



## Cover story

## Treating resistant tumors using HER3-targeted nanobiologics



Over the last few decades, various attempts have been made for selective delivery of anticancer drugs to tumors, mostly using nanoparticles, such as liposomes, polymer micelles, and drug crystals in nanoscale, which are decorated with ligands known to bind to tumor cells. Unfortunately, however, such generic approaches have not resulted in any clinically viable formulations to date. It is time to understand the underlying causes of such disappointments and find new approaches. Many targeted therapeutics currently used in the clinic are aimed at mitigating the activity of particular cell surface receptors that support cell growth and survival [1]. While these targeted therapies have shown efficacy on newly treated tumors, there is little effective recourse in combating the resistance that develops in the majority of cases.

In this issue, Professor Medina-Kauwe and her team provide a new way of treating patients with inherent or acquired resistance to receptor blockade therapies [2]. Their study shows that a protein-based therapeutic exhibits augmented homing and toxicity to the resistant tumors associated with ErbB3/HER3. They utilized a “Franken-protein”, in which functional domains of naturally occurring gene products have been stitched together through recombinant DNA technology to form a newly created protein chimera. Unlike the majority of clinically approved growth factor receptor inhibitors whose primary function has been to abrogate receptor signaling, the nanobiologic by the Medina-Kauwe team is disguised as an essential ligand for HER3-mediated access to the tumor interior. Like a Trojan Horse, noncovalently-captured drugs contained by the protein can unleash tumoricidal attack once past the tumor cell barrier. The functional domain facilitating this breach is derived from a capsid protein contributing to the same membrane penetrating activity of the adenovirus.

The HER3 specificity of the nanobiologic predicts applicability to a broad range of tumor types, as HER3 is identified as a biomarker on a growing list of different tumors [3]. More importantly, the augmented expression of HER3 associated with therapeutic resistance suggests that such tumors could be particularly high-profile targets for these nanobiologics. The study by the Medina-Kauwe team shows enhanced nanobiologic efficacy on tumor cells with resistant and metastatic phenotypes, which in turn exhibited high cell surface levels of HER3. Models of both acquired and inherent resistance to the ErbB2/HER2 inhibitor, Herceptin<sup>®</sup>, showed elevated expression levels of HER3 and concomitantly augmented nanobiologic activity. As previous studies show that a HER3 increase is also associated with resistance to ErbB1/HER1 (or EGFR) inhibition as well as combination therapy [4], these findings suggest that the nanobiologic could serve as a follow-up therapy for recurrent tumors surviving targeted inhibition of other growth factor receptor family members. An advantage of using a nanobiologic approach for the HER3 targeting is the non-reliance on signal-modulation to effect therapeutic outcome.

The work by the Medina-Kauwe team additionally highlights the compensatory upregulation of HER3 that can occur in acute response to HER2/tyrosine kinase inhibition [5]. This study shows that such a scenario can be exploited by priming naïve tumor cells with HER2

inhibitors several hours before nanobiologic treatment, resulting in increased HER3 display and cornering such tumors for nanobiologic attack. These findings suggest that targeted inhibitors of receptors such as EGFR and HER2 could be repurposed as adjuvants, sensitizing tumors to HER3 nanobiologics. A strategic clinical regimen could thus be undertaken whereby eligible candidates for existing EGFR and/or HER2 targeted therapies receive an initial round of such treatment followed by a chaser of HER3-targeted therapy.

While the nanobiologic approach is highly promising, its clinical efficacy remains to be determined. There are various factors to consider in translation from the mouse model to clinical trials. For example, the non-covalently-captured drugs in the nanobiologics should not be released during blood circulation in humans, and be released only after uptake by the tumor cells. The drastic difference in the blood volume between mice and humans makes it difficult to predict the drug loss during blood circulation. In addition, solid tumors grown in mice may not be the same as the tumors grown in humans over a long period of time. With these cautions in mind, however the nanobiologic approach provides an intriguing paradigm for the future of precision medicine. As the need for more customized precision medicine grows, technologies that can mediate precision delivery of therapies may contribute to the progress and evolution of medical practice. The study in this issue upholds the growing focus on using HER3 as a biomarker for tumor progression and resistance, and indicate that a nanobiologic approach could provide effective supplementation of existing targeted therapies used in the clinic.

## References

- [1] J.T. Hartmann, M. Haap, H.G. Kopp, H.P. Lipp, Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects, *Curr. Drug Metab.* 10 (2009) 470–481.
- [2] J.D. Sims, J.M. Taguam, F. Alonso-Valenteen, J. Markman, H. Agadjanian, D. Chu, J. Lubow, R. Abrol, D. Srinivas, A. Jain, B. Han, Y. Qu, P. Mirzadehgan, J.-Y. Hwang, A. Rentsendorj, A. Chung, J. Lester, B.Y. Karlan, H.B. Gray, Z. Gross, A. Giuliano, X. Cui, L.K. Medina-Kauwe, Resistance to receptor-blocking therapies primes tumors as targets for HER3-homing nanobiologics, *J. Control. Release* 271 (2018) 127–138.
- [3] Y. Lee, J. Ma, H. Lyu, J. Huang, A. Kim, B. Liu, Role of erbB3 receptors in cancer therapeutic resistance, *Acta Biochimica et Biophysica Sinica* 46 (2014) 190–198.
- [4] J.T. Garrett, C.R. Sutton, M.G. Kuba, R.S. Cook, C.L. Arteaga, Dual blockade of HER2 in HER2-overexpressing tumor cells does not completely eliminate HER3 function, *Clin. Cancer Res.* 19 (2013) 610–619.
- [5] J.T. Garrett, M.G. Olivares, C. Rinehart, N.D. Granja-Ingram, V. Sanchez, A. Chakrabarty, B. Dave, R.S. Cook, W. Pao, E. McKinley, H.C. Manning, J. Chang, C.L. Arteaga, Transcriptional and posttranslational up-regulation of HER3 (ErbB3) compensates for inhibition of the HER2 tyrosine kinase, *Proc. Nat. Acad. Sci.*, 108 (2011) 5021–5026.

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