A nuclear imaging-guided bioorthogonal system reveals the antitumor immune function of pyroptosis

With the support by the National Natural Science Foundation of China, the research team led by Liu ZhiBo (刘志博) at Peking University and Shao Feng (邵峰) at Beijing Institute of Biological Sciences revealed the antitumor immune function of pyroptosis by a novel bioorthogonal system. This study, titled "A bioorthogonal system reveals antitumour immune function of pyroptosis" was published in *Nature* (2020, 579: 421—426).

Bioorthogonal chemistry that can achieve tumor-selective manipulation of a target protein without causing unwanted effects is of high value for both biomedical research and clinical usage, but is also a formidable challenge. In this work, scientists established a bioorthogonal chemical system—a cell-enterable nuclear imaging probe phenylalanine trifluoroborate (Phe-BF_3) desilylates and "cleaves" a designed silyl ether-containing carbamate linker. When combined with gold nanoparticle (NP)-mediated delivery, Phe-BF_3-catalyzed desilylation could tumor-selectively release a client protein from an NP conjugate. A further application to releasing a gasdermin showed a low percentage of tumor cell pyroptosis was sufficient to clear the entire tumorgraft. The tumor regression was absent in immune-deficient nude mice or upon T-cell depletion, and correlated with augmented antitumor immune responses.

This work demonstrates that the nuclear imaging—guided Phe-BF_3 desilylation-based bioorthogonal system is a powerful chemical-biology tool; its application reveals that pyroptosis-induced inflammation triggers robust antitumor immunity and can synergize with the checkpoint blockade, providing a new direction for the development of anti-tumor immunotherapy strategy and controllable drug release systems.

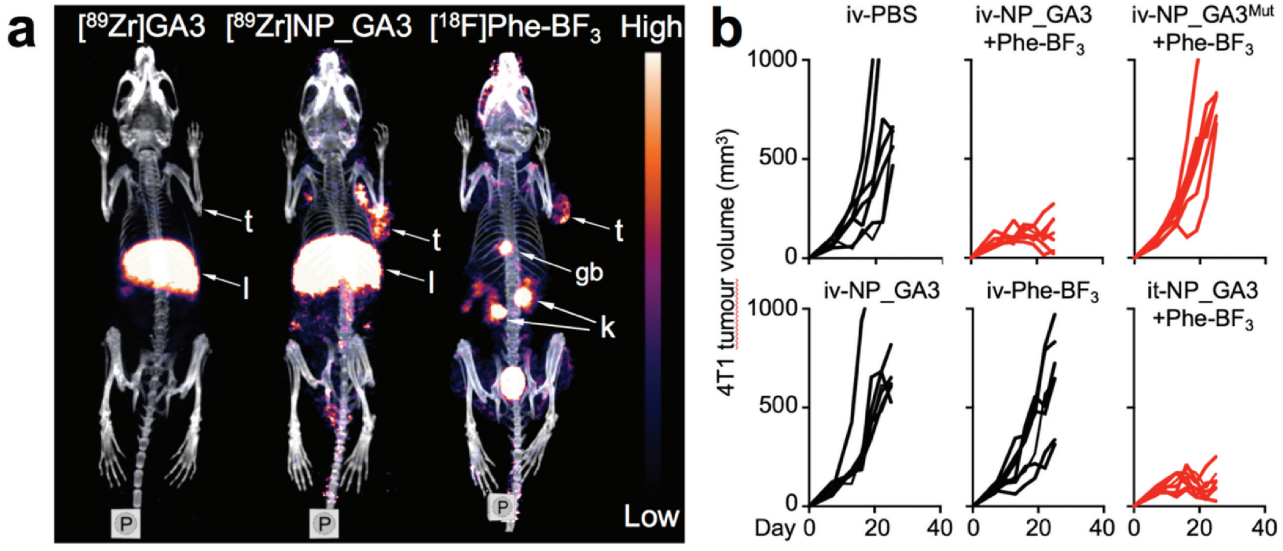

Figure Nuclear imaging—guided NP_GA3+Phe-BF_3 treatment triggers tumor regression in **mice.** a, Representative PET-CT 3D projection images of 4T1 tumor-bearing mice intravenously injected with [^{89}Zr]GA3, [^{89}Zr]NP_GA3 or [^{18}F]Phe-BF_3. *t*, tumor; *l*, liver; *k*, kidney; *gb*, gallbladder. b, Tumor volume of individual mouse at indicated time points after implantation.