Another aspect in use of DMSO in medicinal chemistry

Drug discovery and development might be a long and arduous journey. A brave traveler steps forward enthusiastically, but unfortunately and almost always gets lost and comes back to the beginning, and thus only rarely gains a fruit in mind. Rather, the envisioned fruit is often found to be in turn a superficial artifact that is generated by a false positive hit at the initial screening. In other words, a misconception in the early stage unintentionally masks a sign of misfortune and merely invites us to a futile journey. How do we justly decline the catchy invitation? Or is there any traffic light for go or no go decision in the very early stage of journey?

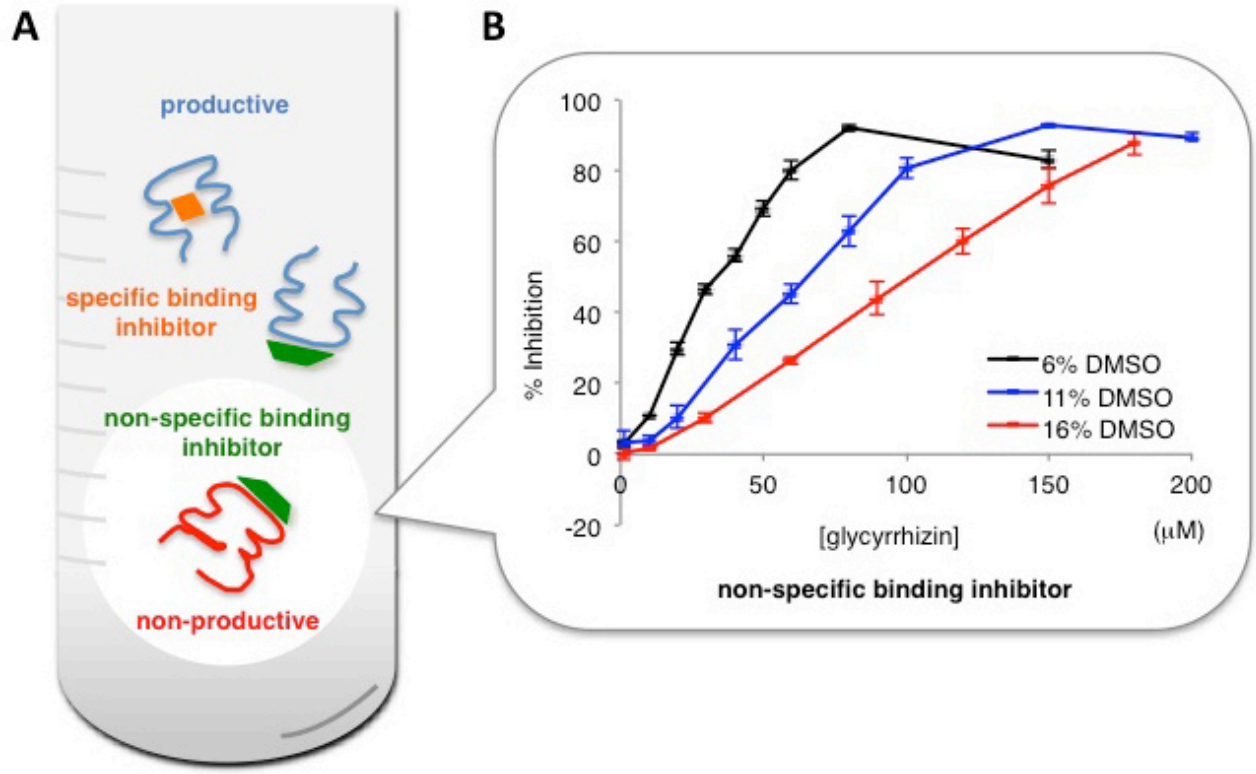

Fig. 1. A: Under in vitro DMSO-perturbed assay conditions, a non-productive enzyme captures a non-specific binding inhibitor. B: Concentration-response curve of non-specific binding hyaluronidase inhibitor.

A DMSO (dimethyl sulfoxide) dissolves both hydrophobic and hydrophilic molecules easily, and thereby serves as a lubricant over the whole course of drug discovery and development. It is also well known that DMSO perturbs dynamic conformation of enzyme and therefore has been widely used to the structural or mechanistic characterizations of enzyme concerning the native structure, folding/unfolding process, reactivity, and binding affinity to ligand. Thus, DMSO plays a central role

in the field of structural biology. Here, can the effect of DMSO in the field of drug discovery and development be ignored? Rather, could DMSO possibly act a central character and shed some light on the concerns in drug discovery and development?

Here, we provide the answers for these concerns. A DMSO causes the conformational changes in native enzyme in a concentration-response manner. Although the conformational changes of enzyme in the presence of DMSO could not be explicitly described because of the existence of multiple dynamic conformations, the overall species could be reduced to two populations in terms of catalytic site availability: one is an assembly of productive enzymes with ability to react with original ligand, and the other is non-productive one. Here, an intriguing implication of our study is that a non-productive enzyme is an assembly of effective species to capture non-specific binding inhibitor (Fig. 1A), and the interaction attenuates the inhibitory activity of non-specific binding inhibitor. The attenuation under DMSO-perturbed assay conditions could be easily observed in usual concentration-response curves of inhibitors (Fig. 1B).

In our study, structurally diverse eight hyaluronidase inhibitors were mechanistically evaluated both under a well-established detergent-addition conditions (Shoichet's protocol) and our DMSO-perturbed assay conditions to identify two aggregating inhibitors and three non-specific binding inhibitors, respectively. Thus, we could successfully highlight non-specific binding inhibitors, one aspect of false positives, under DMSO-perturbed assay conditions.

Honestly, we have to say that this fledgling methodology still remains to be fully established for the following reasons. Firstly, the present study has been developed only with a relatively small group of hyaluronidase inhibitors. Secondly, although a key implication of this description is that the DMSO-perturbed assay conditions generates non-productive enzyme, the proof of its generation has remained to be well provided. Therefore, a future study will be focused on the validation with other enzyme inhibitors as well as the characterization of conformational changes of enzyme under DMSO-perturbed assay conditions. A better understanding of our methodology will then provide us with a pleasant journey of drug discovery and development.

Keisuke Tomohara
Department of Hospital Pharmacy, University of Toyama, Toyama, Japan

Publication

Interpreting the behavior of concentration-response curves of hyaluronidase inhibitors under DMSO-perturbed assay conditions.
Tomohara K, Ito T, Onikata S, Furusawa K, Kato A, Adachi I
Bioorg Med Chem Lett. 2016 Jul 1