Ligand Targeted NIR Dye/Fe3O4 Nanoconjugates for dual (Optical/MRI) Imaging and Hyperthermia to Treat Metastatic Castration Resistant Prostate Cancer

Name of all Researchers from LUH and IIT Indore and their designations/institutes including coordinating persons from LUH and IIT Indore:

Name	Contact details	Institute	University	
Prof. Dr. Andreas Kirschning	E-mail: Andreas.Kirschning@oci.uni-hannover.de Tel: +49 511 762 4613	Institute of Organic Chemistry	Leibniz University Hannover	Schneiderberg 1b 30167 Hannover
Dr. Gerald Dräger		Institute of Organic Chemistry	Leibniz University Hannover	Schneiderberg 1b 30167 Hannover
Assistant Professor Dr. Chelvam Venkatesh	Tel: +91 731-2438789	Discipline of Chemistry	Indian Institute of Technology Indore	Indore-453552 Madhya Pradesh, India

Project Description

As metastatic castration resistant prostate cancer (mCRPC) is resistant to anti-androgen therapies and chemotherapeutic drugs, our aim is to deliver 2-[3-(1,3-dicarboxypropyl) ureido] pentanedioic acid (DUPA, a ligand specific to PSMA overexpressed in mCRPC) conjugated Cy5.5 and Fe3O4 for dual (optical and MRI) imaging and therapeutic purposes to cancer cells. This project presents the design, synthesis and biological evaluation of a dual imaging probe containing optical imaging NIR Cy5.5 dye, which provides functional details of molecular events and Fe3O4 for magnetic resonance imaging (MRI) to obtain anatomical information required for accurate mCRPC spread. As compared to conventional spherical nanoparticles, Fe3O4 nanorods of similar material volume provide a superior T2 contrast effect with 1.5–2 times higher relaxivity (R2) value for efficient visualization in MRI. The Fe3O4 nanorods as contrast agent can also be used for therapy using hyperthermia principle. The enhanced MRI contrast and hyperthermia properties of nanorods are attributed to the higher surface area and anisotropic morphology. Furthermore, as compared to spherical nanoparticles, nanorods offer longer blood circulation times, stronger interaction with tumors, enhanced retention at tumor sites and improved targeting efficiency, making them excellent candidates as targeting carriers or MRI contrast agents.

The project will be carried out in five stages, which will be realized by one PhD student at IIT Indore and LUH each:

1. (3 Months) Synthesis of DUPA ligand for targeted detection of mCRPC tumors.
    a. Synthesis of small molecule inhibitor DUPA binding to PSMA protein.
2. (6 Months) Preparation of DUPA conjugated NIR fluorescent probe through solid phase peptide synthesis for detection of CRPC tumors.
    a. Preparation of peptidic spacer conjugated small molecule ligand via solid phase peptide synthesis (SPPS) using chlorotrityl cysteine resin.
    b. Attachment of NIR dye with the free –NH2 group present in the peptidic spacer in the same solid phase synthetic strategy.
3. (6 Months) Preparation of DUPA targeted optical/magnetic nanoconjugates as a dual imaging and theranostic tool.
    a. Synthesis and surface modification of Fe3O4 nanorods.
    b. Characterizations of functionalized Fe3O4.
    c. Preparation of DUPA-Cy5.5- Fe3O4 nanoconjugates.

4. (6 Months) In vitro evaluation of imaging (fluorescent and MRI) and hyperthermia (Fe3O4) agents on PCa cell lines.
    a. Optical and MRI imaging by DUPA-Cy5.5- Fe3O4 nanoconjugates.
    b. Magnetic hyperthermia measurement in vitro in cancer cell lines expressing PSMA protein.
5. (10 Months) In vivo studies on androgen-suppressed mouse model to examine the application of newly developed diagnostic and therapeutic tools.
    a. In vivo optical and MRI imaging of DUPA-Cy5.5- Fe3O4 nanoconjugates.
    b. Magnetic hyperthermia in vivo for ablation of tumor xenograft in athymic nude mice using DUPA-cy5.-Fe3O4 nanoconjugates.

Sustainability Factors

1. Scientific papers will be prepared with the project results.
2. Based on the results and papers obtained, DFG-DST applications for joined projects will be filed.