Patient-Specific Nanoparticle Targeting in Human Leukemia Blood

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Achieving precise delivery of nanomedicines to cancer cells while minimizing off-target toxicity remains a key challenge in oncology.[1] In this study, we established a fully human ex vivo model using fresh blood from 15 patients with chronic lymphocytic leukemia (CLL) to investigate how antibody-functionalized nanoparticles interact with leukemic and healthy immune cells.[2] Using a panel of PEGylated nanoparticles—including PEG-MS particles, clinically relevant Doxil liposomes, and low-fouling pure PEG particles—functionalized with bispecific antibodies against CD20 or CD28, we revealed striking interpatient variability in targeting efficacy (up to 234-fold) and phagocytic uptake (up to 112-fold).

Mechanistically, we identified anti-PEG immunoglobulins as key modulators of nanoparticle behavior. Elevated levels of anti-PEG IgG correlated with increased phagocytic uptake, while high anti-PEG IgM levels were associated with reduced CLL targeting—likely through steric hindrance of targeting ligands. Additionally, the expression of CD20 and CD28 antigens on target cells influenced nanoparticle engagement, particularly for low-fouling particles.

Importantly, we observed that off-target uptake of Doxil by phagocytes led to substantial monocyte death, highlighting a major safety concern. These findings emphasize the need for individualized assessment of nanoparticle formulations and immune interactions. Our platform offers a patient-specific approach to guide the development of safer, more effective nanomedicines for blood cancers.

References:

1. Ju, Y.; et al. *Nat. Nanotech.* **2025***, 20,* 576–579.
2. Ju, Y.; **Li, S;** et al. *ACS Nano.* **2024**, *18*, 29021–29035.