

Title of Research Project: Molecular Basis for Androgen Receptor Antagonism in Prostate Cancer Therapy (2 years in U.S.A.+2 years in NUS graduate programme)

Name of Supervisors:

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Short Description

Prostate cancer is a very common cancer worldwide and in Singapore. Prostate cancer depends on male sex hormones called androgens to grow. Androgens act through the androgens receptor, a member of the very important nuclear /steroid receptor superfamily of transcription factors. In response to the binding of the physiological androgens-testosterone or 5- α -dihydrotestosterone (DHT), AR directs a transcriptional program that is required for normal male development and homeostasis of muscle and skeleton systems. Since AR plays important roles in initiation and maintenance of prostate cancer, increasing research is now focused on this receptor. As such AR is an established target of pharmaceutical intervention for prostate cancer, including the treatment of antiandrogens such as bicalutamide and flutamide, which bind to the androgen-binding pocket in the C-terminal ligand binding domain (LBD) to inhibit hormone dependent activation of AR. This project is to understand how these chemicals induced AR antagonism and what corepressors interact with AR when these antagonists bound. This study will provide a molecular basis for designing the next generation of AR antagonists for prostate cancer therapy. This unique multidisciplinary research collaboration is supervised by two renowned and very well published investigators: NUH clinician-scientist (Prof. Yong) and Dr Eric Xu, a top biologist from Van Andel Research Institute, U.S.A. This program allows the student to participate a "2+2" graduate programme and have access to patient material and many facilities in different laboratories. Systematic training will be provided from experienced lab technicians/senior research fellows/associate professor and to master the core techniques including recombinant protein expression on mammalian system and gene transcription regulation by realtime RT-PCR, ForteBio's Octet biosensor and Amplified Luminescent Proximity Homogeneous Assay to understand biomolecule interaction, protein large scale expression and affinity purification by FPLC, protein crystallization using Phoenix crystallization robot which are required for the study. Detail on this project can be acquired by sending email request to: Dr. Li Jun (Tel: 65165168, obglj@nus.edu.sg or jun.li@vai.org). Further details see: http://www.nus.edu.sg/ngs/supervisors_cv/yong_eu_leong.pdf
<http://www.vai.org/Research/Labs/StructuralSciences.aspx>

Recent Relevant Publications:

1. Zhou XE, Suino-Powell KM, Li J, Yong EL, and Xu HE (2009) Molecular Basis for Functional Interplay between Androgen Receptor and SRC-3/AIB1 in Prostate Cancer. **Cancer Cell** (in review)
2. Wang Z, Zhou XE, et al, Xu HE, Mangelsdorf DJ. (2009) Control of Nematode Parasitism by Conserved Nuclear Receptor Signaling. **Nature** (in review).
3. Xu HE and Li Y (2008) Ligand-dependent and -independent regulation of PPAR γ and Orphan Nuclear receptors. **Science Signaling**1(48):pe52 (Cover Article)
4. Kruse SW, Suino-Powell K, Zhou E, Krestchman JE, Reynolds R, Vonrhein C, Xu Y, Wang L, Tsai SY, Tsai MJ, Xu HE (2008) Identification of COUP-TFII Orphan Nuclear Receptor as a Retinoic Acid Activated Receptor. **PLoS Biology**, 6(9):e227.
5. Loy CJ, Sim KS, Yong EL. (2003) Filamin-A fragment localizes to the nucleus to regulate androgen receptor and coactivator functions. **Proc Natl Acad Sci U S A**. 100(8):4562-7. Epub 2003 Apr 7.
6. Yong EL, Loy CJ, Sim KS. (2003) Androgen receptor gene and male infertility. **Hum Reprod Update**. 9(1):1-7.
7. Wang Q, Lu J, Yong EL. (2000) Ligand- and coactivator-mediated transactivation function (AF2) of the androgen receptor ligand-binding domain is inhibited by the cognate hinge region. **J Biol Chem**. 276(10):7493-9.
8. Lim J, Ghadessy FJ, Abdullah AA, Pinsky L, Trifiro M, Yong EL. (2000) Human androgen receptor mutation disrupts ternary interactions between ligand, receptor domains, and the coactivator TIF2 (transcription intermediary factor 2). **Mol Endocrinol**. 14(8):1187-97.
9. Ghadessy FJ, Lim J, Abdullah AA, Panet-Raymond V, Choo CK, Lumbroso R, Tut TG, Gottlieb B, Pinsky L, Trifiro MA, Yong EL. (1999). Oligospermic infertility associated with an androgen receptor mutation that disrupts interdomain and coactivator (TIF2) interactions. **J Clin Invest**. 103(11):1517-25.