Stimuli-responsive polyboronate ester polymer nanocarrier as potential boron drug for combined BNCT and PD-1/PD-L1 Checkpoint Blockade Immunotherapy

Polyboronic acid奈米免疫治療和中子捕獲治療-使癌症治療更加有

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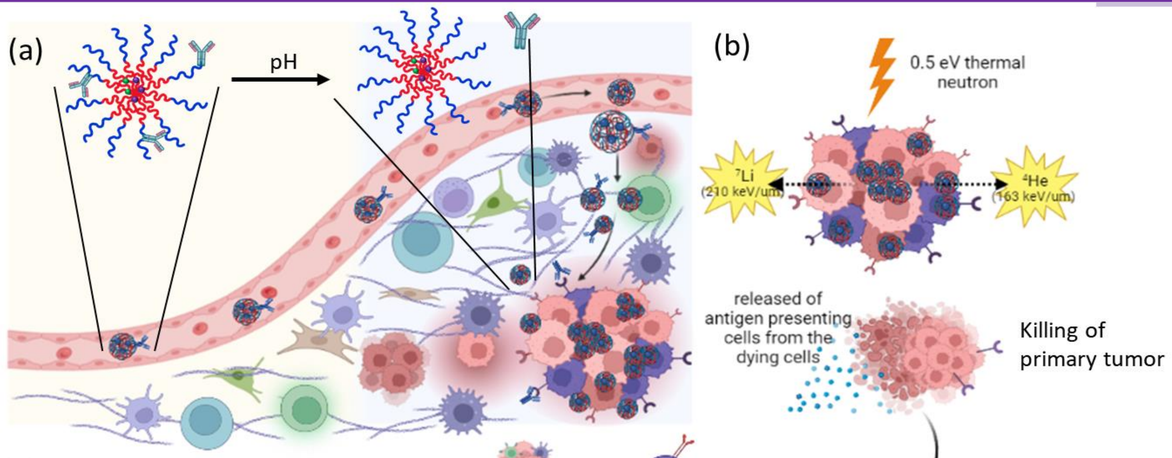
Pei Yuin Keng*, *Yi-Lin Chiu, Wan Yun Fu, Han Yu Lee, Wei Yuan Huang, Tzu-Wei Wang*

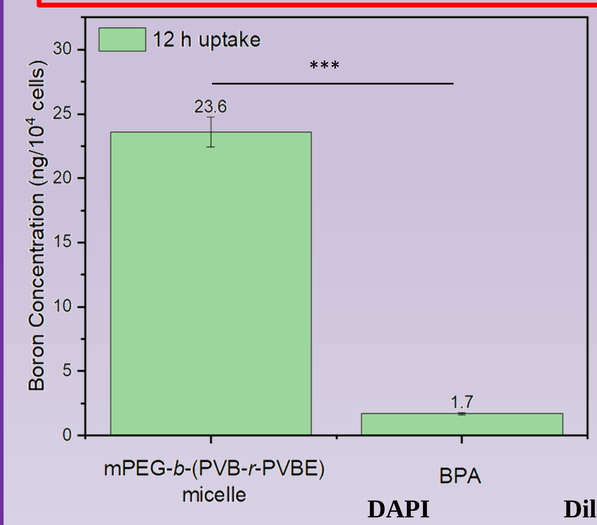
Department of Material Science and Engineering, National Tsing Hua University, Hsinchu City 300, Taiwan

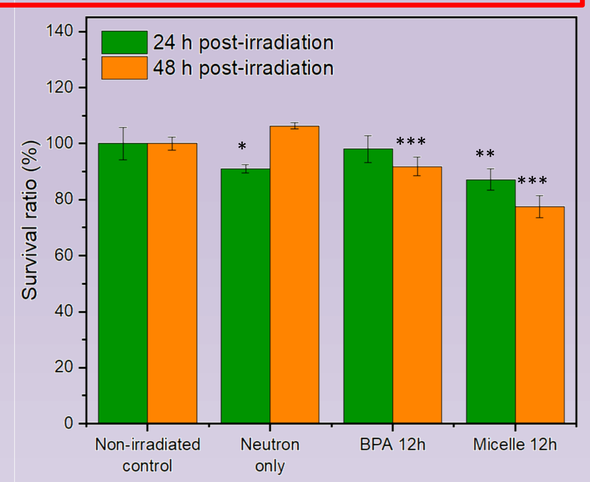
Abstract: Boron neutron capture therapy (BNCT) is an emerging cancer treatment modality that allows selective destruction of individual cancer cells when a selective boron drug is administered without harming neighboring healthy cells upon low energy epithermal neutron irradiation. BNCT combines both radio- and chemotherapy when a sufficient concentration of boron-10 drug can be selectively accumulated into the tumor cell. The proposed plan aims at combining nanomedicine, BNCT, and immunotherapy in combating melanoma while maintaining the patients' quality of life. We have synthesized two amphiphilic block copolymers, namely, poly(ethylene glycol)-block-poly(4-vinylphenylboronate ester) (mPEG-b-PVBE) and poly(ethylene glycol)-block-random copolymer of poly(3-vinylbenzaldehyde) and poly(4-vinylphenylboronate ester) (mPEG-b-(PVB-r-PVBE)). Utilizing mPEG-b-PVBE as a model system, we optimized block copolymer synthesis, micelle preparation, and encapsulation of imaging contrast agents and chemotherapeutics, serving as theranostic agents for combined BNCT, chemotherapy, and immunotherapy. Our results indicate that $mPEG_{11}$3-b-$PVBE_{36}$ is the optimal amphiphilic block copolymer for generating polyboronate ester micelles with reproducible, uniform sizes ranging between 20 nm and 50 nm. In vitro studies using melanoma B16-F10 cells revealed that these polymeric micelles significantly enhanced intracellular boron uptake and induced cell death, surpassing the performance of boronophenylalanine (BPA). Moreover, in vivo studies employing B16-F10 melanoma-bearing mice assessed the antitumor efficacy of BNCT monotherapy as well as a combination of BNCT and immunotherapy. The results demonstrated significant tumor growth delay, particularly in mice treated **using polymeric micelles combined therapies**, leading to a tumor growth delay (TGD) of **6.6 days**, as opposed to a TGD of **0.9 days** in mice treated with **BPA combined therapies.**

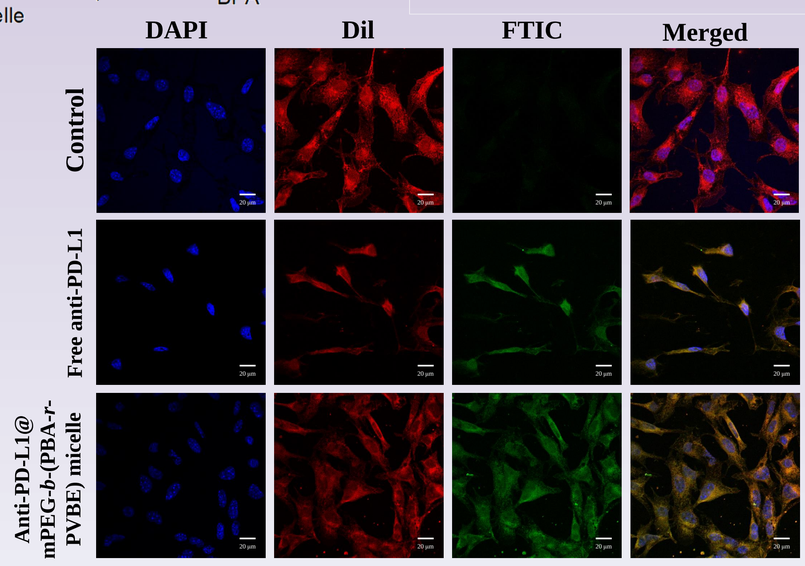


Schematic of the combined BCNT and immunotherapy treatment using the stimuli-responsive polyboronic acid micelles

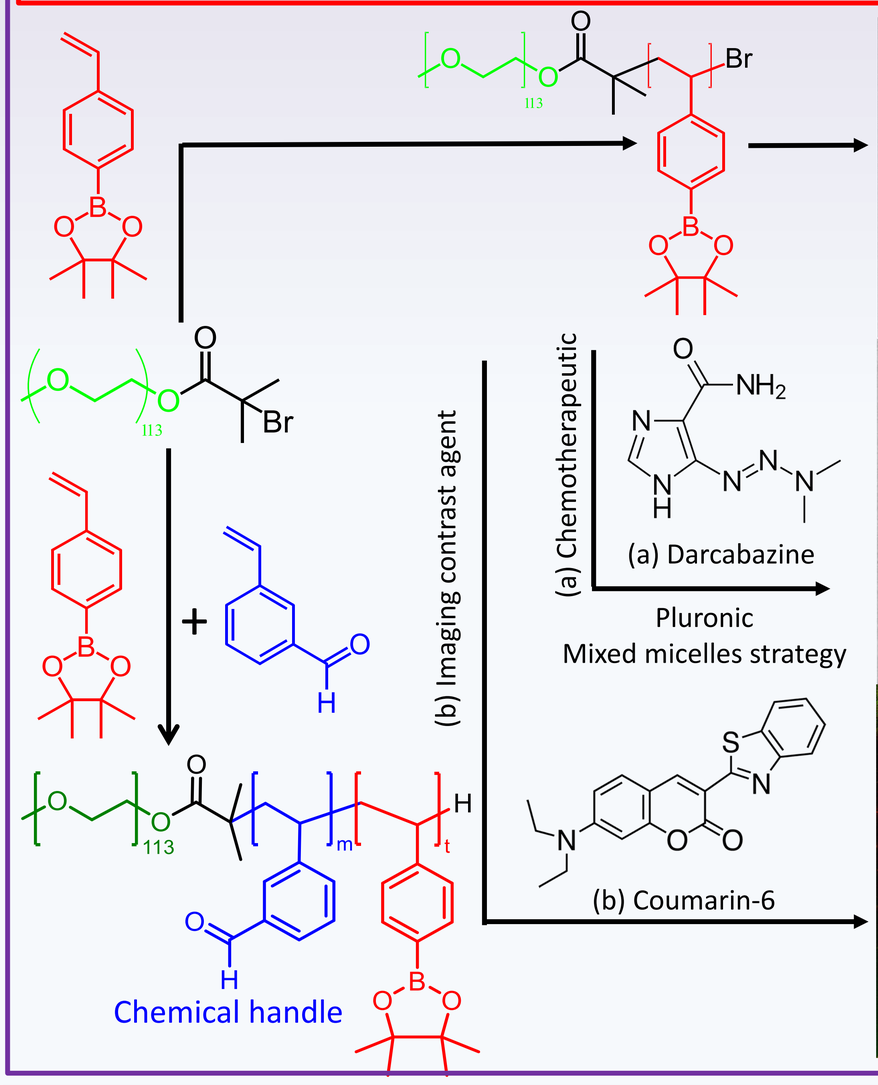
In-vitro investigation of the polyboronic acid micelles in B10-F16 cells

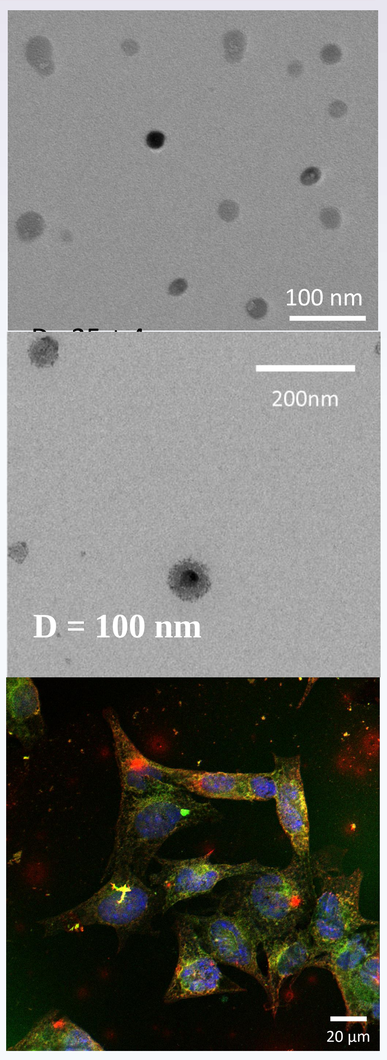




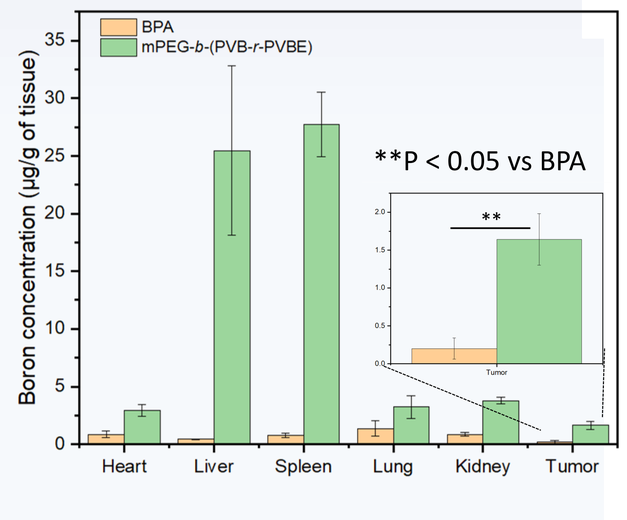


(a) Synthesis of mPEG-*b*-PVBE via ATRP and the encapsulation of chemotherapeutic drugs

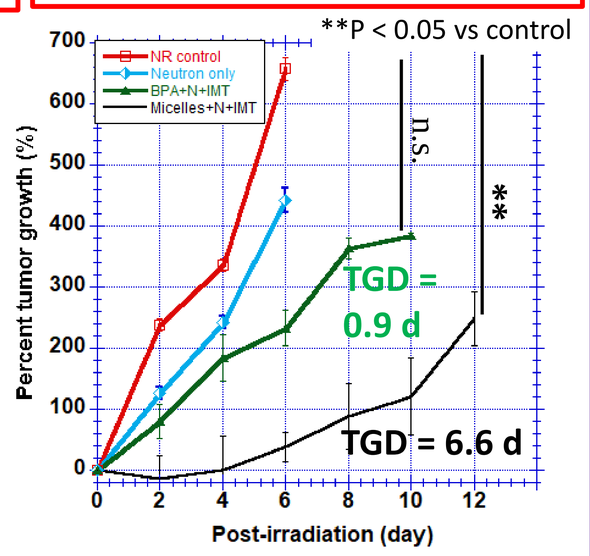




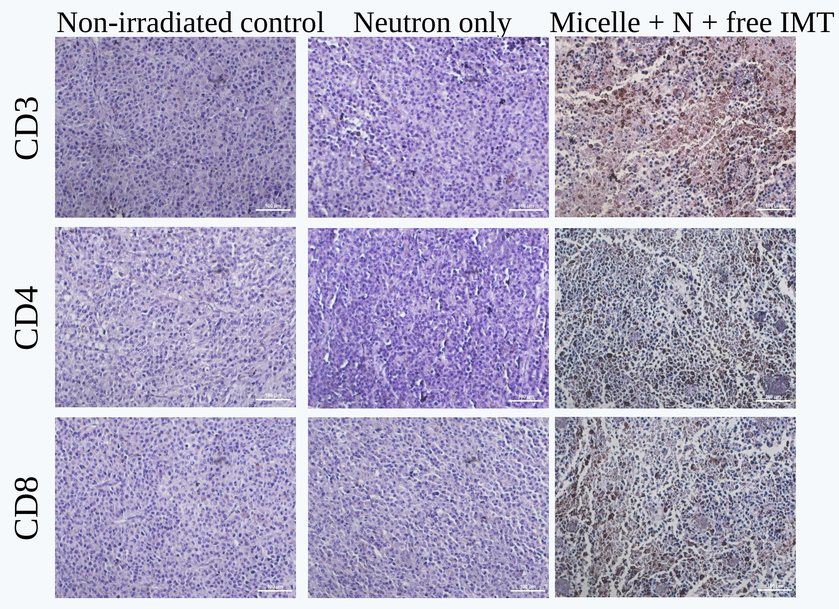
In-vivo biodistribution of the polyboronic acid micelles in mice-bearing B10-F16 tumor



In-vivo combined immuno-neutron capture therapy



Immunohistochemical staining of B16-F10 tumor tissue sections using CD3, CD4, and CD8 antibodies



Preparation of darcabazine@polyboronic acid micelles via the mixed micelles strategy. Release profile of darcabazine of (a) non-mixed micelles and (b) mixed micelles at pH 7 and pH 5