achieved a reliable model capable of producing severe reperfusion injury of the lungs similar to that seen in clinical lung transplantation.

CONCLUSIONS
IR injury remains a substantial cause of morbidity and mortality after lung transplantation. Novel methods to protect allografts during recovery will not only decrease the incidence of PGD and chronic graft failure, but also may embolden centers to use marginal donors with increased ischemic times, thus increasing the currently limited donor supply. In this study, we have examined the use of a long-acting oral PDE inhibitor for donor preconditioning in a model of IR injury. Our data demonstrate that this strategy is effective for improving pulmonary performance and decreasing oxygen-derived free radical levels after reperfusion. PDE enzymes and their downstream effectors may play a critical role in reperfusion injury after lung transplantation.

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References

Discussion
Dr Christine L. Lau (Charlottesville, Va). My congratulations to Dr Weiss and the Johns Hopkins group for another outstanding presentation in the area of lung transplantation.

IR injury remains a major morbidity and potential mortality early after lung transplantation, and, importantly, now it is known to be a major risk factor for the development of bronchiolitis obliterans. In this current study, the authors show in an experimental ex vivo lung transplant model that oral preconditioning of the donor with a PDE inhibitor leads to a decrease in IR injury, as evidenced by markers of Pao2, PAP, and ROS. As pointed out, however, the concept of PDE inhibitors to limit IR injury is not entirely new. Others have shown similar benefits in the treatment of IR to those described in this study with the use of intravenous sildenafil as well as with other PDE inhibitors, specifically PDE-4 inhibitors. This current study, however, does add to the previous investigations.
by looking at an oral long-acting agent and thus has some obvious advantages.

I have two questions. As you know, the primary effect of PDE-5 activity is on cyclic GMP levels and, in turn, stimulation of PKG. Cyclic GMP also can influence other PDEs that in turn regulate cyclic adenosine monophosphate and, thus, lung function. Do you plan to evaluate the synergy with other cyclic nucleotide PDEs, for example, PDE-4 inhibition? Second, what are your plans for future studies? Do you plan to look at leukocyte trafficking and platelet function, histology, and immunohistochemistry, and do you plan any clinical trials?

Dr Weiss. Thank you, Dr Lau, for your critique and for your questions and comments.

You bring up an excellent point regarding PDE-4. Certainly others, including excellent work from the investigators at the University of Virginia, have looked at activation of the PDE-4 enzyme in models of IR injury. To contrast the difference between PDE-4 and PDE-5, PDE-4 breaks down cyclic adenosine and PDE-5 breaks down cyclic GMP; PDE-4 is generally found in inflammatory cells whereas PDE-5 is generally located in endothelial cells. Although these are generalizations, thinking about the enzymes in that manner can help us understand their principal activity. We do not know to what extent tadalafil acts on PDE-4. I suspect that there is some synergy, and we do plan to investigate that aspect in future experiments. The answer to your question is yes. I think that this brings up an opportunity for dual therapy with both PDE-5 and PDE-4 inhibitors. We would be interested in exploring that.

In terms of our future directions, we want to make our model more clinically applicable. For example, we are interested in examining brain death in our model and we are interested in examining the effect in a long-term survival model. There is some indication from our data that the effect may be short-lived, and so we need to focus on dosing and redosing as well. We are also interested in looking at platelet function. Finally, we want to examine the role of PDE enzymes in human lung tissue. We have an approved protocol at our institution to examine human lung tissue after reperfusion that would have otherwise been discarded. These are some of the future directions that we are interested in exploring.

Dr Yolonda L. Colson (Boston, Mass). Is most of this effect just owing to changes in platelet function with your perfusion with the drug on board, and do you have a control to control for changes in platelet function?

Dr Weiss. Thank you, Dr Colson, for that question. Although we know that PDE inhibition can affect platelet function, it is not likely in our model inasmuch as we are pretreating the donor. We flush out most of the blood during recovery and it is therefore unlikely that recipient platelets are exposed to the drug.

Dr Colson. You could argue that the PDE is just changing platelet function, and if you are not having microemboli, your PAP is lower and your oxygenation is higher.

Dr Weiss. That is true. We did not measure recipient serum levels of PDE inhibition to prove that the platelets are unaffected. I think your point is well taken and may be a good reason to give PDE inhibitors to recipients before transplantation, to decrease injurious platelet behavior.