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Nanotechnology approaches for intensifying localized combination therapy for precision treatment of early stage breast cancer

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Ductal carcinoma *in situ* (DCIS) is a noninvasive breast cancer (BC) with possible microinvasions into the breast stroma. DCIS accounts for more than 16% of new BC diagnoses in women. DCIS progresses to Invasive Ductal Carcinoma (IDC) over time in 39-53% of patients, if left untreated. The vast majority of BC cases originate in the mammary duct. In this presentation, a nanoscale delivery system will be described that utilizes transpapillary delivery to achieve molecularly targeted, pathway-specific therapy in cancerous areas of the mammary duct. Our preliminary results with a nanosuspension of ciclopirox (CPX) in an orthotopic model of BC established the concept that sustained ductal exposure could completely suppress BC occurrence *in vivo*. For these studies polymeric NPs (nanoparticles) as well as lipid-polymer hybrid (LPH) NPs were the primary delivery vehicles. In order to achieve sustained precision treatment, HER2, transferrin receptor and/or EGFR were targeted using peptide ligands covalently bound to the surface of NPs. Ligand surface densities of 5% and 10% were evaluated and it was found that surface functionalized NPs enhanced binding and uptake into target cells. Cytoxicity was significantly increased with EGFR or TfR targeted NPs as compared to CPX alone or non functionalized CPX-loaded NPs. A synergistic effect was observed when CPX was administered with gedatolisib, a PI3K/Akt/mTOR inhibitor resulting in a dose reduction index of ~6. In addition, the treatments were effective not only in BC cells but also cancer stem-like cells. Our efforts in addition to describing these studies and results, the engineering of the NPs to enhance ductal retention and specificity will also be described.

Recent Publications

1. Gu Z et al. (2018) The effect of size and polymer architecture of doxroubicin-poly(ethylene) glycol conjugate nanocarries on breast duct retention, potency and toxicity. European Journal of Pharmaceutical Sciences. 121:118-125. Doi 10.1016/j.ejps.2018.04.033.
2. Lee I H et al. (2018) Design and evaluation of a CXCR4 targeting peptide 4DV3 as an HIV entry inhibitor and a ligand for targeted drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. pii: S0939-6411(18)30013-30014. Doi: 10.1016/j.ejpb.2018.06.004.
3. Singh Y D et al. (2012) Influence of molecular size on the retention of polymeric nanocarrier diagnostic agents in breast ducts. Pharmaceutical Research. 29(9):2377-2388. Doi:10.1007/s11095-012-0763-z.
4. Singh Y D et al. (2011) Noninvasive detection of passively targeted poly(ethylene glycol) nanocarriers in tumors. Molecular Pharmaceutics. 9(1):144-155. Doi:10.1021/mp2003913.

Biography

Patrick J Sinko is a Pharmacist (BS, Rutgers 1982) and a Pharmaceutical Scientist (PhD, University of Michigan 1988). He joined Rutgers, The State University of New Jersey in 1991 and rose through the academic ranks where he is currently a Distinguished Professor (II) and the Parke-Davis Endowed Chair in Pharmaceutics and Drug Delivery in the Ernest Mario School of Pharmacy. He is the Principal Investigator of an active research laboratory that focuses on biopharmaceutics, pharmaceutical formulations and molecular-, nano- and micro-scale drug delivery with specific applications to the treatment or prevention of HIV/AIDS, breast, brain and lung cancer, chemical terrorism countermeasures. He has received prestigious National Institutes of Health FIRST and MERIT awards and his lab has been continuously funded by the NIH for over 25 years.

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