“THE USE OF ANIMALS IN RESEARCH WILL BE NECESSARY TO HELP DRIVE SCIENTIFIC DISCOVERY IN” (CARDIAC SURGERY)!

To the Editor:

Our study¹ on the efficacy of St. Thomas' Hospital “polarized” blood cardioplegia elicited a commentary from Hameed and Gaudino² that questions the relevance of biomedical research and, in particular, clinical relevance of our study. In the last century, medical knowledge about the cardiovascular system has been defined by biomedical research (eg, isolated organs, discovery of heparin in animal liver extracts) and, finally, the development of cardiopulmonary bypass by Gibbon³ has paved the way for cardiac surgery.

We chose to model clinical cardiopulmonary bypass using pigs due to their anatomical and cardiac similarity to the human heart⁴ to avoid as much heterogeneity⁵ as possible. Our aim was to progress this novel cardioplegia from our initial basic science studies in isolated rat hearts to a “first-in-human” clinical trial. Therefore, we described the effect of 60 minutes of ischemia without adding any potential interactions of additional surgery. As known by anyone who has ever tried to translate science into clinical practice, one needs to address certain safety milestones (for example, testing new drugs in 2 independent species, route of application, temperature, etc) to receive ethical and regulatory approval.⁶ Indeed, without these porcine experiments, study patients would, potentially, have to deal with significant consequences, such as insufficient cardiac arrest due to only estimated optimal temperature at administration, incomplete myocardial protection due to untested dosage of components, and unknown intervals of administration. It is a *conditio sine qua non* for biomedical research scientists that any animal experiment, independent of the species, has to be constantly re-evaluated by the 3 Rs (reduction, refinement, and replacement). Although we follow these principles in our daily practice, specific research relating to advances in cardiac surgery, such as the development of a novel cardioplegic solution, cannot be performed solely on the bench.⁴ For our upcoming “first-in-human” trial, these reported results¹ have been

of eminent importance and requested by the ethical committee!

We have been pursuing this “ultimate goal of animal research”⁵ over the years, which is “translation to human clinical research.”⁵ Noteworthy, this next step will confirm that our animal study is within the one third of publications that finally translate into clinical trials.⁷ In addition, it underlines that our biomedical research team has the vision to be prepared for future challenges of cardiac surgery: older and sicker patients.

We invite the critics of animal studies to consider for themselves whether they would be prepared to undergo a new surgical procedure or device implantation that has never been previously tested in any comparable living species. If animal experiments should not be performed before “first-in-human” trials, would these critics be willing to serve as the first study patients or would they prefer someone else to step ahead? So, yes, we fully agree with the recent review from Robinson and colleagues,⁵ in which it is stated that “The contribution animal’s models have had to human research is undeniable. Many modern advancements simply would not have been made possible without a high fidelity, highly producible model, with the added benefit of preventing potential human harm.”

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The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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REPLY FROM AUTHORS: ARE WE REALLY REDUCING, REFINING, AND REPLACING?

Reply to the Editor:

We read Santer and colleagues' letter on our Commentary regarding their study on St Thomas' Hospital polarized blood cardioplegia in a porcine model.¹

Their reply is both welcome and expected. There is no doubt that animal models have contributed greatly to the field of medicine, and, more specifically, cardiovascular surgery. As we move into a new decade of innovation, however, we must question the clinical relevance of current studies.

As we wrote in our Editorial Commentary, physicians and scientists should not kill, especially for nothing. Although animal research is important, it should be limited to studies with a solid scientific protocol and rationale, as well as very clear clinical implications. To the former point, it is well established that preclinical animal studies are fraught with methodologic inadequacies, and the report by Santer and colleagues is no exception, as highlighted in our commentary.² This has led to poor clinical translation. Although the authors report that up to one third of animal studies translate into clinical trials, we have found otherwise, with just 20% of more than 400 preclinical animal investigations published over the past 10 years being cited in a subsequent human clinical trial (Figure 1).³ Furthermore, less than one half of the studies had solid methodology, and the majority of them provided results that were then contradicted by larger randomized trials (19%) or published findings that were never tested in humans (45%).⁴

Clinical translation is made more difficult by the complexity of the contemporary patient population undergoing cardiac surgery. In a recent publication in the *European Heart Journal*, Cesarovic and colleagues⁵ discuss the need to transition away from single- to multi-disease models, a feat that is becoming increasingly difficult as patients undergoing cardiac surgery become older and have multiple comorbidities. In their

FIGURE 1. In an analysis of 411 studies using surgical animal models published between 2008 and 2018, it was found that the original article was cited a median number of 1 time with a majority of citations in animal/basic science articles (78.6%) and a minority in human/clinical research studies (21.4%). Interpretation: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; thick horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Circles represent outliers. Adapted from Ruan and colleagues.³