Leveraging Artificial Intelligence to Uncover Molecular Targets and Therapeutics for Rare Cancers

Rare cancers account for over 20% of all cancers diagnosed worldwide, with an occurrence of less than 6 per 100,000 individuals annually. Many rare cancers in adults, adolescents, and children are not curable, and patients and providers often face severely limited treatment options. The lack of detailed molecular understanding of how or why rare cancer cells originate and spread, the paucity in investment from major stakeholders including the pharmaceutical industry and government bodies, and challenges in carrying out clinical trials in very small patient populations represent some of the main challenges of tackling rare cancers.

We propose developing an Artificial Intelligence (AI)-based platform that cuts to the core of these challenges: employing patient-derived tissues obtained within hours after surgery, we are leveraging the rapid gains in computational power to identify new and effective treatment regimens that do not require mechanistic understanding. My lab has established a series of machine learning approaches, called KiDNN (**K**inase **i**nhibitor prediction using **D**eep **N**eural **N**etworks), and KiR (**Ki**nome Regularization) that utilizes a large scale drug-target profiling efforts and algorithms that, when functioning together, mimic aspects of the human brain. These AI-based approaches have the capability of mimicking highly complex and dynamic signaling pathways to predict the effect of drugs on a variety of cellular processes. These tools are "trained" by inputting a small subset of drugs into the system; the eventual output is ~500 drugs and up to 13 million drug combinations that may target a patient's cancer cells. This proposal will generate proof-of-concept data by applying our platform to three different types of rare cancers: Fibrolamellar cancer, Ependymomas, and Neuroblastoma. If successful, our findings would provide a game-changing solution for the treatment of rare cancers. First, it uniquely addresses a fundamental therapeutic challenge of rare cancers; most patients do not respond to existing therapies. Second, our study includes FDA-approved small molecules, thus repurposing existing drugs that can be immediately prioritized in clinical trials and clinical-grade molecules that promise clinical development. Third, if our platform succeeds and is deployed, it will enable us to deliver personalized therapies. We will seek to develop a companion diagnostic test based on the drug target observed for a given patient. Ultimately, our strategy offers the best chance of a cure and, importantly, the healthiest survivorship possible for patients with rare cancers. Our approach could be applied in the longer term to reduce the overall pre-clinical burdens and accelerate the development of effective candidates for other rare cancers.

Innovation. Our cutting-edge research combines state-of-the-art methods from the bedside (patient-derived experimental systems) and the computer lab. Our approach does not require a biological understanding of why a drug candidate could work but instead employs massively powerful computation to predict which of millions of drug combinations is most likely to be effective in a rare tumor. By applying machine and deep learning approaches to assist in model design and selecting compounds for pre-clinical drug discovery, our method can accelerate the prioritization of compounds and lower barriers of pre-clinical trials by reducing the experimental search to smaller, model-predicted subsets. Most importantly, our novel methodology will provide innovative treatment strategies for rare cancer patients.

Specific Aims.

Aim 1. Development and application of an AI-based screening approach to identify molecular targets and therapeutics for three different types of rare cancers: Fibrolamellar cancer, Ependymomas, and

Neuroblastoma. We will generate proof-of-concept data demonstrating our AI-based platform can (**i**) identify specific proteins and signaling networks that are important for the survival and growth of these rare cancer cells; **(ii)**) predict responses to ~500 FDA-approved or clinical-grade inhibitors *in silico* and rank order 13 million drug combinations that act synergistically to compromise the growth or survival of these rare cancer cells and (**iii**) experimentally validate top predicted inhibitors and combination in state-of-the-art pre-clinical models.

Aim 2. Engage rare cancer community stakeholders for the dissemination of AI-based chemical screening libraries. Our KiDNN screening approach offers unique advantages over other screens. **First**, a full KiDNN screen consists of only ~30 computationally-chosen, broadly specific compounds and can be completed in a matter of days-weeks, allowing this technique to be applied to multiple models in a high-throughput manner. A clear advantage of this approach over genetic or RNAi is that small molecule inhibitors can easily be adapted for both primary and difficult-to-transfect cell lines such as *ex vivo* models. **Second**, the polypharmacology of broadly selective chemical tool compounds captures potential redundancies and interdependence of intracellular signaling. This facet is often lost in other approaches. **Third**, our pharmacological approach includes a large number of FDA-approved drugs, many of which are already in use. Thus, repurposing these drugs either as single agents or in combination, will expedite treatment for rare cancers. To enable researchers in the rare cancer community with these AI-based tools, we will distribute copies of our AI-based chemical screening library (a 96-well plate consisting of 30 computational-determined small molecule inhibitors) to 100 labs across the world. Patient advocates (patients, caregivers, clinicians, and other members of the rare cancers community) will be intimately involved in selecting labs and rare cancer types.

Aim 3. **Develop a cloud-based platform for the analyses of AI-based chemical screening**. We will generate a cloud-based infrastructure allowing users (identified in Aim 2) to upload their screening results. Machine learning algorithms will analyze the datasets in the back-end and provide (**i**) ranked order list of ~500 FDA-approved or clinical-grade inhibitors *in silico;* (**ii**) rank order list of 91 thousand two-drug combinations and 13 million three-drug combinations; (**iii**) rank order list of kinases predicted to be essential for the phenotype such as growth or viability or migration of rare cancer cells and (**iv**) generate networking topology maps illustrating critical signaling pathways that are predicted to be essential for the phenotype.

Overall, successful completion of these aims will provide critical proof-of-concept that supports our paradigm-shifting approach for discovering novel treatments for undruggable rare cancers. In the short term, these results will lead to an immediate and effective treatment option for Fibrolamellar cancer, Ependymomas, and Neuroblastoma rare cancers. The proposed studies will also lay the foundation and position our lab to apply our novel approach to other undruggable pediatric cancers in the U.S.

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