

Nanoparticles transport active ingredients directly to their site of action

Tiny Trojan horses



Researchers from Bayer HealthCare are now packaging active ingredients in nanoparticles. Ideally, these tiny warriors successfully reach the affected tissue while remaining unrecognized by the body's defense system, systematically releasing their active ingredient at the right location. They can thus be used to intensively combat tumor cells – without damaging healthy tissue.

Some innovations are still state-of-the-art even after several thousand years. The Greeks are said to have once conquered the city of Troy with a cunning ruse. The Hellenic warriors hid in the belly of a huge wooden horse. The Trojans, thinking it was a gift, pulled the horse into the city. When night fell, the soldiers crept out, killed the guards and opened the city gates, allowing the army to pour in and capture Troy in a surprise attack. This trick from the annals of Greek mythology is currently experiencing a renaissance in the field of medicine: tiny active ingredient molecules are concealed in a ball of long molecule chains. Thus disguised, they are channeled through the body to their destination, where they proceed to cunningly ambush diseases.

Two scientists making use of this Trojan-horse tactic are Dr. Sascha General and Dr. Katrin Fischer of the Bayer Schering Pharma Division. The disguised, nanoformat active ingredients they are developing have one key advantage: they are not recognized by the body and can transport their cargo to its site of action more effectively. Tumor cells are one special target for such nanoparticles. The researchers hope

that, thanks to their size and surface texture, the small particles will tend to collect in these cells, resulting in them causing less damage to healthy tissue and being better tolerated by the body than conventional medications.

These potent particles with a circumference of approximately 200 nanometers are a thousand times smaller than the thickness of a human hair and cannot even be seen under a high-powered light microscope. From the researchers' point of view, they are the ideal size: "The particles can pass through the sieve-like structures in the walls of the tumor blood vessels but are too large to penetrate healthy tissue," reports Fischer. One reason is that tumor tissue usually grows faster than healthy tissue, forming highly permeable structures with holes that can be up to 800 nanometers in size. Once the tiny active ingredient particles become caught in the tumor tissue, they are tough to expel. "A functional lymph

Nanomedicine: using particles in nanoformat (large picture, left), researchers from Bayer Schering Pharma are seeking to accomplish such feats as attaching active ingredients (red) directly to a virus (right), receptor or tumor cell, thus reducing the side effects of the drugs in the human body. In order to do so, Dr. Sascha General (photo, right) and his team are relying on the same tactic the ancient Greeks once employed in the battle for Troy.





Finely distributed: Dr. Katrin Fischer visually examines the nanoparticles floating in a dispersion like drops of essential oil in ice-cold anise schnapps.

Size does matter: a laser measuring device that registers each individual particle in the dispersion and determines its size helps the researchers at Bayer learn which special nanoparticle sheath design best prevents the tiny active ingredient capsules from clumping.

system which permanently frees healthy tissue from the body's own waste products and foreign substances only exists to a limited extent in tumor tissue," explains the pharmacist. The enveloped particles thus remain stuck there.

In order to make the nanoparticles suitable for therapeutic purposes, the researchers at Bayer Schering Pharma are now concentrating their work on the chemical design of the active ingredient sheaths. These consist of numerous chains of molecules, known as polymers, which either envelope the active ingredient molecules like cotton or form a network in which the active ingredient particles are embedded like raisins in a cake. No matter which type they are, the sheaths are specially customized: "The polymers we choose and how we modify them depends on both the properties of the active ingredient and the kind of tumor," explains General. The initial priority was preventing immune reactions to the medication by the body. The immune system must therefore be fooled into thinking that the nanoparti-

cles are the body's own substances. The researchers design the external chemical packaging of the particles accordingly. Ideally, the particles should look "like a sip of water", says General. After all, water is the main component of all bodily fluids and is therefore regarded as entirely unsuspecting by the immune system.

Nanoparticles affix themselves to the receptors on tumor cells

The researchers also cleverly stud the active ingredient sheaths with molecules which conform perfectly to the nanometer-sized surface structures of the tumor cells, known as receptors, thus firmly affixing the particles to the cell membrane. A particle then fits into the lock of the cell like a unique key, giving it good chances of being admitted. That works like this: the cell membrane pulls inward at the site where the nanoparticles are attached, surrounding a large number of these particles like a tiny bag. The membrane then closes this

bag from the outside, leaving the particles inside the cell, where the particle surfaces and the charges on them play a role in, among other things, determining the further route taken by the nanoparticle. "We know that the membranes of a cell, including the membrane of the nucleus, have different properties such as negative partial charges," explains General. These are caused, for example, by proteins and polysaccharides embedded in the membranes. The researchers now want to make targeted use of this knowledge. They want to help the particles navigate to precisely where the cancer medication should ultimately take effect. The exact details of how this guidance system will work are not yet clear, however. The scientists must therefore test the suitability of various sheath versions for each active ingredient.

The researchers are also adjusting the stability of the sheath polymers, which determines how fast the shell around the active ingredient dissolves in the body. "We usually try to achieve

Interview



“New possibilities for diagnostics and therapy”

What opportunities does nanomedicine offer? *research* spoke with Dr. Oliver Bujok, an expert for nanomedicine at the VDI Technologiezentrum GmbH of the Association of German Engineers (VDI) in Düsseldorf.



What potential does nanomedicine harbor?

Nanomedicine opens up entirely new possibilities in the fields of diagnostics and therapy, in particular regarding active ingredient transport and targeting, e.g. targeted release of active ingredients at the site of action. For instance, this makes it possible to concentrate contrast medium in a tumor or center of inflammation. In addition, nanotechnologies have great potential for in vivo diagnostics and last but not least implants and regenerative medicine. They can be used to systematically structure or coat the surface of implants so that the body is more likely to accept them. Large pharmaceutical corporations and more than 150 small and mid-sized companies worldwide are now focusing on nanomedicine. Universities are naturally staying on the ball as well and public support funding is increasing.

Which nanomedicine products are already on the market?

At present, there are just under 40 products on the market around the world, generating annual revenue of some US\$ 7 billion. The majority of these are nanoparticle or colloidal drug delivery systems which significantly boost tolerability of drug products.

Will there be medicines that move through the bloodstream of their own accord?

The first interesting approaches have already been taken here. For instance, medical active ingredients are attached to magnetic particles and can then be drawn to their site of action by external magnets. In contrast, particles that propel themselves through the blood using their own source of energy, like miniature submarines, remain a mere vision. Not only is suitable technology lacking, such particles offer neither medical nor economic advantages from today's viewpoint.

Can nanomedications cause damage as well?

Like all drugs, nanomedicine products are extensively tested and not approved for market launch until the outcome of meticulous benefit-risk analyses is positive for patients.

slow dissolution in order to ensure that the active ingredient is released in the cell and not on the way there. This creates a high concentration of the active ingredient in the tumor cell in comparison to healthy tissue," says General in describing the strategy.


Sheath design requirements are as widely varied as the production procedures themselves. "We usually form these particles from active ingredient and polymer molecules," says General. In order to do so, he blends polymers with the active ingredient dissolved in liquid, milliliter by milliliter. As soon as the particles have grown to an appropriate nanometer size, the liquid takes on a cloudy, milky appearance due to the small, finely distributed particles floating in it like drops of essential oil in ice-cold anise schnapps. The scien-

tists usually add tenside to stabilize the particles in the liquid. These molecules settle like adapters between the particles and the molecules of liquid, preventing the nanoparticles from clumping and settling to the bottom.

Initial medications already successful in clinical tests

The work performed by Fischer and General requires extensive knowledge in a wide variety of areas. "Our research is very interdisciplinary in nature," underscores Fischer. The scientists must be familiar with the unique features of the type of cancer to be treated, the active ingredient to be used, the biochemical and biophysical processes in the body and naturally with the chemicals of the sheath polymers. When a sheathed

active ingredient is ready for clinical testing, an intensive dialog with doctors is necessary as well. Neither Fischer nor General has any doubt that these tiny Trojan horses in nanoformat will cause quite a stir in the world of medicine. The first medications have already proven their potential in clinical tests and have been approved for therapeutic use in humans.

 <http://cordis.europa.eu>
Information on nanomedicine is also available on the website from the EU information service. Simply enter the key word "nanotechnology".