amino acid side chain or in between two amino acids. Cellular uptake of the new bioconjugates was investigated with different methods like fluorescence microscopy, atom absorption spectroscopy or flow cytometry. High accumulation could be observed in different tumour cells. Furthermore, cell viability assays showed that those organometallic peptide conjugates are very potent and possess promising cytotoxic properties.

See references below for additional reading
1. Stewart KM, et al. *Org Biomol Chem* 2008;**6**:2242–55.
2. Neundorf I, et al. *Pharmaceuticals* 2009;**2**:49–65.
3. Neundorf I, et al. *Chem Commun* 2008;**43**:5604–6.
4. Splith K, et al. *Dalton Trans* 2010;**39**:2536–45.

doi:10.1016/j.drudis.2010.09.396

A48
Polyelectrolite complex based microspheres for colon specific anticancer drug delivery

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Localized delivery of chemotherapeutic agents has long been the aim of clinical colon cancer therapy in order to limit the indiscriminate activity of many anti-cancer drugs on rapidly dividing cells, including normal tissues. The ideal drug delivery system (DDS) is envisioned to selectively and efficiently transport the anticancer drug to the target cells. It will not only minimize side effects associated with inappropriate drug distribution, but will also enhance therapeutic efficacy by increasing local drug concentration. The goal of our study was to develop wheat-germ aglutinin (WGA) functionalized chitosan-Ca-alginate microspheres (MS) loaded with acid-resistant nanoparticles (NP) of 5-FU, as colon targeting DDS and evaluate its *in vitro* efficacy and *in vivo* biodistribution. The rationale behind the design of the formulation is the presence of high level of polysaccharides of microbial origin in the human colon and the possibility of direct binding of MS to the mucosal surface by nonspecific or specific ligand–receptor interactions using biological molecules (WGA), thus enabling active uptake of 5-FU in the target cancer cells. A simple one-step spray drying procedure was used to produce polyanion/polycation MS loaded with acid-resistant NP of 5-FU with mean diameter of ~14.74 μm, high production yield (~50%) and encapsulation efficiency (~72%). Using 1,1′-Carbonyl-diimidazol as a surface group activation agent, successful conjugation of WGA to MS surface was achieved (~50%). Haemagglutination test confirmed that WGA, treated by covalent coupling procedure, still retained its specific carbohydrate binding activity on the surface of MS. *In vitro* efficiacy was evaluated by investigating 5-FU permeability and [methyl-3H]thimidine uptake in Caco-2 cells. The cumulative amount of transported 5-FU through Caco-2 cells was 15.1% and 6.5% for 5-FU solution and WGA conjugated MS, respectively. Cell culture studies also indicated a marked decrease in [methyl-3H]thimidine uptake for WGA decorated MS compared to 5-FU solution, suggesting that immobilization of WGA onto MS surface, due to the improved interaction and enhanced tissue accumulation of 5-FU could led to improved efficacy in targeted anticancer colon therapy. *In vivo* biodistribution studies were conducted with oral administration of ^{99m}Tc labeled MS on fasted male Wistar rats. The imaging was performed at different time intervals post administration. The results showed that MS traversed fairly quickly through upper part of GI tract and resided in the colon for relatively longer period of time, probably due to the particle size, pH dependent swelling and surface properties of the MS. Overall, the results of this work showed that cross-linked polycation/polyanion MS loaded with 5-FU and decorated with WGA, were able to effectively deliver 5-FU to colon region, thus affecting the transport of 5-FU into the cells and consequently improving the efficacy.

doi:10.1016/j.drudis.2010.09.397

A50
Engineering macrophages to synthesize recombinant adenoviruses in hypoxic areas of human prostate tumours

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Background: Like many other forms of human malignancy, prostate carcinomas contain multiple regions of transient and chronic hypoxia. New therapies targeting the hypoxic areas of tumours need to be designed as these sites are highly resistant to conventional cancer therapies. We have recently shown that macrophages accumulate in these hypoxic areas of prostate tumours, so we investigated the possibility of using these cells to deliver therapeutic genes to these otherwise inaccessible sites. *Materials and methods*: We designed a novel system in which macrophages are used to deliver hypoxia-regulated therapeutic adenovirus. In this approach, macrophages are co-transduced with a hypoxically activated E1A/B plasmid and an a hypoxia-regulated E1A/B construct and an E1A-dependent oncolytic adenovirus, whose proliferation is restricted to prostate tumor cells using prostate-specific promoter elements from the TARP, PSA and PMSA genes. *Results*: When co-cultured with prostate tumour spheroids, these 'armed' macrophages migrated into the hypoxic centres of the 3D tumour masses where E1A/B protein expression was upregulated, resulting in replication of the latent E1A/B-deficient adenovirus. Multiple copies of the virus (~5000/macrophage) were released and infected neighbouring prostate tumour cells, resulting in widespread gene expression. Systemic administration of co-transduced macrophages into mice bearing human prostate xenografts resulted in their subsequent trafficking into the hypoxic areas of tumours leading to viral replication and widespread infection of neighboring tumour cells, resulting in the marked inhibition of tumor growth and reduction of pulmonary metastases. *Conclusions*: We show for the first time that macrophages can be engineered to express high titres of a therapeutic adenovirus

specifically in hypoxic areas of human prostate tumours and that expression of the gene being delivered in the adenovirus can be restricted to prostate tumour cells by placing it under the control of a prostate-specific promoter (PSA). This novel approach employs three distinct levels of tumour-specific targeting; the homing of the macrophages to tumours, the synthesis and release of therapeutic adenovirus only in hypoxia tumour areas, and the targeting of therapeutic gene expression to prostate tumour cells.

doi:10.1016/j.drudis.2010.09.398

A51
Targeted nanodrug delivery systems for the treatment of tuberculosis

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South Africa currently has the highest incidence of TB in the world at 358 per 100,000 people. In 2007 alone 112,000 people died of TB in South Africa, of which 94,000 (72%) were co-infected with HIV [1]. Although TB treatments exist, poor patient compliance and drug resistance pose a great challenge to programs worldwide. To improve the current inadequate therapeutic management of TB, a polymeric anti-TB nanodrug delivery system, for anti-TB drugs, was developed that could enable entry, targeting, sustained release for longer periods and uptake of the antibiotics in the cells, hence reducing the dose frequency and simultaneously improve patient compliance. The aim was to prepare functionalised polymeric nanodrug delivery vehicles to target TB infected macrophage cells. Successful nanoencapsulation of anti-TB drugs and a targeting agent, mycolic acids (MA) was achieved. MA (a lipid molecule on the cell wall of M.tb) was explored due to its cholesteroid properties [2] that could attract it to the infected macrophages/foam cells. The nanoparticles were characterized and subjected to *in vitro* analyses in THP-1 and U937 cells in order to determine their uptake and localization. Cytotoxicity in different cell lines was also analysed. In another approach targeting was achieved via attaching nucleic acid aptamers [3], onto the surface of drug-carrying PLGA nano-particles. The aptamers were prepared via the SELEX process [4], specifically against the mannose receptor (MR), which is significantly over-expressed during the activation of the macrophages in the presence of M.tb. Uptake of the MA PLGA nanoparticles was achieved where little co localization was observed with endocytic markers, indicating that they could be localized in the cytosol. Vesicles bearing these particles were also observed in the cell membrane of these cells. We will report the uptake of the aptamers to THP-1 cells illustrating the feasibility of using the nucleic acid species for active targeted drug delivery. The success of these two approaches of anti-TB drug targeting will greatly address the challenges of poor bioavailability, reduced efficacy and adverse side effects for diseases such as TB.

See references below for additional reading

1. WHO (2009). Global tuberculosis control: epidemiology, strategy, financing: WHO report. WHO/HTM/TB/2009.411.
2. Benadie Y, et al. Cholesteroid nature of free mycolic acids from *M. tuberculosis*. *Chem Phys Lipids* 2008;**152**:95–103.
3. Stoltenburg R, et al. SELEX—a (r)evolutionary method to generate high affinity nucleic acid ligands. *Biomol Eng* 2007;**24**:381–403.
4. Levy-Nissenbaum W, et al. Nanotechnology and aptamers: applications in drug delivery. *Trends Biotechnol* 2008;**26**:442–9.

doi:10.1016/j.drudis.2010.09.399

A52
Targeted SAINT-O-Somes, a novel type of liposomes for improved delivery of siRNA

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Gene silencing by siRNA has become a powerful technique with a great potential for therapeutic application. Increased insight in the role of endothelial cells in the pathology of cancer and inflammatory diseases has shifted the interest in the development of siRNA drug delivery devices for pharmacological intervention towards these cells. Additionally, endothelial cells are readily accessible for substances transported by the blood and their heterogeneity allows for specific drug targeting approaches. Liposomes represent a drug-carrier system for the delivery of siRNA that can be tailored on demand to introduce cell specificity. However, unlike in macrophages or in many tumor cells, in endothelial cells the processing of liposomes and subsequent release of drug content is inefficient due to the absence of adequate intracellular processing machinery which limits pharmacological efficiency. Therefore, we developed a lipid based drug delivery system with a superior intracellular release characteristic which is suitable for the *in vivo* delivery of siRNA. The design of the carrier is based on long circulating conventional liposomes that were formulated with a cationic amphiphile, 1-methyl-4-(cis-9-dioleyl)methyl-pyridinium-chloride (SAINT-18). These so-called SAINT-O-Somes have a diameter of 100 nm and showed a 10-fold higher encapsulation efficiency for siRNA compared to liposomes without SAINT and protect the siRNA from degradation for at least 6 weeks. Moreover, SAINT-O-Somes are fully stable in a biological relevant milieu (i.e. presence of serum), but are destabilized in the lower pH in endosomes of endothelial cells, enabling release of siRNA into the cytoplasm of the cell. In order to efficiently target activated endothelial cells, SAINT-O-Somes were equipped with antibodies against E-selectin or VCAM-1 adhesion molecules that are (over)expressed at sites of inflammation.