# Targeting Myc-driven tumours
## BETing on ATR

### Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet, kommer att offentligen försvaras i hörsal Waldemar Sjölander, Medicinaregatan 7A, Göteborg
Fredagen den 8:e April 2016 kl. 9.00

Av
Somsundar Veppil Muralidharan

Fakultetsopponent: Prof. Dr. Martin Eilers
University of Wuerzburg, Tyskland

Avhandlingen baseras på följande delarbeten:

I. *BET and HDAC inhibitors induce similar genes and biological effects and synergize to kill in Myc-induced murine lymphoma*. Joydeep Bhadury, Lisa M. Nilsson, **Somsundar Veppil Muralidharan**, Lydia C. Green, Zhoulei Li, Emily M. Gesner, Henrik C. Hansen, Ulrich B. Keller, Kevin G. McLure, and Jonas A. Nilsson. PNAS 2014 111 (26) E2721-E2730; doi:10.1073/pnas.1406722111 (PMID:24979794).

II. *BET bromodomain inhibitors synergize with ATR inhibitors to induce DNA damage, apoptosis, senescence-associated secretory pathway and ER stress in Myc-induced lymphoma cells*. **Somsundar Veppil Muralidharan**, Joydeep Bhadury, Lisa M. Nilsson, Lydia C. Green, Kevin G. Mclure and Jonas A. Nilsson. Oncogene, published online 25 January 2016; doi:10.1038onc.2015.521 (PMID:26804177).

III. *Therapeutic implications for melanoma of combined ATR and BET bromodomain protein inhibition*. **Somsundar Veppil Muralidharan**, Berglind Einarsdottir, Joydeep Bhadury, Mattias Lindberg, Eric Campeau, Roger Olofsson Bagge, Ulrika Stierner, Lars Ny, Lisa M. Nilsson and Jonas A. Nilsson. Manuscript.

UNIVERSITY OF GOTHENBURG

# Targeting Myc-driven tumours
## BETing on ATR

**Somsundar Veppil Muralidharan**

**Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg**

## ABSTRACT

Cancer arises from loss of function of tumour suppressors and/or gain of function mutations in proto-oncogenes that disrupt the delicate balance required for homeostatic cell division, resulting in uncontrolled cell proliferation. Oncogenic transformation of multifaceted proto-oncogene - transcription factor - MYC can give rise to cancers and it is found to be deregulated in more than 70% of the tumours. Targeting MYC directly or identifying the Achille's heel of MYC-driven tumours is thus a promising therapeutic approach to treat these tumours. This thesis investigates and demonstrates novel therapeutic approaches against MYC-driven tumours.

In the first publication (Bhadury et al, 2014), we characterize a novel and orally bio-available BET bromodomain inhibitor (BETi) RVX2135. We also identified BET bromodomain proteins as a valuable therapeutic target against MYC driven tumours in vitro and in vivo. Gene expression profiling to identify these transcriptional changes enabled us to identify subset of genes that are commonly altered by both BETi and HDACi. This study also demonstrates that HDACi and BETi can synergize to hinder Myc-induced lymphoma progression.

The second publication (Muralidharan et al, 2016) in this thesis investigates the role of BET proteins in regulating cell cycle and replication. BETi disable the entry of cells into S-phase of cell-cycle, hamper DNA synthesis and cause DNA damage. A pharmacogenetic screen identified BET inhibitors to synergize with inhibition of PI3K/mTOR family of proteins, to which ATR, an upstream kinase of DDR pathway belongs. Further studies revealed that the thus identified PI3K/mTOR inhibitors indeed affect ATR-Chkl DDR pathway leading to the discovery of a strong synergy between BETi and ATRi in apoptosing Myc driven tumours in vitro, and in vivo and (by) it induces SASP and ER stress.

The third study translates the above findings into the field of melanoma, a form of skin cancer. We validate the BETi-ATRi synergy in cell lines in vitro and in Patient Derived Xenografts (PDX) in vivo. Using B16F10 in vivo syngenic transplant melanoma model, we also demonstrated that this combination therapy can be safely combined with Immune Therapy, the front line treatment against melanoma in clinic today.

Taken together, this thesis puts forth a multifaceted approach to treat cancer. It thoroughly describes the effects of BETi and ATRi on cancer cells and how they can be combined to enhance the therapeutic efficacy.

ISBN: 978-91-628-9751-2 (Print)
ISBN: 978-91-628-9750-5 (PDF)