LETTER

REPLY TO KATSU AND BAKER: Using zebrafish PDX to screen drug sensitivity of endocrine-dependent cancers

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Katsu and Baker (1) highlight a potential weakness in using zebrafish patient-derived xenografts (zPDX) (2) for endocrine-dependent tumors. Katsu and Baker (1) report that, unlike human estrogen receptor (ER), progesterone may activate zebrafish mineralocorticoid receptor (MR) instead of inhibiting it (3). Treatment of zPDXs with progesterone would, therefore, possibly activate zebrafish MR and block human MR, leading to a tumor-autonomous effect that would contrast with a nontumor effect in the host.

We would like to highlight the following points regarding their concern. First, zPDXs were primarily designed to screen for chemotherapy standard of care where biomarkers of response are not yet available and where several equivalent chemotherapy options are possible in the therapeutic guidelines. Endocrine-dependent tumors have recognized and validated predictive factors that guide endocrine therapy decisions, namely ER expression status (4). Therefore, endocrine-sensitivity assessment through zPDXs was not a goal of our initial work, as clinicians today have other tools for the prediction of endocrine response. In contrast, the focus of our current research is the prediction of chemotherapy response, mainly in triple-negative or other highly proliferative breast cancers (BC) where chemotherapy is deemed indispensable.

Second, Katsu and Baker (1) studied the evolution of MR and the response to different corticoids of MR of different species, such as human, chicken, alligator, frog, and zebrafish (3). Katsu et al. show that zebrafish MR is activated by progesterone, whereas the human MR is not (1, 3). However, the authors do not take into account the existence of another zebrafish MR (*nr3c1*). This is particularly important because *nr3c1* is the one that has been reported to be expressed during the embryonic/larval stages (the relevant time window for zPDX), whereas *nr3c2* [the zebrafish MR described and studied by Katsu and Baker (1) (NP_001093873)] was described to be only expressed in adults (5).

Third, nonsteroidal aromatase inhibitors and selective ER modulators (tamoxifen or fulvestrant) comprise the mainstay of treatment in ER^+ BC both in the adjuvant and advanced setting and not the progestins (6). In BC clinical practice progestins (like megestrol acetate) are, at the present time, rarely used, being mainly reserved for palliative care to manage cancer-associated anorexia and cachexia.

In summary, because of differences between fish and mammal biology, we anticipate that zPDX may not be adequate for all therapy studies. However, we advocate that controlled experiments should be performed with positive and negative controls for each tested compound, and predictability should be challenged by comparing response to therapy in patients with their matching zPDX.

1 Katsu Y, Baker ME (2018) Progesterone activation of zebrafish mineralocorticoid receptor may influence growth of some transplanted tumors. *Proc Natl Acad Sci USA* 115:E2908–E2909.

2 Fior R, et al. (2017) Single-cell functional and chemosensitive profiling of combinatorial colorectal therapy in zebrafish xenografts. *Proc Natl Acad Sci USA* 114:E8234–E8243.

3 Katsu Y, Oka K, Baker ME (2017) Evolution of steroid specificity in human, chicken, alligator, frog and zebrafish mineralocorticoid receptors: Allosteric interactions affect steroid specificity. *bioRxiv*, 10.1101/151233.

4 Davies C, et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. *Lancet* 378:771–784.

5 Bertrand S, et al. (2007) Unexpected novel relational links uncovered by extensive developmental profiling of nuclear receptor expression. *PLoS Genet* 3:e188.

6 Cardoso F, et al. (2017) 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol* 28:16–33.

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The authors declare no conflict of interest.

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Published online March 12, 2018.