Scientific Symposium (Sat, 24 Sep, 11:15−13:15)
Nanotechnologies for Targeted Drug Delivery

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Nanoplatforms for Targeted Drug Delivery

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The origin of the nano-delivery drug targeting approach for the treatment of cancer started in the 60's. This approach has led to a new generation of nanomedecines that are aimed at enhancing the efficacy of anti-cancer drugs and improving the patient's quality of life. The rational behind this new concept of nanotherapeutics relies on the use of nanocarriers that can help bioactive compounds to overcome critical biological barriers, i.e. degradation in the blood-stream, biodistribution and internalization by the target cells. Currently, important efforts are being oriented towards this goal and the prospect is that these nanotherapeutic strategies will soon represent a great milestone in cancer treatment.
During this presentation, a number of examples of nanocarriers designed in our laboratory for the targeted delivery of anticancer drugs will be overviewed. These nanocarriers, named nanocapsules, are composed of an oily container and a polymer corona. The container has the capacity to accommodate the anticancer drug and/or the adjuvant compound (i.e. immunomodulatory agent) and control their release. The polymer corona may have a multifunctional character, namely (i) to prolong the residence time of the drug in the blood stream, (ii) to target specific cancer cell populations, and (iii) to attach macromolecular adjuvants and drugs. This corona has so far been made of polymers such as polyglutamic acid, polyasparagine, polyarginine and hyaluronic acid. The results obtained until now for specific anticancer molecules, i.e. docetaxel and aplidin, have provided evidence of their enhanced uptake by cancer cells, modified pharmacokinetics and reduction of the systemic effects as a consequence of their association to the nanocapsules. Overall, during the presentation, the level of success achieved with these nanocarriers will be discussed.
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Nanocarrier Pharmacokinetics and Pharmacodynamics: Watching Where Nanoparticles Go

Abstract not received

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Temperature Sensitive Drug Nanocarriers for Local Delivery

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Drug-loaded temperature sensitive nanocarriers such as liposomes were more than 30 years ago suggested for a new approach in local cancer therapy. At body temperature, a small molecular weight drug is stably loaded into the aqueous lumen of the liposome, which prevents rapid and unwanted distribution of the drug across all tissues. Upon heating to mild hyperthermia (T = 41−42ºC), which coincides with the melting temperature of the liposomal membrane, the lipid bilayer becomes leaky leading to a rapid and fast drug release. For local drug delivery application, the challenge is to maintain in a well defined target tissue hyperthermia in a non-invasive way for 30 minutes and more. Secondly, a non-invasive way to monitor the drug delivery process and achieved drug concentration is highly warranted.
High Intensity Focused ultrasound allows non-invasive heating to establish hyperthermia (40−43ºC) in almost any tissue that can be acoustically reached. MRI plays in this procedure a pivotal role thanks to its superb resolution for soft tissue as well as the possibility to acquire 3D temperature information. Consequently, MRI scanners emerged with an (high focused) focused ultrasound transducer embedded in the patient bed (MR-HIFU), where the MRI is used for treatment planning, and to provide a spatial and temperature feedback to the HIFU during the treatment. In this talk, recent studies on hyperthermia induced drug delivery in tumour bearing rats using MR-HIFU will be presented, employing temperature sensitive liposomes (TSLs). Loading TSLs with a drug and an MRI contrast agents allows monitoring and quantifying the drug delivery with MRI. The challenge is to find TSL systems that stably encapsulate dox and the contrast agent at body temperature, while rapidly releasing both under hyperthermia. The release kinetics of dox and MR agent upon heating is studied *in vitro* and in gel phantoms using MRgHIFU. Biodistribution of the TSLs and dox are assessed in 9L glioma rat model using radiolabeling and dox extraction from tissues. In-vivo studies in tumour bearing rats show that MR-HIFU allows to maintain hyperthermia inside the tumour at T = 42ºC for 30 min. Heated tumours receive about 10−20 times more doxorubicin compared to non-heated tumours. Furthermore, the contrast change observed non-invasively with MRI across the tumour tissue scales with the dose of doxorubicin delivered to the tissue, showing that MRI allows a non-invasive way to visualize the drug delivery process and to quantify the drug dose.

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Polymeric Nanoparticles and Drug Targeting

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Tumour targeting using nanoparticles has been in the forefront of academic and pharmaceutical research for the last several decades. Both passive (enhanced permeation and retention based) and active (ligand based) targeting technologies have been explored and tested on a number of preclinical models. Polymeric nanoparticles have been employed in a number of these studies due to the fact that polymers can encapsulate a variety of actives and the nanoparticles can be functionalized using well developed chemistry methods. Till date, the success of targeting and achieving efficacy in clinical outcomes is very scarce although several human trials have been initiated recently. Needless to say, translation of efficacy from a xenograft or orthotopic animal model to demonstration in human clinical trials is the significant bottleneck to bring out novel therapies. Our approach to targeting has been to test the potentials of nanotechnologies that use polymers for encapsulation and sustained release using pipeline molecules that already partitions to a good degree in solid tumours as evidenced in human clinical trials via oral administration. The objective would also be to be understand if adding a ligand would aid the receptor mediated endocytosis process towards achieving higher local concentrations of the active inside the tumour. Polymeric nanoparticles can act as local depot in the tumour tissues and can enable controlled release at the local acidic pH. Imaging of the nanoparticles − with various size and degree of PEGylation − was utilized to determine their ability to reach target organs and circulation through non tumored rodent via tail vein injection. Data generated using a variety of polymeric nanoparticles such as polystyrene, PLG A, and a cross-linked diblock polymeric nanoparticles would be shared.

Special Session (Sat, 24 Sep, 14:15−15:15)
Peritoneal Surface Oncology − The Evidence for Locoregional Treatment

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Peritoneal Carcinomatosis of Colorectal Origin

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Peritoneal carcinomatosis (PC) is a common event in the natural history of colorectal cancer, presenting as synchronous disease in 5−11% of cases and as metachronous disease in 20−50% of the cases. In the past, carcinomatosis from colorectal cancer has been regarded as a terminal disease. The progress of chemotherapy and biological agents has led to substantial improvement in outcomes, but without long-term survival. Another promising therapeutic option is cytoreductive surgery (CRS) with hyperthermic intra-peritoneal chemotherapy (HIPEC) which gives a median survival of 30−60 months for patients in whom complete cytoreduction is achieved, with 11−30% of patients alive at 5 years. These results were reported by groups using the combination of a comprehensive cytoreductive surgery to treat macroscopic disease with perioperative intraperitoneal chemotherapy to treat microscopic disease. Mitomicin and oxaliplatin (ox) are the most commonly used agents for HIPEC in colorectal cancer. Substantial results in survival have been obtained with these drugs associated to systemic 5-FU or in association with irinotecan, with a median overall survival reaching up to 60 months (ox) after complete cytoreductive surgery. From then on, surgical results are fairly acceptable as well, ranging from 20 to 50% grade III & IV postoperative morbidity rate and 2 to 5% mortality rate. Considering the survival benefit obtained in this situation, morbidity rates should no longer be considered sufficient reason for not using the CRS+HIPEC approach. However, the exact effects of each steps of this combined procedure are currently unknown. The proper role of the