Cancer Target Discovery and Development (CTD^2)

Specific Aims

Institution: Emory University

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High throughput screening (HTS) approaches will be employed to establish protein-protein interaction (PPI) networks based on cancer genomics information to populate the cancer PPI target space. The Emory Molecular Interaction Center for Functional Genomics (MicFG) proposes to become a prominent member of the Cancer Target Discovery and Development (CTD^2) network with broad capability in high throughput (HT) biology and genomics informatics and special expertise in *protein-protein interactions (PPI)*, including HT PPI network mapping for novel target discovery. We have a strong foundation from which to contribute to the goals of the CTD^2 network, including extensive research experience in PPI studies and functional genomics investigations, two state-of-the-art HTS platforms for robot-driven HT biology, deep strength in genomics data mining, integration, and analysis as well as database and software systems, and a highly collaborative and productive team science culture. With these strengths, we aim to interrogate cancer genomic alterations to discover novel oncogenic protein-protein interactions and pathways for accelerated therapeutic development.

Recent large-scale cancer genome initiatives based on robust clinical data, such as TCGA, TARGET, CGCI and ICGC, have generated a compendium of genomic alterations in a number of cancer types, such as *ovarian, lung, breast, colon, and kidney cancers*. As these initiatives expand to the proposed 20 cancer types within the TCGA program and 50 cancer types from ICGC, a vast amount of genomic data will be publically available with catalogued cancer-associated changes. However, translation of this valuable information into effective therapeutic strategies remains a daunting challenge. Our functional genomics approach is intended to bridge this gap by establishing and targeting oncogenic PPI interfaces for therapeutic intervention. Genomic alterations in tumors often lead to re-wired PPI networks, resulting in re-programmed processes that drive tumorigenesis and progression. Our **central hypothesis** is that tumor-associated genomic alterations transmit signals through PPI nodes and hubs that integrate tumorigenic pathways to exert tumor transformation phenotypes. Therefore, "pathway perturbation" through the disruption of these PPIs will allow a novel approach for functional interrogation and identification of tumor-associated molecular pathways critical for tumorigenesis, progression, and metastasis. The validated PPI interfaces will serve as new molecular targets for therapeutic interventions in drug discovery. **Thus, these dysregulated PPIs define a new dimension in the cancer target space for therapeutic exploitation**. To test this hypothesis, we have established highly efficient HT PPI technology platforms for in vivo cell-based PPI-mapping and in vitro validation, a panel of high density plate-based HT tumorigenesis and invasion functional assays, and

a set of bioinformatics tools for data analysis and integration in support of the following proposed aims.

Aim 1: To discover novel targets through oncogenic PPI network mapping for cancer-associated genes as defined by TCGA and other genomic datasets. Three complementary HT PPI detection technologies will be employed for orthogonal screening experiments to systematically establish molecular nodes and hubs that connect oncogenic pathways based on cancer-type specific PPI networks. Structural elements that mediate selected key PPIs will be identified and used to validate signaling hubs and nodes for tumor initiation and progression.

Aim 2: To mine cancer genomics datasets to prioritize PPI network studies and establish connectivity of newly identified PPIs to oncogenic pathways and networks. Bioinformatics data analysis will utilize existing and new genomic datasets to identify candidate genes and integrate PPI data into connectivity maps and biological models. We propose to become a critical node in the CTD^2 network, providing expertise in HT PPI-based cancer target discovery and modulator discovery. We will systematically analyze new -omics datasets and generate new functional PPI data and tools for validation of potential PPI targets. With participation in trans-network collaborative pilot projects, the functional role of key PPI nodes and hubs in cancer can be investigated in diverse tumor models offered by other CTD^2 centers and optimized HTS assays will be used to discover small molecule PPI modulators as joint collaborative projects.