the context of a prospective trial, we cannot exclude the possibility of multiple vaccine interactions; however, it appears unlikely at this time.

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A Simple, Inexpensive, Rapid, and Accurate Preclinical Model for In-Stent Restenosis

With great interest we read the recent review by Schwartz et al. (1) regarding preclinical animal restenosis models. Detailed descriptions of the current available animal restenosis models, the pathophysiology of in-stent restenosis (ISR), and the usefulness of animal restenosis models to predict clinical outcomes are presented. In the final remarks it is concluded that preclinical models are important but imperfect standards. A simple, inexpensive, rapid, and accurate preclinical model would be useful. However, in their description of available restenosis models, Schwartz et al. (1) overlooked two important and recently developed animal models of ISR. In these models, stents are implanted in the carotid artery (2) or in the abdominal aorta (3) of the rat. Pathophysiological processes of neoinitmal formation, such as thrombus formation, inflammation, and smooth muscle cell proliferation, evolve in an identical manner as seen in the rabbit iliac and pig coronary artery models. Moreover, in the rat abdominal aorta model, a positive correlation is found between the mean injury score and the neointimal area (2,3).

Rat ISR models enable thorough pathophysiological studies, as many antibodies to cellular proteins are available in the rat as compared to rabbits and pigs. By elucidation of the pathophysiology of ISR, more purposeful experiments to prevent ISR can be carried out. Rat models of ISR could provide important indications for the development of new anti-restenotic strategies (3). Generally, rat studies are preferable over rabbit or pig studies; only mainstream surgical equipment is required, animal facilities have large housing capacity for rats, and the costs for purchase are low.

Discrepancies between efficacy of anti-restenotic agents in preclinical and clinical studies have caused skepticism about the rat carotid artery model. For rat stent models this skepticism should be tempered, because differences in pathophysiological mechanisms between neointimal formation after balloon dilation alone and stent implantation are evident. Furthermore, rapamycin-eluting stents have been shown to inhibit neointimal formation in the rat abdominal aorta, a clear relation between preclinical and clinical outcomes in this model (3). In addition, these rat models enable stent research in transgenic diabetic and hypertensive strains. This offers a truer reflection of clinical settings in preclinical experiments, and might result in a better prediction of efficacy of anti-restenotic agents in clinical trials (2,3).

In conclusion, rat models are simple, inexpensive, rapid, and accurate preclinical models for ISR.

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REPLY

We read with interest the comments of Dr. Langeveld and colleagues concerning our recent review of preclinical restenosis models (1). These investigators write that stenting the rat carotid or abdominal artery provides a "simple, inexpensive, rapid, and accurate preclinical model for in-stent restenosis." We have several comments in response regarding the utility of the rat model.

A useful in-stent restenosis animal model should accurately predict: 1) safety, 2) efficacy, and 3) pathophysiologic mechanisms. These are addressed as follows.

Safety. The major safety issues for stents are thrombosis (acute or subacute) and neointimal thickening causing luminal stenosis. Although the rat model sometimes induces stent thrombosis, it does so to a lesser extent than the porcine and rabbit models. Total occlusion and severe stent stenosis do not generally occur in the rat model.

Efficacy. Rat carotid restenosis models were abandoned years ago because virtually all therapies that were tested and effective in rats later proved ineffective in patients. Such studies included