ALDH2 for the heart

By Brian Moy, Staff Writer

Researchers at **Stanford University School of Medicine** and **Indiana University School of Medicine** have shown that activation of the mitochondrial aldehyde dehydrogenase 2 enzyme correlates with less ischemic heart damage following myocardial infarction. The group also has identified a small molecule activator of the enzyme that could be useful for limiting ischemia-induced cardiac damage that occurs in MI and coronary artery bypass graft surgery.[1]

According to university and industry researchers polled by *SciBX*, therapeutic application of these findings will hinge on timing, dosage and potential side effects of such aldehyde dehydrogenase 2 (ALDH2) activators, as well as identifying the most appropriate patient populations for treatment.

As published in *Science*, Daria Mochly-Rosen, professor in the Department of Chemical and Systems Biology at the Stanford medical school, and colleagues from both universities used a proteomic approach to identify proteins whose phosphorylation correlated with less cardiac damage from ischemia. In ischemic rat hearts, they found that increased phosphorylation of ALDH2 was consistently associated with cardioprotection from ischemia.

Additionally, a high throughput screen for activators of ALDH2 identified Alda-1, a small molecule substituted dichlorobenzamide. In a rat model of acute MI, administration of Alda-1 into the left ventricle five minutes before an ischemic event lowered infarct size by 60% compared with that seen in vehicle-treated controls ($p<0.01$).

Mochly-Rosen told *SciBX* that "the importance of Alda-1 is not only that the compound activates basal activity of ALDH2, but it also prevents inactivation of the enzyme by its substrate," an aldehyde called 4-hydroxynonenal (4HNE).

4HNE is a toxin that accumulates during cardiac ischemia.[2] It induces rapid inactivation of ALDH2 by forming protein adducts within the enzyme.

In vitro, Alda-1 blocked 4HNE-induced inactivation of ALDH2. Thus, the authors wrote that the molecular basis for Alda-1-induced ALDH2 protection "is probably due to prevention of 4HNE adduct formation on ALDH2."

Alda-1 also is able to restore the activity of ALDH2*2, an inactive mutant form of ALDH2 found in about 40% of East Asian populations. "It is rare to find a small molecule that can specifically rescue a mutation in humans," the researchers wrote.

According to Gregory Bell, SVP of development and CMO at **KAI Pharmaceuticals Inc.**, another potential use of Alda-1 is to mimic ischemic preconditioning of the heart or other organs, such as the brain, kidneys or liver.

Preconditioning is a protective mechanism in which short periods of low or no oxygen to the heart or other organs can confer resistance to longer periods of ischemia and therefore limit the amount of damage that occurs to the organ following ischemia. "A treatment that mimics ischemic preconditioning is something that researchers have been trying to develop for years," said Bell.

Furthermore, said Mochly-Rosen, Alda-1 may be useful in conjunction with nitroglycerin treatment. Nitroglycerin is often administered chronically to patients with unstable angina, acute MI and acute coronary syndrome (ACS); the drug confers cardiac protection when it is metabolized by ALDH2 and generates the vasodilator nitric oxide (NO).

But prolonged treatment with nitroglycerin decreases ALDH2 activity,[3] so individuals with an ALDH2*2 mutation might benefit more from Alda-1 than carriers of wild-type ALDH2.

"Patients with ALDH2*2 are expected to have already reduced natural protection from ischemic injury, and treatment with nitroglycerin may reduce this protection even further," said Mochly-Rosen. Thus, Alda-1, which inhibits nitroglycerin tolerance and increases bioconversion of nitroglycerin to NO, may be more beneficial in those with an ALDH2*2 mutation, she said.

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> *—Gregory Bell, KAI Pharmaceuticals Inc.*

Mochly-Rosen also noted that ALDH2 is located in mitochondria, which are permeable to small molecules, suggesting that a compound such as Alda-1 should be highly effective in activating the enzyme.

Optimal activation

Junichi Sadoshima, vice chairman of the Department of Cell Biology and Molecular Medicine at **New Jersey Medical School**, said that "because cardiac ischemia is one of the leading causes of death, a small molecule that can greatly reduce myocardial injury would have a significant impact."

However, he thinks it is too early to talk about the use of Alda-1 in the clinic. "It is not clear how the compound would be delivered or what the side effects and pharmacokinetic properties of the compound are," he said.

In addition, it is not clear what sort of patient population would benefit most from a compound that activates ALDH2.

Indeed, patients do not know when an MI will occur, so a molecule that activates ALDH2 would need to be chronically administered to be effective in lowering infarct size during an MI.

"You would have to deliver the drug immediately before the ischemic event occurs," which is difficult in patients presenting with MI,

noted Elizabeth McNally, a professor in the Department of Medicine and director of the Institute for Cardiovascular Research at the **University of Chicago**.

"A small molecule activator of ALDH2 would be most useful in an acute, short-term setting in patients who are at high risk for ischemic injuries during planned surgeries, such as coronary artery bypass graft surgery or other major vascular surgery," said Bell.

KAI is developing KAI-1455, a protein kinase C_ε (PKC_ε) activator in Phase I testing to treat ischemia-induced reperfusion injury. Mochly-Rosen, who is also the founder of KAI, and colleagues previously showed that ethanol and selective activation of PKC_ε mimic ischemic preconditioning and lower infarct size.[4]

In contrast to Bell, Kai Pinkernell, head of research at **Cytori Therapeutics Inc.**, thinks Alda-1 could be well suited to longer-term use. "Chronic administration of an ALDH2 activator could be useful for treating patients at high risk for MI, such as those with angina or chronic ischemic heart disease," he said.

Cytori's adipose tissue–derived stem and regenerative cell therapy device is in feasibility testing to repair heart muscle damaged from heart attacks or chronic ischemic heart disease.

Ongoing studies by Mochly-Rosen and colleagues are aimed at improving the pharmacokinetics of Alda-1, investigating the benefits of administering the compound following ischemic damage and determining the effects of chronic treatment.

Additionally, the researchers are investigating whether Alda-1 has utility in other diseases associated with higher accumulation of 4HNE and lower ALDH2 activity, as well as diseases that occur more frequently in individuals carrying an ALDH2*2 mutation. These include chronic conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD).

The findings of the *Science* paper, as well as Alda-1 and its derivatives, are patented by Stanford and available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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