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Drug Design 2020: Pharmaceutical development of injectable nanomedicine targeting breast cancer - Igor Chourpa- University Francois Rabelais of Tours.

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Abstract:
Anti-cancer theranosis (therapy and diagnosis) using nanomedicine may be a promising perspective, associated with an opportunity to mix several diagnostic and therapeutic functions so as to potentiate them. Superparamagnetic iron oxides (SPIONs) are often used as nanomedicine platforms due to the possibility to stimulate their intratumoral staining and drug delivery with help of a magnetic field as well as to contrast tumors on Magnetic Resonance Imaging (MRI). In order to inject superparamagnetic iron oxides intravenously, their biocompatibility and efficacy has got to be improved by coating the surface with neutral biocompatible polymers like Polethylene Glycol (PEG) functionalized with molecular cancer targeting ligands like peptides and antibody fragments. We are developing biofunctionnalized and PEGylated injectable nanovectors supported PEGylated SPIONs. Their polymeric shell is covalently coupled with membranotropic cell-penetrating peptides gH625 and/or with scFv fragments of antibody trastuzumab which binds specifically to membranes of HER2 positive breast cancers. The nanosystems can thus act as vectors of chemotherapeutic drugs of anticancer-active siRNA. The pharmaceutical development strategy we apply includes not only a rational design of the nanosystems but also step-by-step optimization of their structure in order to reach the better biocompatibility/bioactivity. For each of the nanoform, tens of independent batches were generated and their physical and chemical characteristics (size and zeta potential, structure and chemical composition) were established. Prior to in vivo essay on carcinoma xenografts in mice, the nanoforms interaction with cancer cells has been studied in vitro, on various neoplastic cell lines, overexpressing or not cancer-specific receptors. Comparison of biological behavior of the ligand free vs. ligand carrying PEGylated nanovectors allowed us to demonstrate that the moderate presence of ligands was not able to affect the nanomedicine forms size and zeta potential. Nevertheless, the bio-ligands enhanced the nanomedicine-cell interactions, both quantitatively (intracellular accumulation) and qualitatively (internalization, subcellular distribution and cargo delivery/ transfection).

Principle, challenges and limits of magnetic drug targeting:
The principle of magnetic drug targeting is relatively simple:
After intravascular injection, magnetic nanoparticles can be transported by the blood circulation and concentrated at the tumour with the aid of a magnetic field applied at the affected zone.
Particles of iron oxide with diameters below 30–40 nm are of particular interest because they exhibit super paramagnetic behaviour. This means that once the magnetic field is removed, they do not retain any magnetization (no hysteresis). Super paramagnetic iron oxide nanoparticles are already used as contrast media in magnetic resonance imaging, and their low toxicity has been demonstrated for a long time.

The iron oxide nanoparticles constitute the core of the final forms of therapeutic nano vectors. From a physicochemical point of view, the main objective in the preparation of magnetic nano particles consists in a strict control of particle size and colloid stability/dispersibility under physiological conditions. These properties can be modulated by coating the particles in two different ways: either the iron oxide nano particles are physically incorporated in a polymer matrix, or their surface is functionalized with polymer molecules. As for the drug, it can be dispersed in the polymer matrix by chemically bounding to the polymer, or directly attaching to the surface of iron oxide.

After coating, the particle size is increased, but it still should remain in the sub-micron range. In this case, they will not block vessels and capillaries and thus avoid embolization. Moreover, size and surface of resulting particles are determinant with respect to pharmacokinetics in vivo, where major limitations are quick blood clearance and non-specific uptake by macrophages. To increase the circulation time and targeting ability, the optimal size should be not less than 100 nm in diameter and the surface must be hydrophilic in nature. Ideally, these properties should render the particles “furtive”, which means that they are not cleared by the reticulo-endothelial system. In addition to biocompatibility, the coating should regulate drug loading rates and release kinetics.

Once at the target site, the drug is released from the magnetic carrier creating a high local concentration in the tumour tissue while minimizing the amount of the drug throughout the rest of the body. However, this implies that the magnetic field must be applied long enough for the drug delivery. The magnet must create a sufficiently strong magnetic field to retain nanoparticles at the desired site. The success of the method depends on the competitive forces between the external magnetic field and blood flow pressure in the arteries and capillaries. Another problem is the depth of the target site because the strength of the magnetic field decreases with distance. This implies that one can use this technique only in the case of solid tumours close to the surface of the body.

These trials followed pre-clinical studies that documented tolerance and efficacy. In the first trials, epirubicin was ionically sure to a modified carbohydrate layer on iron oxide nanoparticles. The authors clearly observed the accumulation of nanoparticles in the target area after exposure to the magnetic field. However, the drug release was rather hooked in to variable physiological parameters. Thus, technological improvements were necessary to make this treatment more effective. Nevertheless, the feasibility of the technique was demonstrated, and

This work is partly presented at 13th International Conference and Exhibition on Nanomedicine and Pharmaceutical Nanotechnology on July 24-25, 2017 at Rome, Italy

these results were encouraging for many researchers all over the world.

Conclusion:

Magnetic drug targeting is a novel drug delivery system that has been proven feasible resulting in an increase in local drug concentration and thus permitting a reduction of side effects. Nevertheless, the clinical trials highlight numerous problems still to be resolved. If the principle of magnetic drug targeting is straightforward, the event of magnetic vectors is complex. The optimisation of critical parameters is size, biocompatibility, magnetization and drug loading and release. Although for the time being no preparation satisfies all requirements simultaneously, most research groups succeed to produce biocompatible magnetic vectors with controllable sizes in the nanometer range. This is a source of optimism for a real possibility of magnetically targeted chemotherapy.

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