

## Targeted nanomedicines

G. Storm

*Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University (G.Storm@uu.nl)*

Many candidate and established drugs have less than ideal properties with consequently unfavourable therapeutic implications. Particulate drug targeting systems can be designed to improve the therapeutic behaviour of such drugs, which are commonly administered orally and parenterally. Nanoparticulate-based drug targeting has come a long way since Paul Ehrlich introduced the concept early in the last century. Progress has been slow, but several products have reached the market. Nanotechnology-inspired approaches to particle design and formulation, an improved understanding of (patho)physiological processes and biological barriers to drug targeting, as well as the lack of new chemical entities in the 'pipeline', are causing large pharmaceutical companies problems in bringing new drug compounds to the market. This indicates that there is a bright future for targeted nanoparticles as pharmaceuticals. It is now well known that a reliable targeting system is essential for successful drug delivery in many serious disease situations. Targeting systems can target a drug to the intended site of action in the body, thus enhancing its therapeutic efficacy (site-specific delivery), and/or direct a drug away from those body sites that are particularly sensitive to the toxic action of it (site-avoidance delivery). A multidisciplinary research approach, employing the combined forces of many scientific disciplines, is a key factor for success. It is becoming increasingly recognised that a major limitation, impeding the entry of targeted delivery systems into the clinic, is that new concepts and innovative research ideas within academia are not being developed and exploited in collaboration with the pharmaceutical industry. Thus, an integrated 'bench-to-clinic' approach realised within a structural collaboration between industry and academia, is required to safeguard and promote the progression of targeted nanomedicines towards clinical application.

The development of effective, safe, and innovative drug targeting systems, is a complicated multi-step process. There is an increasing need to select and / or identify appropriate matrix materials, surface coatings, and targeting ligands with advanced properties. Therapeutic agents (small molecules, but also macromolecules like proteins and nucleic acids) to be loaded into nanocarriers vary widely in their physicochemical properties and it remains a challenge to balance the nanoscale dimensions of the particulate with the types and amounts of drugs that are clinically required. Proper structural and physicochemical characterisation is required to guarantee reproducible effects in vivo. Advances in particle engineering (e.g. surface modification with 'stealth' polymers, like poly(ethyleneglycol) (PEG) and targeting ligands) have already yielded nanoparticles which can reach major pathological sites in vivo, after intravenous and local routes of injection. Examples of target sites that are accessible in vivo include sites of malignancy and inflammation. Here, the most common method of targeting is passive extravasation through 'leaky' vasculature (the Enhanced Permeability and Retention (EPR) effect) using stealth polymer coated nanoparticles, which circulate in the bloodstream for a sufficiently long period of time ('passive targeting'). Ligand-mediated targeting ('active targeting') to endothelial cells lining blood vessels present within the site of pathology has also been used successfully. Vascular targeting ligands are directed against receptors, which are specifically (over)expressed on the pathological vasculature because of the angiogenesis process. To date, most research in this field has been directed towards solid tumours.

MEDITRANS represents a multidisciplinary Integrated Project (FP6) dealing with targeted nanomedicines. Platform technologies are being developed with broad applicability to disease treatment, as exemplified by the choice for chronic inflammatory disorders (rheumatoid arthritis, Crohn's disease, multiple sclerosis), and cancer as target pathologies. Nanomedicines (based on carrier materials like polymeric and lipidic nanoparticles, nanotubes, and fullerenes) will be endowed with superior targeting and (triggerable) drug release properties. In parallel, MRI imaging probes will be designed that report on the in vivo localization of the targeted nanomedicines, specific biomarkers, the drug release process and therapeutic outcome (imaging-guided drug delivery). The consortium consists of 30 partners from 9 EU member states (including 1 new member state) and 3 associated states, and includes 13 industrial companies, 11 universities and 6 research institutes. The total budget is € 16.1M, with € 11M from the EC and € 5.1M from MEDITRANS' industrial partners.