Tumor-Targeted Byfunctional Nanoparticles for Cancer Therapy and Tumor Imaging

Faculty:
Yong Ba, Ph.D. & Yun Yen, M.D. Ph.D.

Project for Student Scholars:
Cancer ranks as one of the leading causes of death in industrialized countries. Cancer is defined by three characteristics: (1) A group of cells displaying uncontrolled growth; (2) These cells then intrude and destruct adjacent tissues; and (3) In some cases, spreading to other locations in the body via lymph and/or blood. Despite significant efforts in the field of oncology, the cancer therapy remains a challenge. Chemotherapy is primarily used in treating hematological malignancies and metastasized tumors. A severe problem with cancer chemotherapy is that chemotherapeutics cause terrible damage to normal tissues when used at doses required to eradicate cancer cells. Thus, strategies to selectively attack cancer cells could significantly enhance the therapeutic efficacy and diminish their toxicity to the body.

Nanoparticle carries have been widely studied for selective delivery of drugs to cancer tumors through two mechanisms: (1) passive targeting; and (2) active targeting. Passive targeting refers to the accumulation of drug or drug-carrier system at a particular site due to physicochemical/pharmacological properties of cells/tissues. Naoparticles were found to have enhanced permeability and retention in solid tumors, referred to as EPR effect. Unlike the tight blood vessels in most normal tissues, adjacent endothelial cells lining the interior surface in blood vessels to tumors have gaps as large as 600-800 nm. Drug carriers in the nanometer size range can extravasate through these gaps into the tumor interstitial space. Tumors have impaired lymphatic drainage, thus the carriers accumulate in tumors. Active targeting to tumor can be achieved by ligand-receptor or antibody-antigen interactions. This may also lead to receptor-mediated cell internalization of drug carrier system. Nanoparticles offer versatility for targeting tumors through surface engineering for specific interactions of ligand-proteins/receptors expressed on cancer cells.

A number of polymers have been tried in formulating biodegradable nanoparticles. Among them, polylactide (PLA) and poly (D, L-lactide-co-glycolide) (PLGA) have been most extensively studied for drug delivery applications. PLGA-PLA-based polymers have a number of desirable properties for drug delivery including their biodegradability, biocompatibility, and approval of use by FDA for human body. To have the nanoparticles remain in the blood circulation for long is needed for their extravasations in the tumor vasculature. Thus, it is essential to avoid their engulfment by the reticuloendothelial system (RES). It was found that particles smaller than 100 nm and coated with hydrophilic polymers such as polyethylene glycol (PEG) are effective in avoiding their uptake by the RES.

Imaging of cancer tumor is the key for guiding clinical treatment and monitoring the efficacy of therapeutics. The use of tumor-targeted nanoparticles for image contrast and enhancer can identify specific biomarkers, in addition to their passive accumulation in cancer tissue. This has the potential to improve detection, classification, and treatment
of cancer. Cancer detection through procedures such as **Magnetic Resonance Imaging** (MRI) and optical-based imaging have been improved by the use of these nanoparticles.

In searching for bifunctionalized anticancer drugs, we found that anticancer **alkylating agent**, such as chloramucil, after conjugated with **tempol** has synergized potency to cause cell death compared with the original anticancer agent. Besides their role in increasing the drug’s potency, the nitroxide radical in tempol also provides a magnetic probe for **EPR** (electron paramagnetic resonance), **NMR** (nuclear magnetic resonance) and **MRI** (magnetic resonance imaging) characterizations. Delivery of the bifunctionalized anticancer drugs with tumor-targeted nanoparticles is the specific focus of this research. Long term goal of this research is to invent innovative drug delivery systems for cancer chemotherapy. Students in this program will participate in the synthesis of anticancer drugs, engineer the drug loaded PLGA-PEG nanoparticles and their surface modification with ligand and perform *in vitro* cytotoxicity assays for anticancer drugs and drug-loaded nanoparticles for cancer cell lines. The students will also be involved in fluorescent and MRI imaging studies using the human cancer xenograft models.

**Contact Information:**

**Yong Ba, Ph.D.**
Department of Chemistry and Biochemistry
California State University, Los Angeles
yba@calstatela.edu

**Yun Yen, M.D., Ph.D.**
Professor and Director, Clinical & Molecular Pharmacology
Associate Cancer Center Director, Translational Research
Co-Director, Animal Tumor Models Core Facility
Beckman Research Institute and Comprehensive Cancer Center
City of Hope
yyen@coh.org