Project Title: TLR Agonists as Plasmacytoid Dendritic Cell-based Cancer Immunotherapy

TLR 激動劑作為基於漿細胞樣樹突狀細胞的癌症免疫療法

PI: Prof Kwan T CHOW

Breast cancer (BC) is one of the most common cancers affecting women in Hong Kong and the leading cause of cancer-related death in women worldwide. BC is classified into several molecular subtypes, of which triple negative breast cancer (TNBC) shows the worst prognosis and represents a grave challenge due to their aggressive nature and unresponsiveness to hormone therapy. There is currently no targeted therapy against TNBC, and metastatic TNBC is generally considered incurable. TNBC is characterised by high myeloid infiltration and severe immunosuppression. The team therefore aimed to target the toll-like receptor (TLR) pathway to reactivate immune cells for effective TNBC immunotherapy.

Using the 4T1 TNBC mouse model, a panel of TLR agonists in combination with paclitaxel (current standard treatment) was tested in their efficacy in inhibiting tumor growth: Pam3CSK4 (TLR1/2). Poly I:C (TLR3), LPS (TLR4), imiquimod (TLR7), R848 (TLR7/8), CPG-ODN 2395 (TLR9). It was found that all TLR agonists had some effect in suppressing tumor progression, with the stimulation of TLR7/8 and 9 being particularly effective (Fig. 1); these effects were contributed by the TLR agonists, and not the paclitaxel alone (Fig. 2). These findings suggest that TLR activation is a viable way to reactivate the immune system for effective anti-tumor immunity. The team has been currently dissecting the molecular mechanisms underlying the role of TLR stimulation in tumor regression.

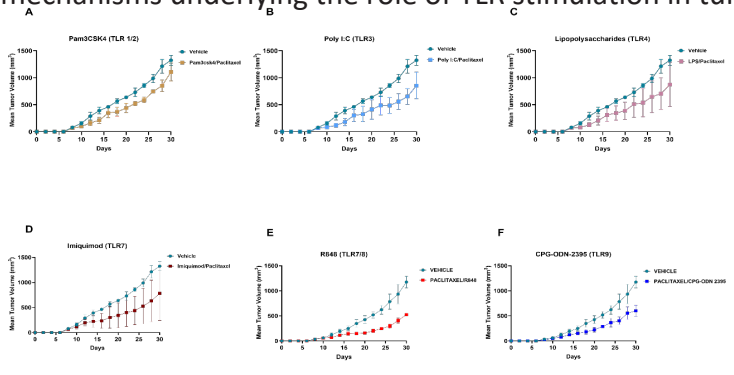

Fig.1 Screening of TLR agonists in combination with paclitaxel. Graphs showing tumor volumes of mice treated with Paclitaxel. (A): Pam3CSK4 (B): Poly I:C (C): Lipopolysaccharides (D): Imiquimod (E) R848 (F): CPG-ODN-2395

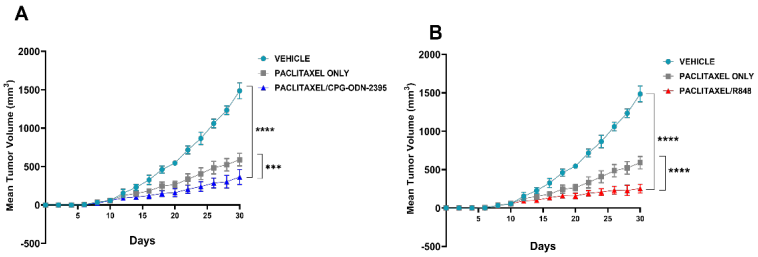

Fig.2 Treatment of Paclitaxel with R848 or CPG-ODN-2395 (A): Tumor volume of mice treated with Paclitaxel/CPG ODN 2395 ***(***p=0.0009)*** *(B): Tumor volume of mice treated with Paclitaxel/R848* ***(****p<0.0001)***