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Drug-resistance facilitates tumor-targeting of nanobiologics, HerGa and HerDox

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Elevation of the human epidermal growth factor receptor subunit 2 (HER2) characterizes HER2+ tumors. HER2 elevation amplifies tumor growth signaling, facilitating recalcitrance to standard therapies. Whereas HER2 inhibitors, trastuzumab and lapatinib, target HER2+ tumors by blocking HER2 signaling, up to 70% of cases resist or acquire resistance to these targeted therapies. Recent studies indicate that elevation of the HER2 dimerization partner, HER3, facilitates this resistance. We have developed HerGa and HerDox: nanobiological particles capable of targeting resistant tumors by binding HER3 and inducing rapid entry of toxic molecules into tumor cells by receptor-mediated endocytosis and membrane penetration. These particles circumvent the need to modulate signaling. HerGa and HerDox are both comprised of the recombinant protein, HerPBK10, delivering a different toxic molecule: either a gallium corrole or doxorubicin, respectively. HerPBK10 is a fusion of the receptor binding domain of the HER ligand, heregulin, appended to a membrane penetration domain derived from the adenovirus capsid penton base protein. HerPBK10 binds HER3 and triggers rapid receptor-mediated endocytosis into endocytic vesicles via the heregulin domain. Vesicle escape and passage into the cytosol (necessary for cytotoxicity) is facilitated by the penton base domain. HerPBK10 also contains a positively-charged domain for binding anionic compounds. HerPBK10 can noncovalently self-assemble with either drug, forming 10-20 nm diameter round particles that are stable under different storage conditions and in blood. While HerGa and HerDox can target HER2+ tumors because HER2 elevation enhances HER3 affinity for heregulin, preference for drug resistant tumors is even higher due to HER3 elevation.

Biography

Lali K. Medina-Kauwe received her Ph.D. in Molecular Biology from the University of California Los Angeles and completed postdoctoral studies in Gene Therapy Vector Development at the University of Southern California Keck School of Medicine. She is an Associate Professor of Biomedical Sciences at Cedars-Sinai Medical Center and Associate Director of the Graduate Program in Biomedical and Translational Research. She has served on several NIH grant review panels related to gene and drug delivery. Her studies focus on developing targeted nanotherapies, some with both imaging and therapeutic capabilities, derived from the natural cell penetration and delivery properties of pathogens.

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