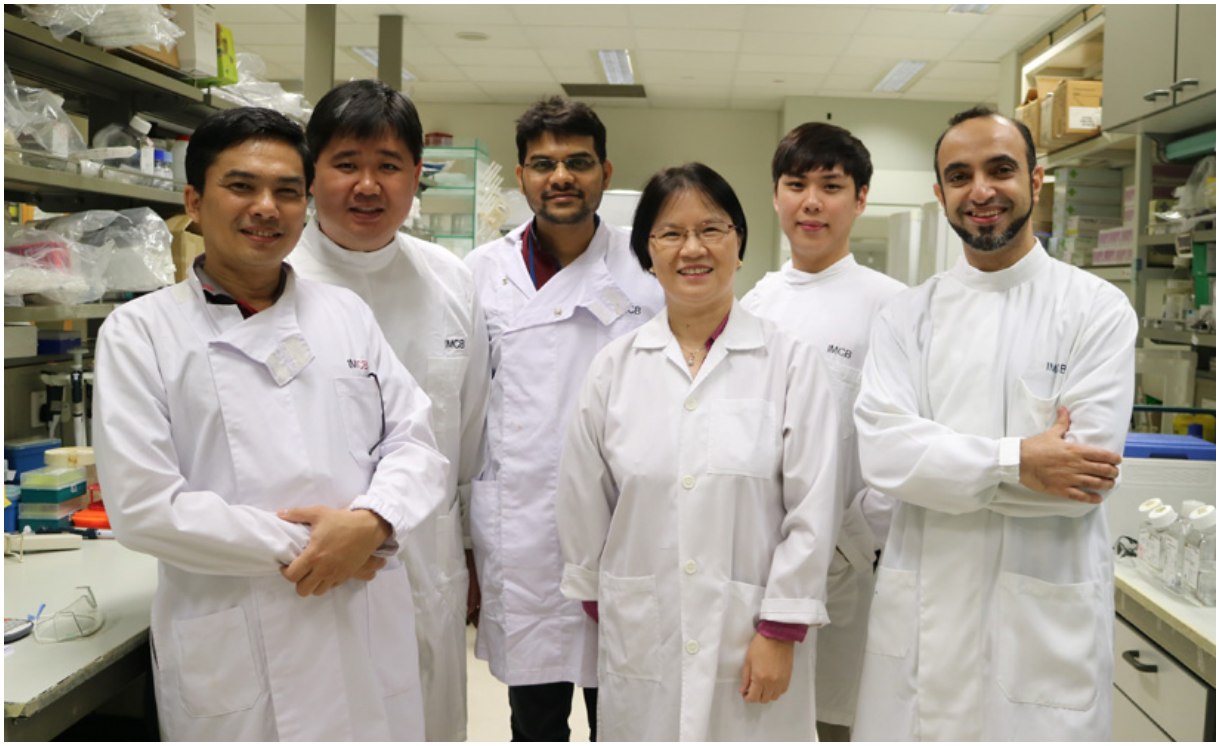
PRL3-zumab as an immunotherapy to inhibit tumors expressing PRL3 oncoprotein

Wednesday, 12 Jun 2019



From left: Min Thura, Joel Xuan En Sng, Abhishek Gupta, Qi Zeng, Nicholas Yan Zhi Tan, Abdul Qader Al-Aidaroos

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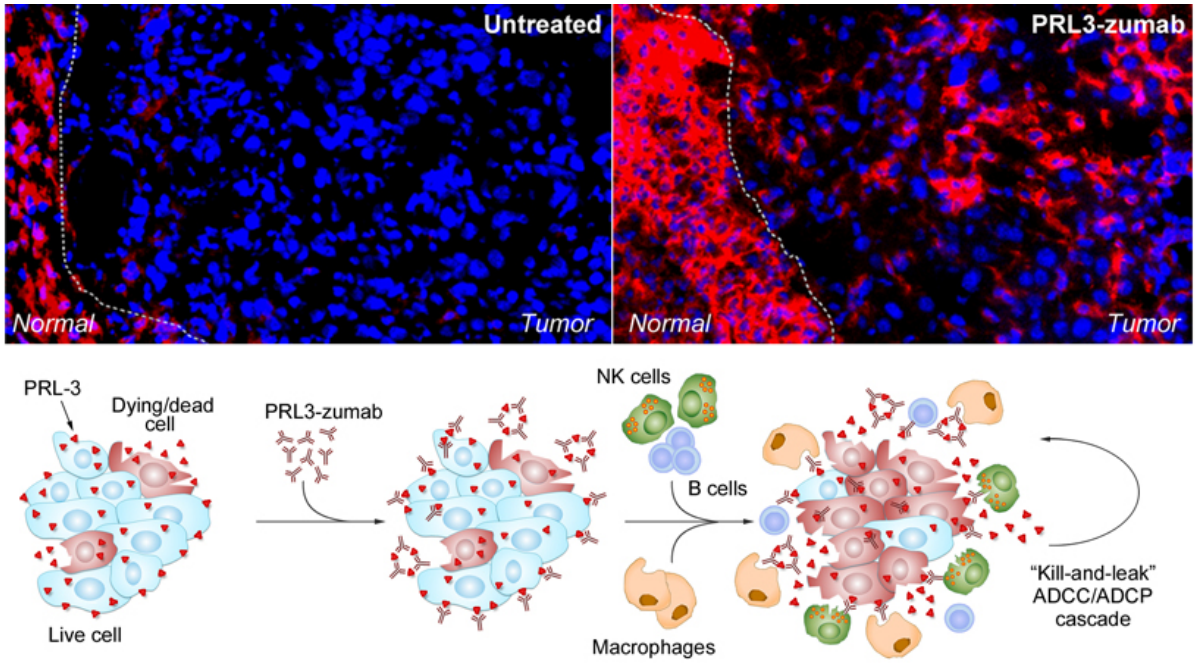
Published online in *Nature Communications* on 05 June 2019.

(Open access article – please see https://rdcu.be/bFIj4)

Abstract

Tumor-specific antibody drugs can serve as cancer therapy with minimal side effects. A humanized antibody, PRL3-zumab, specifically binds to an intracellular oncogenic phosphatase PRL3, which is frequently expressed in several cancers. Here we show that PRL3-zumab specifically inhibits PRL3+ cancer cells in vivo, but not in vitro. PRL3 antigens are detected on the cell surface and outer exosomal membranes, implying an 'inside-out' externalization of PRL3. PRL3-zumab binds to surface PRL3 in a manner consistent with that in classical antibody-dependent cell-mediated cytotoxicity or antibody-dependent cellular phagocytosis tumor elimination pathways, as PRL3-zumab requires an intact Fc region and host FcγII/III receptor engagement to recruit B cells, NK cells and macrophages to PRL3+ tumor microenvironments. PRL3 is overexpressed in 80.6% of 151 fresh-frozen tumor samples across 11 common cancers examined, but not in patient-matched normal tissues, thereby implicating PRL3 as a tumor-associated antigen. Targeting externalized PRL3 antigens with PRL3-zumab may represent a feasible approach for anti-tumor immunotherapy.

Figure:



PRL3-zumab promotes immune cell infiltration into the tumor microenvironment for tumor clearance. *Upper panels*, immunofluorescence images of adjacent normal and tumor boundary regions in untreated (left) and PRL3-zumab-treated (right) liver tissue sections in mice. *Red*, F4/80 macrophage marker; *blue*, DAPI nuclear stain. Note the pronounced increase of F4/80 macrophage infiltration into the tumor niche in treated mice. *Lower panel*, proposed model for PRL3-zumab anti-tumor activity.