Ongoing Research in My Group

I. Analysis the role of extracellular vesicles (Exosomes) in drug tolerant persister cells and its contribution to cancer-initiation.

Cancer drugs typically produce short-lived clinical remissions due to acquired drug resistance, which can be spontaneously reversible over time. Exposure to high doses of anticancer drugs can induce the emergence of a subpopulation of weakly proliferative and drug-tolerant cells/persister cells, which display markers associated with stem cell–like cancer cells. These drug-tolerant cell population emerged, are highly expressed undruggable transcription factors, epigenetically silenced genes, de-novo mutations, epithelial mesenchymal transformation/autophagy. Our group focus on basic mechanism of chemotherapy induced extracellular vesicles (exosomes) in breast tumor dormancy and its cancer initiation **(SERB-SRG 2021).** In India, there are more than 145, 000 new cases of BC have been 6 reported every year with more than 70,000 deaths, both numbers being higher than any other cancer site in both genders. Exosomes are EVs that are 30-150nM in diameter having bidirectional communication between cells and their microenvironment, plays a mechanism of cell-cell communication. Tumor secreted extracellular vesicles influence noncancer cells to generate a TME that are the critical messengers in tumor progression and metastasis. Exosomes also triggers differentiation of fibroblasts in to pro-angiogenic and pro-tumorigenic cancer associated fibroblasts (CAFs). We hypothesize that exosomes also induce the phenotypic changes by transfer of functional oncoproteins to recipient cells, in which they activate different signaling pathways (MAPK, PI3K-AKt-mTOR) in drug tolerant persister cells (Fig:1).

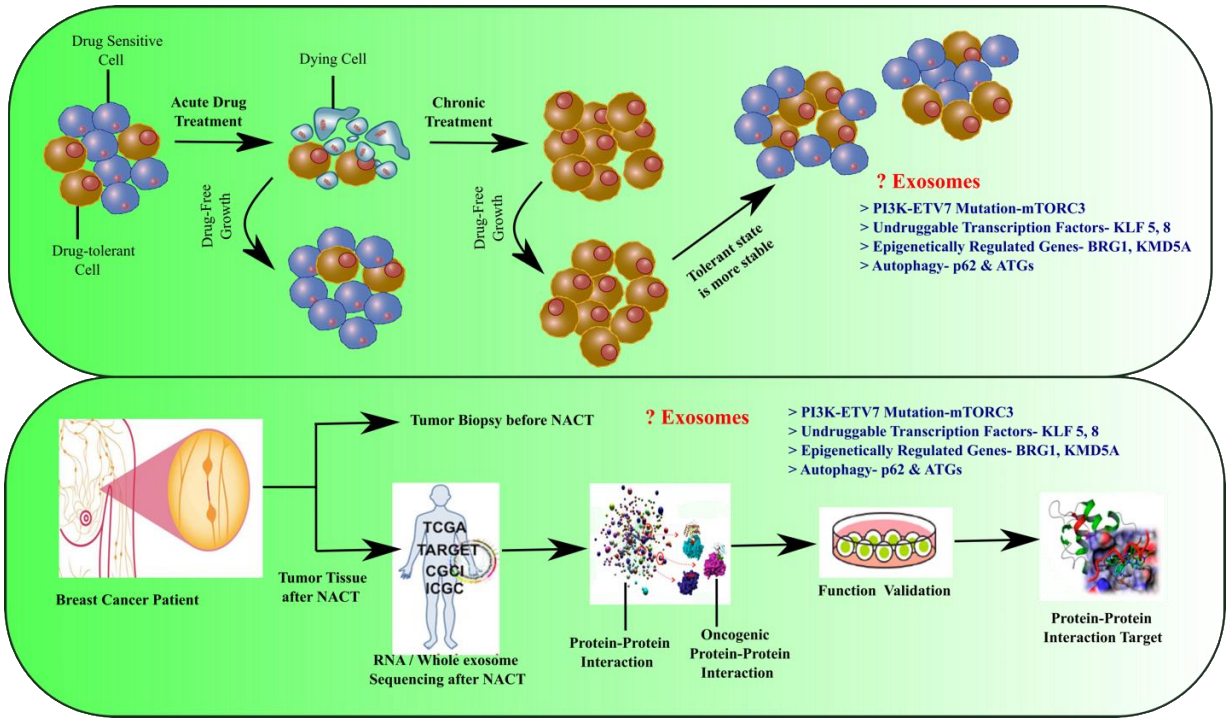

Figure:1

II. Molecular reprogramming landscape of pre- and post-neoadjuvant chemotherapy in breast cancer and its therapeutic implications by orally active CDK-9 Inhibitor.

Cyclin-dependent kinase 9 (CDK9) promotes transcriptional elongation through RNAPII pause release and essential for maintaining gene silencing at heterochromatic loci. We hypothesize that targeting CDK9, reactivates epigenetically silenced genes, hypersensitize to chromatin-modifying agents within the drug-tolerant sub-population and therapeutic intervention of undruggable transcription factors in cancer by invitro, in-vivo model and 3D organoid model (Fig-2) from cancer patients from Indian Population. Recently one of our orally active CDK-9inhibitor (SK Guru et al., 2018. **US Patent 9,932,327**. **Journal of Medicinal Chemistry**. 2018; 61: (4) 1664–1687) approved for clinical trial in India.

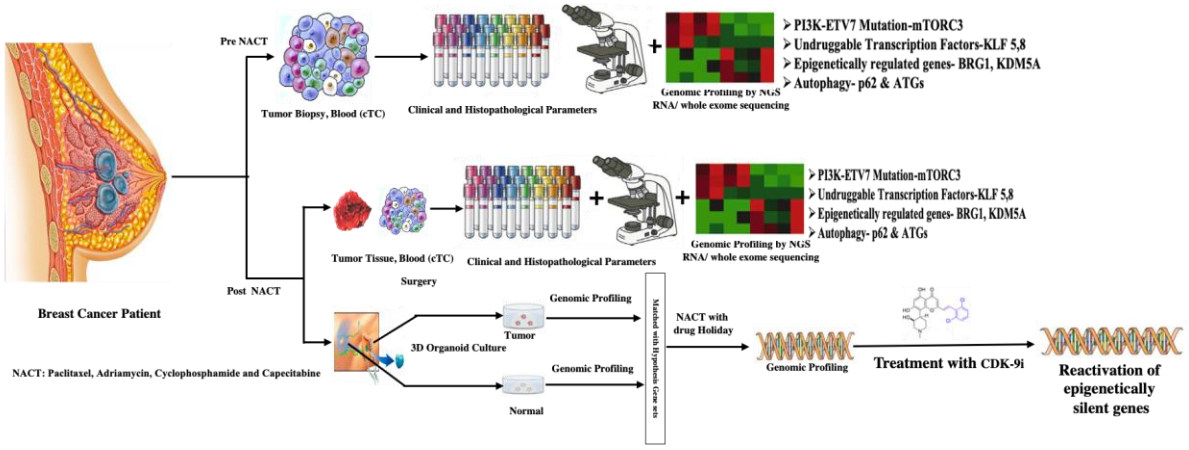

Figure:2

III. To explore the novel target specific agents for drug tolerant breast cancer persister cells.

Effective long-term cancer treatment remains challenging due to drug resistance. In addition to increased drug efflux and mutations in drug binding sites of targets, several other mechanisms have been suggested as contributing to drug resistance. In recent years, emerging drug-tolerant persister cells (DTPs) have become evident as contributing factors to the emergence of resistance. DTPs are quiescent and are produced in several cancer cell lines following treatment. The altered state of chromatin of these cancers facilitates rapid responses to drug treatment. Interestingly, the emergence of DTPs is not pre-emptive of other mechanisms of drug resistance; cell lines expressing DTPs have been shown to exhibit diverse mechanisms that drive long-term resistance. Chemotherapeutic agents typically produce short-lived clinical remissions due to acquired drug resistance, which can be spontaneously reversible over time. Exposure to high doses of anticancer drugs can induce the emergence of a subpopulation of weakly proliferative and drug-tolerant cells/persister cells, which display markers associated with cancer-initiating cells (cancer stem cells). To address this need, we will be generating the Watermelon library, a high complexity expressed library that enables simultaneous tracking of lineage as well as exosome, ATGs, Yap/TAZ, undruggable transcriptional factors (KLFs), epigenetically silenced genes (SWI/SNF-BRG1), EMT, PI3K and proliferative state of each cell in the population during drug treatment. We hypothesize that therapeutic intervention (in-vitro, in-vivo and 3D organoid ex-vivo) of highly selective agents (Natural, Synthetic, or antisense oligonucleotides) are capable of targeting genes exclusively present within the drug-tolerant sub-population (Fig:3).

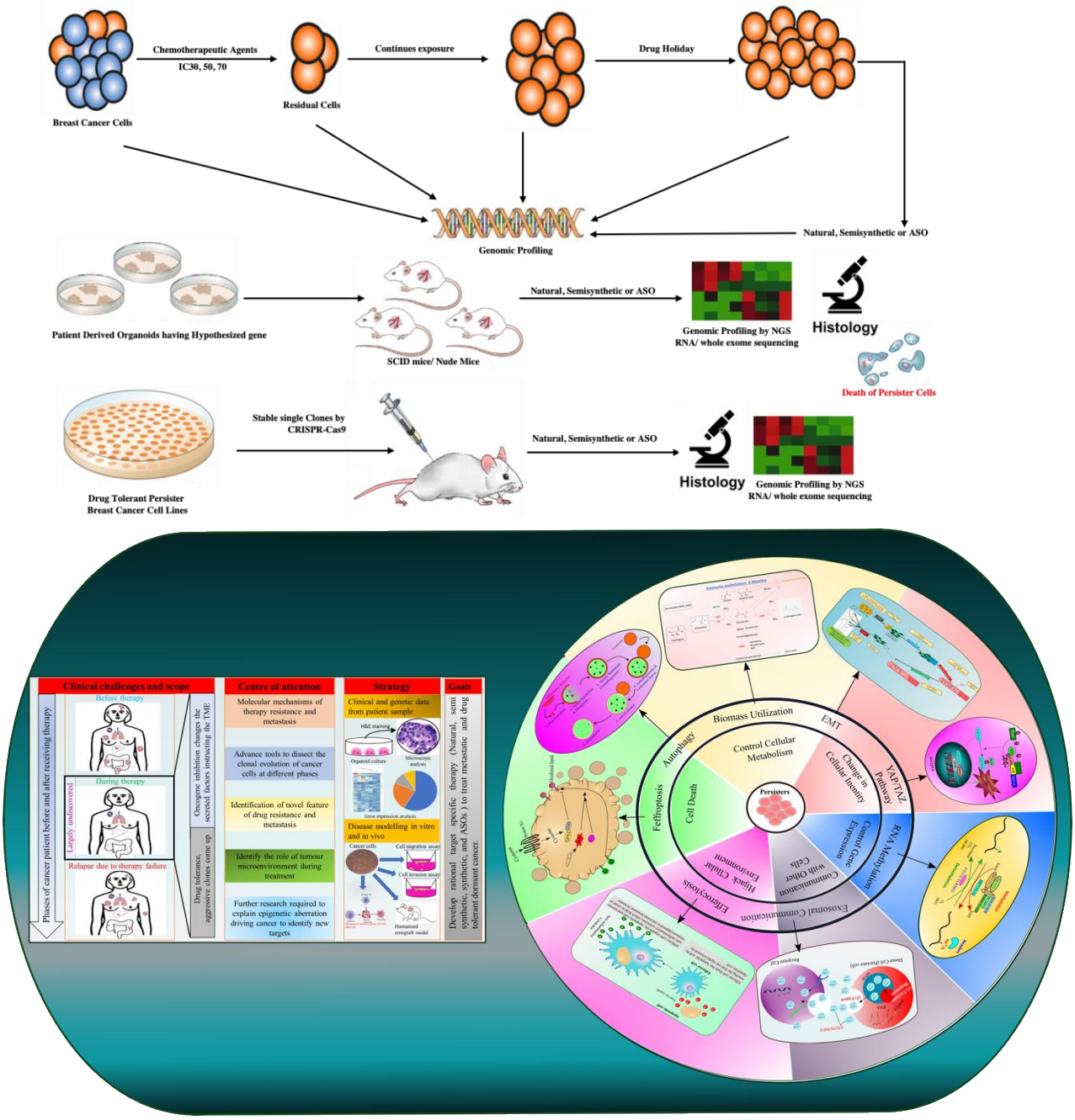

Figure:3

Above all our group now developing 3D organoid model for cancer drug discovery and screening. This organoid drug screening platform can be used to guide patient treatment and clinical trials to accelerate anti-cancer drug development.

- **Collaboration:**
  - IIT- Varanasi, India
  - IIIM-CSIR, Jammu, India
  - CNCI, Kolkata, India
  - IIIT-Allahabad, India
  - ILS, Bhubaneswar, India
  - NIMS-Hyderabad, India
  - Boston University, USA
  - Taipei Medical University, Taiwan
  - VIB, Belgium