Details of the Project sanctioned under the Human Resource Development scheme of Department of Health Research

1. Project Title:

"To study the disruption of oncogenic Hsp90-client protein interactomes to treat cancer"

2. Category of fellowship: Start up Grant

3. PI (Name & Address):

Dr. N.M. Raghavendra,
Professor & Head,
Dept. of Pharmaceutical Chemistry
Gokaraju Rangaraju College of Pharmacy,
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4. Qualifications: M. Pharm, Ph.D and Post Doctorate (USA)

5. Mentor or Co.PI (Name & Address):

Dr. D. Giles,
Associate Professor,
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Acharya Dr. Sarvepalli Radhakrishnan Road
Acharya PO, Bangalore-560107

6. Duration of the project: 03 years

7. Broad area of Research: Life Sciences

7.1 Sub Area: Bioinformatics and Proteomics

8. Summary of the Project:

A major challenge in drug discovery for cancer diseases is the ability to selectively target critical pathways required for sustaining the pathology. Efficient targeting and improved predictability of outcomes in using molecular targeted therapies for next generation cancers will rely on an improved undersigning go the

functional aberrations of the molecular networks driving the specific disease pathologies. Hsp90-client proteins regulate the signal transduction pathways leading to cell growth and survival. Although Hsp90 is expressed in all cells, tumors preferentially contain Hsp90 in higher-order multi-chaperone complexes. We hypothesize that small molecules able to target tumor-enriched Hsp90 complexes can be used to affinity capture Hsp90-dependent oncogenic client proteins. When combined with bioinformatic analysis, this should enable the creation of a detailed molecular map of transformation-specific lesions that can guide the development of combination therapies that are optimally effective for a specific patient. We propose to investigate Hsp90 inhibitor-based chemical and structure proteomics combined with bioinformatics to discover oncogenic proteins and pathways in breast and prostate tumor models.

9. Objectives of the Proposal:

i. *In silico* screening of binding properties of non-peptide antagonists of Hsp90-client proteins interaction.
ii. Mammalian cancer cell based biological screening to identify potential lead compounds
iii. Chemical and structural proteomic investigation of interaction of small molecule Hsp90 inhibitor with tumour Hsp90 complexes

10. Innovations in the project:

Hsp90 protein interactome is the potential target for the discovery of antitumor agents. There are several client protein associated with Hsp90. An attempt would be made to investigate the client proteins which trigger the development of tumor formation in breast and prostate cancer. The proposed work involves the integrated approach of bioinformatics, medicinal chemistry and proteomics which is a novel method of identifying Hsp90-client protein interactomes playing crucial role in tumorogenesis and metastasis.

11. Significance of the outcome of the project:

In this proposal, we plan to carry out an Hsp90 inhibitor-based chemical and structural proteomics combined with bioinformatics approaches to discover oncogenic proteins and pathways in breast and prostate tumor models. The information will be further evaluated in the context of pathways and overall networks associated with heat

shock protein systems. Drug candidate selectivity will be analysed through this process. Distinctions between the heat shock protein interactomes in different disease models will also be used to make predictions about combination therapies that could ultimately be optimally effective for a specific patient.

12. Relevance in Public Health:

Chemotherapy of cancer has lot a of side effects, in fact so much so that, some of the chemotherapeutic drugs itself can lead to cancer if not used in prescribed manner. All these are because of non specificity of the existing drugs. Patients having cancer with Hsp90 and BRAF mutations would be treated by Hsp90 inhibitors having BRAF antagonism. This provides more specificity and reduces toxicity. Today cancer is a global disease, there is an immediate need to discover antitumor agents which are safe and effective. We believe, the work proposed might lead to scientific unfolding on cancer targets regulated by Hsp90-client protein interactomes.

[Dr. N.M. Raghavendra]

Signature of the Fellow /Faculty