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MAMMALIAN MEAT ALLERGY AND ADVANCES IN BIOPROSTHETIC VALVE TECHNOLOGY

Reply to the Editor:

We read with interest the letter to the editor by Ankersmit and colleagues,¹ “When Meat Allergy Meets Cardiac Surgery: A Driver for Humanized Bioprosthesis.” The University of Virginia has led the epidemiologic characterization of the mammalian meat allergy to galactose- α -1,3-galactose (α -gal) believed to arise after inoculation by the Lone Star tick.² We have correlated this to the development of anaphylactic reactions after implantation of bioprosthetic valves in patients who already have the allergy and to the rapid degeneration of bioprosthetic valves in patients who subsequently acquire the allergy.^{3,4} Because all current porcine and bovine bioprosthetic valves contain α -gal, this allergy can be a serious concern for cardiac surgeons and a major consideration in prosthesis selection. In the United States, mammalian meat allergy is primarily concentrated in the

southeast, but cases have been noted throughout the country and internationally. The importance of α -gal, however, is not limited to this specific allergy.

As noted by Ankersmit and colleagues,¹ the link between α -gal and bioprosthetic valves has been known for more than a decade, and the α -gal allergy is likely unmasking immune-related degeneration that is occurring in all patients.⁵ This has been well described and helps explain age-dependent speed of degeneration.⁶⁻⁹ Moreover, immune-related valve degeneration was attenuated in a porcine model deficient of α -gal.¹⁰ Although no α -gal deficient valves are currently available, we disagree that little progress has been made in investigating the impact of and solutions to the problem of α -gal. Ankersmit and colleagues¹ note 2 potential solutions with α -galactosidase and detergent-based decellularization; however, these are certainly not the only options, and might not be the best solutions.

A decade before the discovery of the α -gal-specific humoral response to valve implantation, researchers identified α -gal as one of the main immune targets leading to hyperacute rejection in xenotransplantation.¹¹ Since then, researchers have been trying to sidestep this problem by using α -gal knockout pigs from Revivacor, Inc (Blacksburg, Va). The recent widespread adoption of CRISPR/cas9 genome editing technology has meant rapid genetic modifications that have increased xenograft longevity.¹²

It is to be hoped that recent investment in xenotransplantation will translate to improved and more durable bioprosthetic valves.¹³ As a first step, recent studies demonstrated equivalent physical properties of α -gal-deficient pericardium.^{14,15} The main benefit to CRISPR is the ability to perform multiple genetic manipulations simply and efficiently. Of course, α -gal is not the only immunogenic carbohydrate antigen present in bioprosthetic heart valves, and the next generation of valves should address them all.^{16,17} In this regard, multiple genetic modifications to carbohydrate antigens shows promise in reducing xenograft immunogenicity.¹⁸

Although there is little evidence that device companies are aggressively developing solutions for carbohydrate antigens, the process for bringing these advances to market is long; the Food and Drug Administration regulates not only the new valve but also the genetically modified animal. With 3 potential solutions to alleviate α -gal-related bioprosthetic valve degeneration, we hope that the academic and biotechnology communities can come together to find the best option and bring this to market rapidly. We must work together to continue improving the care of our patients.

Robert B. Hawkins, MD, MSc^a

Ravi K. Ghanta, MD^b

^aDivision of Thoracic and Cardiovascular Surgery

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Department of Surgery
University of Virginia
Charlottesville, Va

^bDivision of Cardiothoracic Surgery
Department of Surgery
Baylor College of Medicine
Houston, Tex

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