CK1δ: an exploitable vulnerability in breast cancer

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We do appreciate the interest and perspectives of Drs. Cheong and Virshup, who succinctly summarize and highlight the advances of our original manuscript (1). In addition to stressing the potential translational importance of our studies, Drs. Cheong and Virshup also note that our studies inevitably raise important questions. Here we elaborate on the questions raised in their perspective.

Cheong and Virshup raise three important issues that we seek to address. In particular: (I) are there off-target effects of SR-3029 that contribute to its anti-cancer activity; (II) is the potent anti-breast cancer activity associated with CK1δ inhibition solely mediated by inhibition of Wnt/β-catenin signaling; and (III) does Wnt/β-catenin signaling drive important aspects of breast carcinogenesis.

As previously documented (2), we have gone to great lengths to characterize the kinase inhibitor profile of SR-3029 using two separate kinase profiling platforms. These analyses, and the crystal structures of SR3029 bound to CK1δ and CK1ε (Roush and Knapp, unpublished), have revealed that SR-3029 is a highly selective dual CK1δ/CK1ε inhibitor, and that other kinases that are weakly inhibited (10-fold lower Kd) by SR-3029 (e.g., FLT3) have little to do with the anti-cancer activity of SR-3029 (2). Further, profiling SR-3029 against a panel of ion channels, GPCRs, and other enzyme targets using the Ricerca Lead Profiling platform revealed that SR-3029 had no significant activity against any of the proteins tested. Along with our genetic studies showing that specific silencing of CK1δ mimics the effects of SR-3029 (1), these data are consistent with CK1δ being the relevant anti-cancer target of SR-3029.

Secondly, the data presented in our studies clearly indicate that inhibition, silencing or overexpression CK1δ all affect β-catenin signaling in breast cancer. Indeed, our findings provide an explanation for the aberrant activation of the Wnt/β-catenin pathway that is manifest in subtypes of breast cancer in the absence of conventional pathway-activating mutations, and they suggest a novel strategy to disable this pathway. We agree with Cheong and Virshup that, in addition to β-catenin, there are likely other CK1δ targets that contribute to the anti-cancer action of SR-3029. Indeed, as the authors note it is well established that CK1δ alters the activity of several protein substrates with known roles in cancer, including MDM2 (3), p53 (4), and Wee-1 (5), and it also phosphorylates Ltv-1, 40S subunit ribosome assembly factor (6). Accordingly, the anti-cancer action of SR-3029 may involve the sum of these actions, and perhaps others that remain to be determined. Regardless, SR-3029 and its analogues will be important tools to interrogate the role of CK1δ in mediating the progression and metastases of breast cancer.

Finally, we respectfully submit that Wnt/β-catenin signaling has been clearly linked to breast cancer. Indeed Muller and colleagues have convincingly shown that β-catenin contributes to ErbB2-mediated mammary tumor progression (7) and nuclear localization of of β-catenin is associated with poor outcome in breast cancer patients (8). Further, recent reports suggest a role for Wnt/β-catenin signaling in breast cancer cell invasion, latency and metastasis (9,10). Interestingly, studies that interrupt autocrine Wnt signaling have reported opposing results,

where Covey and colleagues have reported that blocking Wnt secretion has little effect on the proliferation of most breast cancer cells *in vitro* or *in vivo* (11). In contrast, other groups have shown that blocking autocrine Wnt signaling, via expression of the Wnt inhibitor sFRP1, markedly impairs breast cancer cell proliferation and metastases (12,13). Whether these reports can be reconciled based on how Wnt signaling is interrupted remains to be determined. Our studies demonstrated that silencing CK1δ directly leads to the down-regulation of Wnt3 and Wnt9A expression, and induces the expression of the Wnt antagonist sFRP1.

We thank Drs. Cheong and Virshup for their observations and for the opportunity to respond to their *Perspective*. Defining the mechanism whereby CK1δ activates β-catenin and its importance in promoting breast cancer is the focus of ongoing investigations.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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