競爭型潛力研究團隊

- 大數據分析輔助三陰性乳癌新藥開發

Big data mining assisted drug development for triple-negative breast cancer

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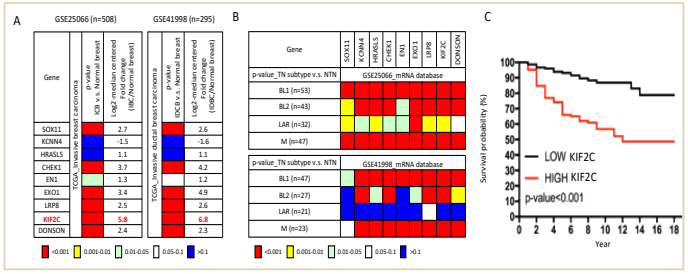
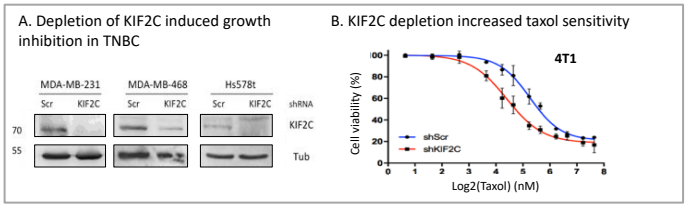
The long-term goal of this team is to develop a first-in-class therapeutics of breast cancer. Identification of a promising and druggable therapeutic target is the first task to be accomplished for this goal. With the application of big-data mining and bioinformatics approaches, we have identified protein KIF2C as a promising and druggable therapeutic target of breast cancer, especially for the triple-negative breast cancer (TNBC). We then teamed up an initial study group with members from National Tsing Hua University, Academia Sinica, and National Health Research Institutes, and expertise in molecular and cellular biology, systems biology, protein crystallization, medicinal chemistry, and animal pharmacology. With support of National Tsing Hua University, we have successfully developed functional assay for characterizing in vitro activity of KIF2C and through which candidate chemical inhibitors are identified. In addition, we also successfully resolved protein crystallography of KIF2C and conducted structural-based drug design through medicinal chemistry. Using the initial lead compound of KIF2C inhibitor, we have successfully demonstrated the anti-tumor activity of our lead compounds in animal mice models carrying TNBC. A summary list of our research progress achieved in past two years is provided in below.

1. As a team, we have extended our research outside the campus and had applied different integrated project for additional funding support. We have successfully obtained the competitive integrative project from National Health Research Institutes/NHRI for two years (2019-2020) with a total budget of 6,000,000 NTD funding support. From year 2022, we also obtained the Innovative Research Grant (IRG) support from NHRI. These funding support will push our research project toward preclinical assessments.
2. Our initial principle component analysis of breast cancer had identified 9 potential candidates of cancer target of breast cancer. Among these candidates, KIF2C showed a

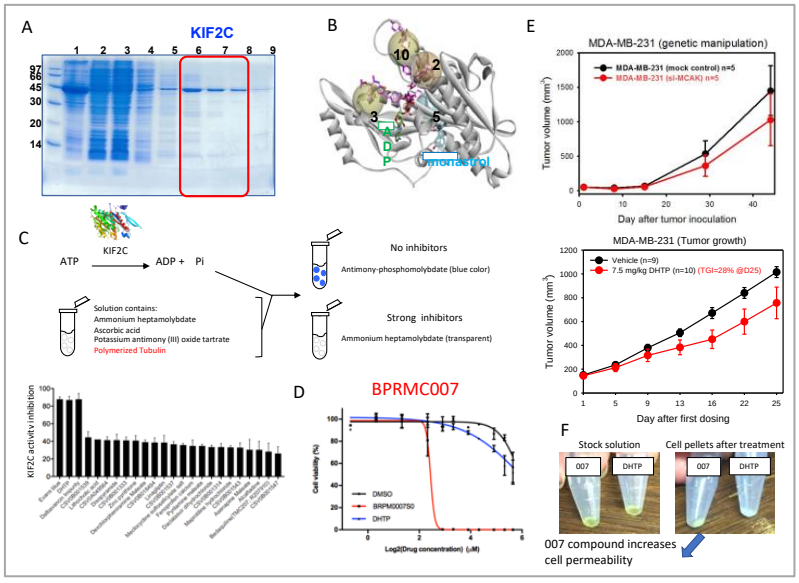
highest fold induction in breast cancer tissues in comparison to normal breast tissues and patients with a high level of KIF2C in breast cancer tissues had a lower survival (Figure 1) ◦



3. Induction of KIF2C overexpression is detected in the taxol-resistant breast cancer lines developed in our lab. We found that the depletion of KIF2C increased chemosensitivity of taxol in 4T1 breast cancer cells (Figure-2). Based on these two pilot studies, we assume that the induction of KIF2C in breast cancer cells may contribute to the development of drug resistance of breast cancer.



4. Here we show the first crystal structure of KIF2C with a high resolution of 1.83A (below figure A and B). In addition, we successfully developed a functional assay of KIF2C (C) and applied this assay for the identification of novel KIF2C inhibitors from an FDA-approved library. Based on the protein structure and initial drug screening, we found DHTP is a suitable starting point for the drug design and synthesized 46 DHTP analogues. From these analogues, we identified compound 007 as a promising KIF2C inhibitor as it induced cytotoxicity in parental TNBC cell lines (D). With the support from NHRI, we also confirmed that compound 007 may block tumorigenesis in the syngeneic mice model of TNBC (E). These results highlight the role of 007 as a novel KIF2C inhibitor with an anti-tumor activity.



5. The most promising finding of our project is to show that cells treated with compound 007 displayed increased drug sensitivity to taxol, even for the taxol-resistant cell lines developed in our lab. Such data provide a strong ground basis for the development of effective KIF2C inhibitors as a new drug of TNBC.