BIOGRAPHICAL SKETCH

NAME: Christopher Kane Breuer

eRA COMMONS USER NAME: cbreuer

POSITION TITLE: Professor of Surgery

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
College of the Holy Cross	BA	08/82-05/86	Biology
Brown/Dartmouth Program in Medicine	MD	08/86-05/90	Medicine
Brown University Program in Surgery		07/90-06/92 & 07/95-06/97	General Surgery
Harvard Medical School		07/92-06/95	Tissue Engineering
Brown University Program in Pediatric Surgery		07/97-06/99	Pediatric Surgery

A. Personal Statement

As the Director of the Tissue Engineering Program at The Research Institute at Nationwide Children's Hospital, I have been given extraordinary resources for performing my work. We have established a Translational Cardiovascular Tissue-Engineering Program. Our overarching goal is to improve our ability to treat infants born with complex cardiac anomalies through the development and application of tissue engineering to create vascular grafts, patches, and replacement heart valves for use in congenital heart surgery. Using the tissue engineered vascular graft as a prototype, our long-term plan is to develop tissue engineered constructs from autologous cells seeded onto biodegradable scaffolds that can be used to make living neotissues, which in turn can be used to repair or replace anomalous or atretic tissues in children with complex congenital heart disease. I have the leadership, training, expertise, and motivation necessary to successfully carry out the research described in this proposal, and hopefully in the process begin to improve the outcomes of children born with congenital cardiac anomalies.

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1) Patterson JT, Gilliland T, Maxfield MW, Church S, Naito Y, Shinoka T, **Breuer CK**. Tissue-engineered vascular grafts for use in the treatment of congenital heart disease: from the bench to the clinic and back again. Regen Med. 2012 May;7(3):409-19. Review.

2) Prestwich GD, Bhatia S, **Breuer CK**, Dahl SL, Mason C, McFarland R, McQuillan DJ, Sackler-Bernstein J, Schox J, Tente WE, Trounson A. What is the greatest regulatory challenge in the translation of biomaterials to the clinic? *Sci Transl Med*. 2012; 4(160):160 cm14.

B. Positions and Honors

Positions and Employment

1999-2003 Attending Pediatric Surgeon, Wilford Hall Medical Center, Lackland AFB, San Antonio, TX
2000-2003 Associate Scientist, Southwest Primate Facility, San Antonio, TX
2003-2009 Assistant Professor, Department of Surgery, Yale University, School of Medicine, New Haven, CT
2007-2012 Associate Professor, Department of Surgery, Yale University, School of Medicine, New Haven, CT
2012-present Professor with Tenure, Department of Surgery, Division of Pediatric Surgery, The Ohio State University, Columbus, OH

2012-present Director of Tissue Engineering Program, Nationwide Children's Hospital Research Institute, Nationwide Children's Hospital, Columbus, OH

Professional Service

Officer United States Air Force (Second Lieutenant - Lieutenant Colonel) (1986-2003)
Peer Review Committee American Heart Association Bioengineering Study Section (2010)
NIH Special Emphasis Panel Congenital Diaphragmatic Hernia (2010)
NIH ad hoc reviewer, Fogarty International and Cooperative Projects (2010)
NIH Special Emphasis Panel New Strategies for Growing 3-D Tissues (2011)
NIH ad hoc reviewer, Small Business Innovation Research (2012)
CIRM Development Award Study Section (2011)
NIH ad hoc reviewer, Transformative R01 Roadmap (2013, 2016)
NHLBI Think Tank on Research Needs for Cell Therapy in Areas of Heart, Lung, and Blood (2014)
CIRM Translational Research Program Study Section (2014-present)
NIH Bioengineering, Technology, and Surgical Science Study Section (2016)

Honors and Awards

Cum Laude, Holy Cross (1986)
Honors Program Graduate, Holy Cross (1986)
Air Force Health Professions Scholarship Recipient (1986-1990)
Surgical Research Fellowship:(sponsored by Advanced Tissue Science) (1994-1995)
Rhode Island Hospital Surgical Chief Resident Award (1997)
Hasbro Children's Hospital Resident Award (1999)
Air Force Achievement Medal (2001)
Ohse Research Award (2003-2004)
American Pediatric Surgical Association Foundation Award (2004-2005)
American Surgical Association Foundation Research Fellowship Award (2005-2007)
National Institute of Health Mentored Clinical Scientist Development Award (2006-2011)
Doris Duke Clinical Scientist Development Award (2007-2010)
American College of Surgeons Jacobson Promising Investigator Award (2008)
Jay and Margie Grosfeld Lecture on Surgical Innovation, American Pediatric Surgical Association (2010)
Emile Holman Lecture, Stanford University (2012)
Scientific Consultant Grey's Anatomy (2013)
Landacre Research Award (2014)
Nationwide Endowed Chair in Surgical Research (2015)

C. Contribution to Science

While working as a post-doctoral research fellow in the Tissue Engineering Laboratories of Dr Jay Vacanti and Robert Langer in collaboration with Dr Toshi Shinoka, I developed the first tissue engineered heart valve and one of the early tissue engineered vascular grafts. Our work focused on the use of autologously seeded biodegradable scaffolds to create neotissue for use in a variety of cardiovascular surgical appliactions with a focus on congenital heart disease.

1) Mooney DJ, **Breuer CK**, McNamara K, Vacanti JP, Langer R. Fabricating tubular devices from polymers of lactic and glycolic acid for tissue engineering. *Tissue Eng.* 1995; 1(2):107-118.

2) **Breuer CK**, Shin'oka T, Tanel RE, Zund G, Mooney DJ, Ma PX, Miura T, Colan S, Langer R, Mayer JE, Vacanti JP. Tissue engineering lamb heart valve leaflets. *Biotechnol Bioeng.* 1996; (50):562-567.

While at Yale University I developed murine models that for the first time enabled investigation of the cellular and molecular mechansims underlying neotissue formation. Using these models we made the seminal discovery that tissue engineered constructs were made from host-derived cells, and not the cells seeded onto the scaffold. This lead to a paradigm shift as we focused our investigations on the host response to the tissue

engineered construct rather than cells seeded onto the scaffold. We subsequently demonstrated that neotissue forms through an immune-mediated regenerative process. We discovered that the immune response is essential for neotissue formation but that excessive inflammation resulted in pathologic neotissue formation.

1) Roh JD, Nelson GN, Brennan MP, Mirensky TL, Yi T, Hazlett TF, Tellides G, Sinusas AJ, Pober JS, Saltzman WM, Kyriakides TR, **Breuer CK**. Small-diameter biodegradable scaffolds for functional vascular tissue engineering in the mouse model. *Biomaterials*. 2008; 29(10):1454-63.

2) Roh JD, Sawh-Martinez R, Brennan MP, Jay SM, Devine L, Rao DA, Yi T, Mirensky, TL, Nalbandian A, Udelsman B, Hibino N, Shinoka T, Saltzman WM, Snyder E, Kyriakides TR, Pober JS, **Breuer CK**. Tissue-engineered vascular grafts transform into mature blood vessels via an inflammation-mediated process of vascular remodeling. *Proc Natl Acad Sci*. 2010; 107(10):4669-74.

3) Hibino N, Villalona G, Pietris N, Duncan DR, Schoffner A, Roh JD, Yi T, Dobrucki LW, Mejias D, Sawh-Martinez R, Harrington JK, Sinusas A, Krause DS, Kyriakides T, Saltzman WM, Pober JS, Shinoka T, **Breuer CK**. Tissue engineered vascular grafts form neovessels that arise from regeneration of the adjacent blood vessel. *FASEB J*. 2011; 25(8):2731-9.

4) Hibino N, Yi T, Duncan DR, Rathore A, Dean E, Naito Y, Dardik A, Kyriakides T, Madri J, Pober JS, Shinoka T, **Breuer CK**. A critical role for macrophages in neovessel formation and the development of stenosis in tissue-engineered vascular grafts. *FASEB J*. 2011; 25(12):4253-63.

5) Duncan DR, Chen PY, Patterson JT, Lee YU, Hibino N, Cleary M, Church SN, Shinoka T, Fahmy TM, Simons M, **Breuer CK**. Tgfbr1 inhibition blocks the formation of stenosis in tissue engineered vascular grafts. *J Am Coll Cardiol*. 2014; Accepted [epub pending].

We have also developed a large animal model for validating our mechanistic discoveries and inventions which we use as a final preclinical studies.

1) Brennan MP, Dardik A, Hibino N, Roh JD, Nelson GN, Papademitris X, Shinoka T, **Breuer CK**. Tissue engineered vascular grafts demonstrate evidence of growth and development when implanted in a juvenile animal model. *Ann Surg*. 2008; 248(3):370-7.

2) Kurobe H, Maxfield MW, Naito Y, Cleary M, Stacy M, Solomon D, Rocco KA, Tara S, Lee A, Sinusas A, Snyder E, Shinoka T, **Breuer CK**. Comparison of a closed system to a standard open technique for preparing tissue engineered vascular grafts. *Tissue Eng Part C Methods*. 2014 May 27.

In collaboration with Dr Shinoka we are in the midst of the first FDA approved clinical trial (IDE 14127) evaluating the use of TEVG in congenital heart surgery.

Complete List of Published Work in MyBibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/1dwc2hpoNYP52/bibliography/48117140/public/?sort=date&direction=ascending.

D. Research Support

Pending Research Support

(1) Title: Improving tissue engineered vascular graft performance via computational modeling
Principal Investigator: Breuer, Humphrey, Marsden
Funding Period 9/1/2017-8/31/2022
Grant #: R01HL139796
The goals of this study are to develop a computational model that can accurately describe and predict the natural history of TEVG stenosis. Then using the model develop new indications for performing angioplasty. Then finally validating the computational model using an ovine TEVG intrathoracic IVC

interposition vascular graft model by comparing outcomes between animals treated using the tradition angioplasty algorithm compared to animals treated using the computational modeling based algorithm. Score: 31 (8th percentile)

Ongoing Research Support

(1) Title: Mechanisms of vascular neotissue formation in tissue engineered vascular grafts
Principal Investigator: Breuer
Funding Period: 01/22/2010-04/30/2019
Grant #: R01 HL098228
The goals of this study are to investigate the effects of cell seeding and matrix porosity on macrophage responses that influence neovessel formation and to examine the effects of pharmacologically altering the temporal and/or spatial characteristics of the macrophage response.

(2) Title: Computational model design of tissue Engineered vascular grafts
Principal Investigator: Humphrey, Wang, and Breuer (MPI)
Funding Period: 7/1/2015-6/30/2019
Grant #: R01 HL128502
The long-term goal of this project is to rationally design an improved vascular graft for use in the arterial circulation using computational modeling. In collaboration with the Yang Laboratory at the University of Pittsburgh and the Humphrey laboratory at Yale University, we are evaluating the effects of varying scaffold design on TEVG function using a murine model. We use these data to inform our computational model and then use the model to optimize our design before finally evaluating the optimized design using our animal models again. We contend that this approach will accelerate the development process.

(3) Title: Development of an Improved Vascular Graft for Use in Congenital Heart Surgery
Principal Investigator: Breuer
Funding Period: 4/01/2016-3/31/2020
Grant #: R01 HL128847
The goal of this project is to elucidate the role of TGF-beta signaling in macrophage mediated neovessel formation and the formation of TEVG stenosis using murine models and then validate our discoveries using a juvenile ovine model.

(4) Title: A pilot study investigating the use of tissue engineered vascular grafts in congenital heart surgery
Principal Investigator: Shinoka (PI), Breuer (co-PI)
Funding Period: 12/1/2011-11/30/2018
Grant #: Gunze Limited
The purpose of this study is to evaluate the safety and growth potential of TEVG used as extracardiac vascular conduits in children undergoing modified Fontan surgery.

Completed Research Support

(1) Title: Nanofiber tissue engineered vascular graft using 3-D printing
Principal Investigator: Hibino (PI), Breuer (site PI)
Funding Period: 8/1/2014-7/31/2015
Grant #: U54 HL 119810
The purpose of this study is to evaluate the utility of using individually customized 3-D printed electrospun TEVG using both a small and large animal model.

(2) Title: Development of an improved graft for use in congenital heart surgery
Principal Investigator: Breuer (PI)
Funding Period: 7/1/2014-6/30/2016
Grant #: Children's Heart Foundation

The purpose of this pilot study is to evaluate the safety and efficacy of losartan for inhibiting the formation of TEVG stenosis using the murine IVC vascular interposition graft model.