



Project Proposal for Ph.D.

Project Details

Project Title

Combating Resistance in/of Broad-spectrum Anticancer Drugs by targeting Epidermal Growth Factor Receptor (EGFR) using plasma modified nano metallic-Drug Conjugates.

Project Summary

(Minimum 500 and maximum 2000 characters)

Problem going to address:

Conventionally, cancers have been treated with chemotherapies which (i) requires a long preparatory process in hospitals before administration of the drug, (ii) many of administered chemo drug distributes across several vital organs, hence adversely affecting their normal functioning, and (iii) having higher cost. In recent years, it was realized that such a treatment strategy may lead to drug resistance more rapidly, since such treatment puts constant pressure on tumors to select those cancer cells that are strongly resistant to the drugs.

Thus, considering the rising number of cancer and limited resources; it is plan to develop a new methodology for effective administration of drug, addressing efflux challenges of drug in cellular system and significantly reduction of cost. Nanotechnology can hold novel promise in circumventing drug resistance in cancer cells.

Project summary

The oncogenic role of epidermal growth factor receptor (EGFR) has been intensively studied. However, its emerging role in drug resistance has not been fully addressed. EGFR are the major contributors of a complex signaling cascade and play integral role in epithelial malignancies by modulating growth, signaling, differentiation, adhesion, migration and survival of cancer cells. EGFR is deregulated in several types of cancers including non-small cell lung cancer (NSCLC), pancreatic, breast, colorectal and head and neck. Their multi-dimensional role in the progression of cancer make EGFR as attractive candidates for anti-cancer therapy. Specifically, the aberrant activity of EGFR has shown to play a key role in the development and growth of tumor cells, where it is involved in numerous cellular responses including proliferation, survival and apoptosis.

EGFR is a transmembrane tyrosine kinase receptors which get stimulated upon binding with EGFR ligand (e.g., TGF- α and EGF) and transmit growth-inducing signals. EGFR (HER1) belongs to the HER (or ErbB) family that includes four members: ErbB-1 (EGFR), ErbB-2 (HER2 or Neu), ErbB-3 and ErbB-4. The activation of the EGFR signaling pathways stimulates downstream signaling cascades involved in cell proliferation (Ras/mitogen-activated protein kinase [MAPK]) and anti-apoptosis (phosphatidylinositol 3-kinase [PI3K]/Akt). Studies investigating the TGF α -EGFR signaling pathways can provide unfathomable understanding of the cellular and molecular factors that promote cancer metastasis, resistance to chemotherapy and poor prognosis. Abrogating signaling pathways through EGFR could provide a good strategy for therapeutic intervention.

Despite the improvement in clinical outcomes derived by the introduction of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in the treatment of cancer, prognosis remains unfavorable because of the occurrence of either intrinsic or acquired resistance. Several mechanisms of resistance have been discussed to EGFR-TKIs, such as secondary mutation (T790M, C797S), the activation of alternative signaling (Met, HGF, AXL, HER2, IGF-1R), the aberrance of the downstream pathways (AKT mutations, loss of PTEN), the impairment of the EGFR-TKIs-mediated apoptosis

pathway (BCL2-like 11/BIM deletion polymorphism) and histological transformation. Tyrosine kinase inhibitor (TKIs) of the epidermal growth factor receptor (EGFR), such as erlotinib and gefitinib targeting NSCLC, have been reported to show high response rate at initial treatment. However, almost 50% of the responsive patients would develop a T790M mutation on EGFR within one year, resulting in resistance to the first and second generations of TKIs. The mutation from threonine to methionine led to a configuration change in EGFR and consequently enhanced ATP binding affinity and impaired binding of gefitinib/erlotinib for the kinase. To overcome the resistance caused by T790M, third generation of TKIs, like osimertinib and rociletinib, has been developed and reported to show clinical efficacy with patients harboring T790M mutation. However, resistance to third-generation inhibitors develops not long after their use, raising the need of developing fourth generation TKIs. One reported major mechanism of the new resistance is due to a mutation in EGFR known as C797S. The loss of the cysteine residue, which is important for TKIs to target the ATP site, impairs the binding of the third generation TKIs to EGFR. Therefore, EAI045, a fourth generation TKI targeting both T790M and C797S, has been designed to bind an allosteric site located on EGFR, attempting to circumvent the mechanism patterns of resistance to the early generations of TKIs which all bind to the ATP sites. Despite of development of large number of TKIs, their therapeutic potential has been hindered by multidrug resistance (MDR) which is commonly caused by overexpression of ATP-binding cassette (ABC) membrane transporters.

Although numerous resistance mechanisms to EGFR-targeted therapies have been reported, EGFR is still important as an integral point for convergent signaling pathways, and therefore, EGFR targeting should form the basis of oncogenic signaling inhibition. One of the alternative plan for everlasting war against drug resistance is to focus on developing strategies to reverse the resistance mechanisms and treating cancer with the existing FDA approved drugs. This approach will save lot of time and resources as marketing a new drug take several years. So, emphasizing on reversing the resistant mechanism could be a better strategy to address drug resistance.

Ph.D. Supervisors

Role	Faculty	Academic Unit in IITD/Institute/University	Email ID (Official)
Supervisor 1	Prof. Marshal	Physics Department	marshal@iitd.ac.in
Supervisor 2	Prof. Manoj Menon	Kusuma School of Biological Sciences	menon@bioschool.iitd.ac.in

Project requirements (Student qualifications, experience required, etc)

- Qualifications as per IIT Delhi guidelines. Preference may be given to the student having a background in biology or laboratory experience in a similar field.

Source of fellowship/funding

(CSIR/UGC/DBT/ICMR/ICAR/NEET-PG/DST-INSPIRE/IRD/FITT Project details, if any)

Candidate with his/her own fellowship

Role of Faculty Members involved:

Dr Marshal

Developing Plasma modified nano metallic-Drug Conjugate. Leading to synthesize, characterize and optimize the methodology for functionalization metal/metal-polymer complex for capabilities of retention and release of drug molecules.

Dr. Menon

Performing a wide range of cell biology assesses