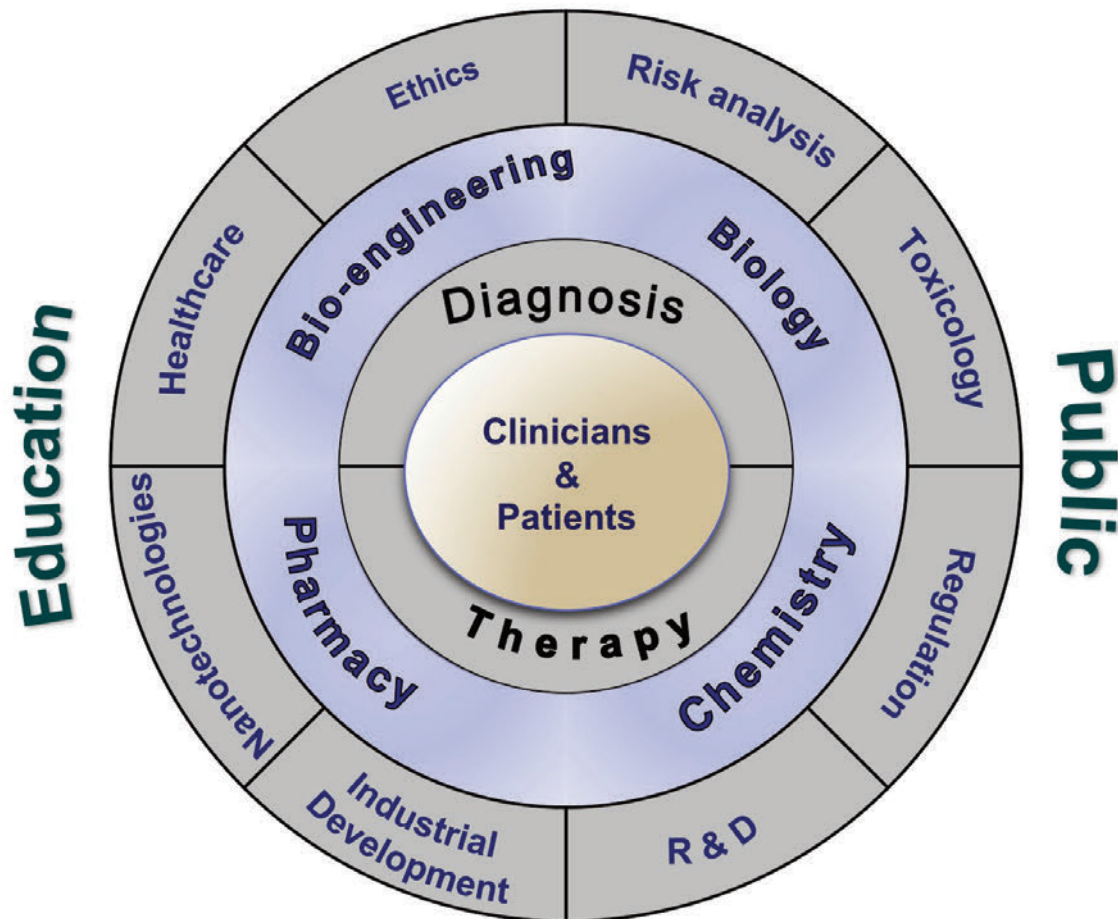
“Because I am professor of health science I work mainly on trying to transfer the knowledge we already have. We need to educate people and tell them these diseases are a waste of our time and we don’t need them.”

1 <http://www.ehnheart.org/cvd-statistics.html>

2 Population-level changes to promote cardiovascular health. Eur J Prev Cardiol. 2012 May 9. <http://cpr.sagepub.com/content/early/2012/05/09/2047487312441726.full.pdf+html>

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