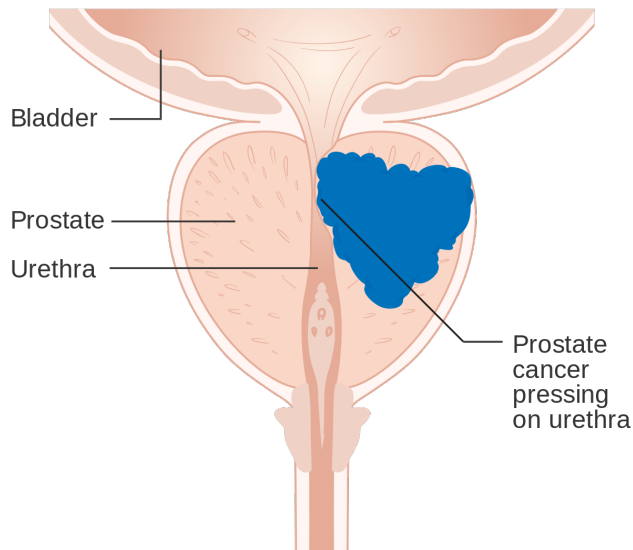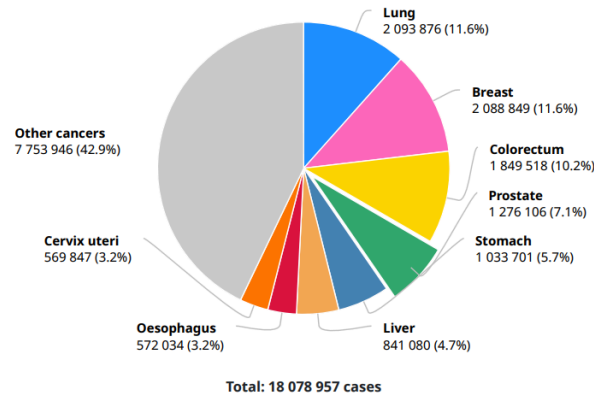# Systems Biology of Cancer Therapy Resistance

Mohit Kumar Jolly
Cancer Systems Biology Group
Centre for BioSystems Science and Engineering
Indian Institute of Science

mkjolly@iisc.ac.in
www.be.iisc.ac.in/~mkjolly

mkjolly15

Drug resistance: an unsolved clinical challenge

Prostate
Source: Globocan 2018

Number of new cases in 2018, both sexes, all ages

- Lung 2 093 876 (11.6%)
- Breast 2 088 849 (11.6%)
- Colorectum 1 849 518 (10.2%)
- Prostate 1 276 106 (7.1%)
- Stomach 1 033 701 (5.7%)
- Liver 841 080 (4.7%)
- Oesophagus 572 034 (3.2%)
- Cervix uteri 569 847 (3.2%)
- Other cancers 7 753 946 (42.9%)

Total: 18 078 957 cases

- Prostate cancer among top 10 cancers in India; numbers expected to double in 2020

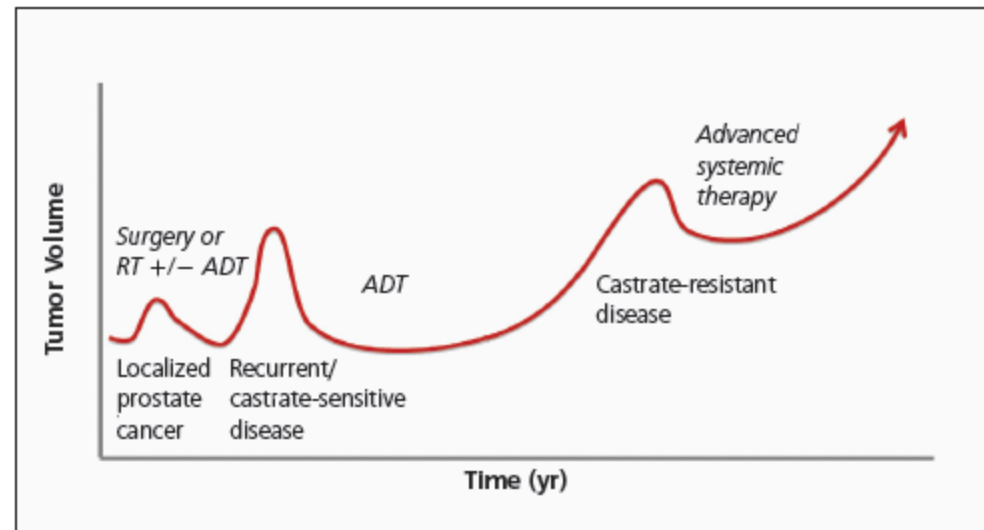- Castration-resistant prostate cancer (CRPC): an incurable disease with a mean survival time of 1-2 years

Bladder
Prostate
Urethra
Prostate cancer pressing on urethra

Figure: The Prostate Cancer Continuum. ADT = androgen deprivation therapy. RT = radiation therapy.

# Dynamics of drug resistance in prostate cancer

Mechanisms of drug/castration resistance are poorly understood.

Are cells selected for or do they adapt during therapy?

Is the selection and/or adaptation at a genetic/epigenetic/non-genetic level?

Is drug resistance determined in a cell-autonomous or a non-cell-autonomous manner (cooperation, competition among cells)?

Can we apply 'adaptive therapy' to cells to reduce drug resistance?

Zong & Goldstein, Nat Rev Urol 2012
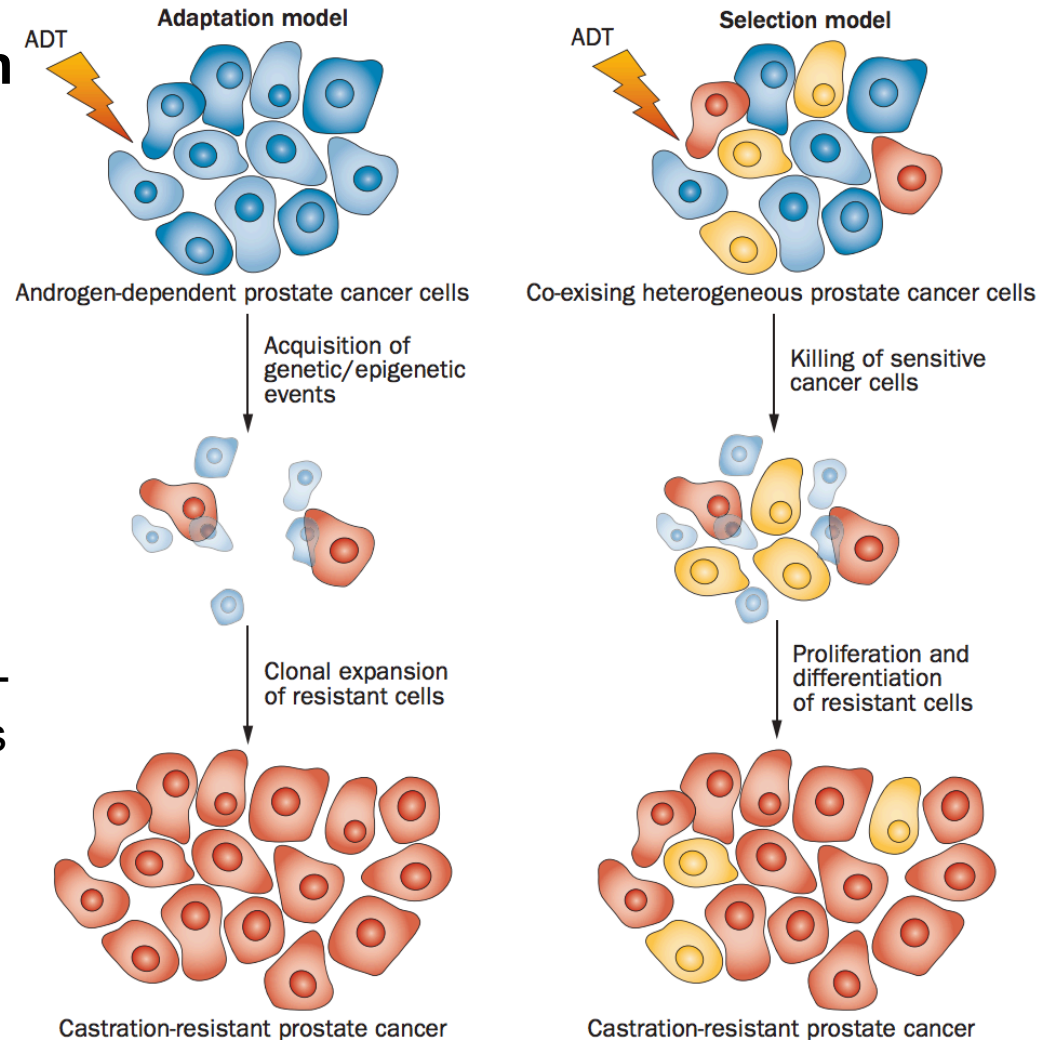
'Reversible' drug resistance in cancer
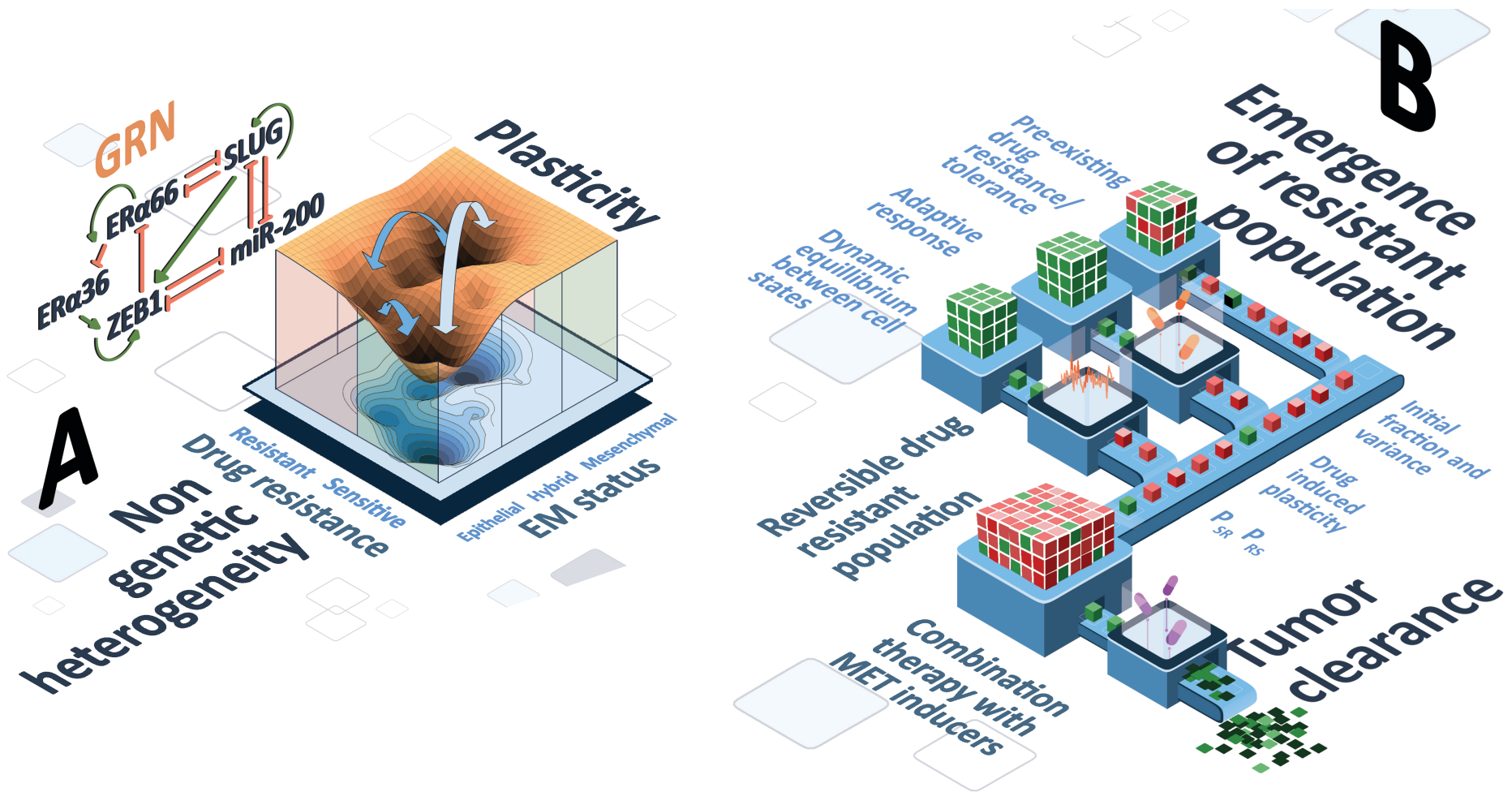
Non-genetic heterogeneity, cell state-switching can enable long-term survival even without mutations.

Tools and techniques used

- Statistical/Computational tools to infer biological networks from dynamics
- Mechanistic mathematical modeling of biological regulatory networks
- Analyzing experimental transcriptomics/proteomics, and clinical data

Required background

- Basic understanding of ordinary differential equations and nonlinear dynamics (or the self-driven will to acquire them)
- Keen interest in pursuing interdisciplinary research (i.e. reading literature in both cancer biology and computational systems biology)
- **Note:** Students from physics/chemistry/mathematics/engineering background are welcome too, provided they show interest in acquiring the relevant understanding of biology

Further reading

Brady-Nicholls R *et al.* (2020) Prostate-specific antigen dynamics predict individual responses to intermittent androgen deprivation, Nat Comm, 11: 1750

Zong & Goldstein (2013) Adaptation or selection – mechanisms of castration-resistant prostate cancer. Nat Rev Urol, 10: 90-98