EDITORIAL COMMENT

The Art of War in Drug Development*

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Drug development is one of the major goals of translational medicine, but for each victory in bringing a drug to market, there are all too many unseen candidate "corpses" relegated to the graveyard of drug discovery. In 2019, there were 16,181 drugs in the research and development (R&D) pipeline according to Pharma R & D Annual Review 2019 (1). Although this number represents an increase of 6.0% over the previous year, a consistently upward trend in the industry, those reaching registration numbered only 152, approximately 1.0% of those in the pre-registration phase (n = 14,585) in 2019. In addition to the low success rate of drug development, the time and cost of bringing a new drug from concept to market are growing, exceeding 10 years and $2.5 billion, respectively (2,3). Recently, various major pharmaceutical companies announced the termination of the following 6 phase III clinical trials of their anti-Alzheimer drugs, apparently because no effectiveness could be demonstrated compared to placebo in each trial: APECS (Efficacy and Safety Trial of Verubecestat [MK-8931] in Participants With Prodromal Alzheimer's Disease [MK-8931-019]; NCT01953601); AMARANTH (An Efficacy and Safety Study of Lanabecestat [LY3314814] in Early Alzheimer's Disease; NCT02245737); CREAD (A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants With Prodromal to Mild Alzheimer's Disease [AD]; NCT02670083); CREAD 2 (A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants With Prodromal to Mild Alzheimer's Disease [AD]; NCT03114657); ENGAGE (221AD301 Phase 3 Study of Aducanumab [BIIB037] in Early Alzheimer's Disease; NCT02477800); and EMERGE (221AD302 Phase 3 Study of Aducanumab [BIIB037] in Early Alzheimer's Disease; NCT02484547).

These sobering facts are stark reminders that the gate to victory in drug development is narrow indeed.

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In this issue of *JACC: Basic to Translational Science*, the study by Ide et al. (4) reports a promising new drug for the reduction of myocardial ischemic injury. As suggested by its name, the Kyoto University substance 121 (KUS121) drug is a part of the drug discovery program at the Kyoto University. In the study (4), the authors showed that KUS121, a selective inhibitor of the ATPase activity of valosin-containing protein, reduced the size of myocardial infarction (MI) (e.g., 25% of the left ventricle) when it was given prior to ischemia or at the time of reperfusion in mice. After several experiments in mice, the authors extended the study to a pig model of 60-min ischemia-reperfusion and reproduced the beneficial effects observed in mice. Specifically, the single intra-coronary administration of KUS121 at the time of reperfusion reduced infarct size in a dose-dependent manner in a clinically relevant animal model. The highest dose achieved a reduction of more than 50% in infarct size compared to that in the control group, highlighting its promising effect, which prompted further clinical translation of this drug. The mechanism of action seems to be multimodal. Using in vitro systems and mouse models, the authors showed inhibition of endoplasmic reticulum (ER) stress, preservation of mitochondrial function, and preservation

of myocardial ATP as potential contributors (4). The main strength of the study by Ide et al. (4) is its use of several experimental models from cells to pigs, rendering the study highly translational. Streamlined translational experiments certainly expedite the drug development process, and the authors already foresee a clinical trial.

Although a multimodal effect of the drug was extensively demonstrated by several approaches, it remained unclear which effect was most important for MI size reduction. Identifying the major effector of the drug is important because that would determine the most effective means of administering the drug for a particular disease. For example, if ATP preservation is the major effect of KUS121, administering the drug after reperfusion may not lead to a significant benefit. This seems not to be the case for KUS121, because the drug was also effective when given at the time of reperfusion. In addition, the lack of a difference in infarct size reduction between the drug given prior to ischemia and at the time of reperfusion (see Figure 4C and Online Figure 3C in the paper by Ide et al. [4]) suggests rather that ATP preservation is not the major effect or, at least, does not offer additional benefit when the drug is also administered at the time of reperfusion. Meanwhile, infarct size in mice given KUS121 just once at the time of reperfusion was approximately 25% in contrast to approximately 20% in animals given multiple doses after reperfusion. Although the infarct size of control animals probably differed because of a different study setting, multiple drug administrations might have resulted in additional infarct reduction. A potential beneficial effect produced by multiple administrations of KUS121 may be related to reduction of ER stress and subsequent attenuation of cell death signals, because theoretically, they can act during the post-reperfusion period. Unfortunately, the effect of additional doses after reperfusion was not tested in pigs. Therefore, the pig study suggests that a single intracoronary dose is effective, but whether it is sufficient to produce a maximal effect remains

unknown. Additionally, the route of delivery also requires careful consideration. Although intracoronary delivery of KUS121 was likely to increase cardiac specificity in the pig study, intravenous injection could be combined before reperfusion if ATP preservation effect was achieved through this approach and offers benefit. Therefore, although the study by Ide et al. (4) demonstrated promising effects of KUS121 in multiple experimental models, there may be room for further improvement. Considering the number of candidate drugs that failed to gain entry into the armamentarium for managing MI, it is prudent for any regimen with the potential to achieve maximum benefit for reducing infarct size to be intensely scrutinized. For that purpose, understanding the major mechanisms of action of a drug is critically important.

In the ancient Chinese military treatise, "The Art of War," SunTzu wrote: "Thus we may say that if you know yourself and know your enemy, you will gain victory a hundred times out of a hundred. If you know yourself but do not know your enemy, you will meet one defeat for every victory. If you know neither yourself nor your enemy, you will never be victorious" (5). This quote from the 5th Century B.C. not only taught ancient generals about strategy on the battlefield, it also guides modern researchers in dealing with the difficult tasks inherent in drug development. Our understanding of the enemy (myocardial ischemic injury) is improving daily, but we are still far from "knowing" it. It is essential that our efforts to know ourselves (how the drug works) are painstaking in order not to become another drug corpse in the battle of drug development.

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