BIOGRAPHICAL SKETCH

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NAME: Naomi Chesler

eRA COMMONS USER NAME (credential, e.g., agency login): ncchesler

POSITION TITLE: Professor of Biomedical Engineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Swarthmore College, Swarthmore, PA	B.Sc	06/1989	Engineering (General)
Massachusetts Institute of Technology (MIT), Cambridge, MA	M.Sc.	06/1991	Mechanical Engineering
Harvard-MIT Division of Health Sciences and Technology (MEMP Program), Cambridge, MA	Ph.D.	08/1996	Medical Engineering
Georgia Institute of Technology and Emory University, Atlanta, GA	Post-doc	09/1998	Vascular Biomechanics

A. Personal Statement

My unique education and cross-training in mechanical engineering, physiology and vascular biology have prepared me well to contribute to advancement in cardiovascular research and training of the next generation of leaders in this field. My expertise is vascular biomechanics, mechanobiology, and computational modeling; I focus on improving our understanding of pulmonary vascular disease and subsequent right ventricular (RV) dysfunction. As a PI or co-I on several NIH-funded grants, I have investigated the interactions between pulmonary arterial stiffening and right ventricular function in small animal models of PAH (R01HL086939), large animals and patients with PAH (R01HL105598) and small animals and patients with bronchopulmonary dysplasia (BPD) (R01HL115061). As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. Prior to joining the faculty of UCI as Director of the Edwards Lifesciences Center for Advanced Cardiovascular Technologies (ELCACT) I have served in various leadership positions at UW-Madison, including several focused on improving diversity, equity and inclusion. I have served as primary supervisor to 22 predoctoral and 8 postdoctoral trainees, most receiving independent training fellowships.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020–present **Professor and Director**, Department of Biomedical Engineering Edwards Lifesciences Center for Advanced Cardiovascular Technologies at the University of California, Irvine, CA.
2014–2020 **Professor**, Department of Biomedical Engineering, UW-Madison. Affiliate Appointments, Departments of Medicine and Mechanical Engineering (2003-present) and Educational Psychology (2009-present).
2008–2014 **Associate Professor**, Department of Biomedical Engineering, UW-Madison.
2002–2008 **Assistant Professor**, Department of Biomedical Engineering, University of Wisconsin-Madison (UW-Madison), WI.
1998–2002 **Assistant Professor**, Department of Mechanical Engineering, University of Vermont, Burlington, VT. Affiliate Appointment, Department of Medicine.

Honors

2021 AIMBE Professional Impact **Award for Mentoring**

2019 ASME McDonald **Mentoring Award**
2015-2018 AIMBE Fellow, BMES Fellow, and IAMBE Fellow
2015 Fulbright scholar, Israel Program
2014 BMES Diversity Award
2013 ASME Fellow and Vilas Distinguished Achievement Professor at UW-Madison
2011 Invited participant in National Academy of Engineering-sponsored Frontiers of Engineering Education Symposium
2009 Fulbright scholar, Belgium-Luxembourg Program
2008 Denice D. Denton Emerging Leader Award, Anita Borg Institute
2004 Invited participant in NAE-sponsored U.S.-Japan Frontiers of Engineering Symposium
2003 Invited participant in U.S. National Committee on Biomechanics-sponsored Frontiers in Biomechanics Symposium
2002 Invited participant in National Academy of Engineering-sponsored Frontiers of Engineering
1999 National Science Foundation CAREER Award for Young Faculty
1994–1995 MIT-Japan Program Ayukawa Fellow and Prize Recipient
1993 Meredith Kamm Memorial Award for Leadership, MIT
1990–1993 National Science Foundation Graduate Research Fellowship, MIT
1989 Phi Beta Kappa, Tau Beta Pi, Sigma Xi, Swarthmore College

C. Contributions to Science

1. Pulmonary artery remodeling
Changes in arterial mechanical properties – that is, arterial biomechanics -- are both a cause and consequence of cardiovascular disease. Indeed, large artery stiffening is an indepenent predictor of mortality from both right and left ventricular failure. I have led the field in quantifying the causes and consequences of pulmonary arterial stiffening *in vivo* and *ex vivo* in preclinical and clinical studies. Some examples are the differential impacts of collagen content and cross-linking on stiffening (a), the differential effetcs of arterial strain and remodeling on stiffening (b), the discovery that arterial viscoelasticity changes are also a consequence of cardiopulmonary disease and may impair ventricular function (c), and the development of mathematical models to detail collagen contributions to arterial mechanical behavior (d).

a) Wang Z and **Chesler NC**. *Role of collagen content and cross-linking in large pulmonary arterial stiffening after chronic hypoxia* (2012) Biomechanics and Modeling in Mechanobiology, Jan;11(1-2):279-89. doi: 10.1007/s10237-011-0309-z. Epub 2011 May 3. PMID 3248635
b) Golob MJ, Tabima DM, Wolf GD, Johnston JL, Forouzan O, Mulchrone AM, Kellihan HB, Bates ML, **Chesler NC**. (2017). *Pulmonary arterial strain- and remodeling-induced stiffening are differentiated in a chronic model of pulmonary hypertension*. J Biomech. 2017 Apr 11;55:92-98. doi:10.1016/j.jbiomech.2017.02.003.PMID: 28262286
c) Wang Z, Lakes RS, Golob M, Eickhoff JC, **Chesler NC**., (2013). *Changes in large pulmonary arterial viscoelasticity in chronic pulmonary hypertension.* PLoS One. 2013 Nov 6;8(11):e78569. PMID24223157
d) Tian L, Wang Z, Liu Y, Eickhoff JC, Eliceiri KW, **Chesler NC** (2015). *Validation of an arterial constitutive model accounting for collagen content and crosslinking.* Acta biomaterialia. PMID:26654765

2. Pulmonary vascular impedance
As noted above, large artery stiffening is an independent predictor of ventricular failure. One mechanism of action of this arterial biomechanical change on ventricular function is pulsatile blood flow dynamics such as pressure and flow wave reflections. In order to measure the hemodynamic effects of arterial stiffening in the pulmonary circulation, I have developed *in vivo* and *ex vivo* protocols for measuring the opposition to pulsatile blood flow in the pulmonary circulation, termed pulmonary vascular impedance. *In vivo*, we have measured impedance in preclinical and clinical studies under the acute stresses of hypoxia and exercise (see (a) and (b) below) or as affected by estrogen, sex and genotype. *Ex vivo,* we modified salt-perfused mouse lung systems to provide not only oscillations in airway pressure for ventilation but also pulsations in pulmonary vascular flow to mimic physiological flow. The critical advantage of measuring pulsatile pressure-flow relationships in isolated lungs *ex vivo* is that molecular mechanisms of pulmonary vascular impedance changes can be investigated using genetically engineered mouse models of disease. We first developed this technique with wild type mice,

generating pulmonary hypertension with embolization and chronic hypoxia, then quantified the effect of vasoactive agents on pressure and flow (c), and have since used this technique with genetically engineered strains. In this proposal, we will adapt our techniques to isolated pig lungs. To date, our work has led to important insights into the determinants of pulsatile flow abnormalities with disease progression and potential new therapeutic strategies for limiting arterial stiffening in pulmonary arterial hypertension (d).

a) Schreier DA, Hacker TA, Hunter K, Eickoff J, Liu A, Song G, **Chesler N**., (2014). *Impact of increased hematocrit on right ventricular afterload in response to chronic hypoxia.* J Appl Physiol. 2014 Oct 15;117(8):833-9. PMID: 25170068
b) Bellofiore A, Dinges E, Naeije R, Mkrdichian H, Beussink-Nelson L, Bailey M, Cuttica MJ, Sweis R, Runo JR, Keevil JG, Francois CJ, Shah SJ, **Chesler NC**. (2017) *Reduced hemodynamic coupling and exercise are associated with vascular stiffening in pulmonary arterial hypertension*. Heart. Mar;103(6):421-427. doi: 10.1136/heartjnl-2016-309906. Epub 2016 Aug 26. PMID: 27566296
c) Vanderpool RR, Kim AR, Molthen R, **Chesler NC**., (2011). *Effects of acute Rho kinase inhibition on chronic hypoxia-induced changes in proximal and distal pulmonary arterial structure and function.* J Appl Physiol Jan;110(1):188-98. PMID: 21088209
d) Schreier DA, Hacker TA, Song G, and **Chesler NC** (2013). *The role of collagen synthesis in ventricular and vascular adaptation to hypoxic pulmonary hypertension*. J Biomech Eng. Feb;135(2):021018. doi: 10.1115/1.4023480. PMID: 23445063

3. Right ventricular-pulmonary vascular coupling

The cause of death in pulmonary hypertension is typically right ventricular failure. However, various metrics of right ventricular function are in use clinically, most of which do not account for the right ventricular afterload generated by the diseased pulmonary vasculature. One metric that does take a systems-level view of the cardiopulmonary unit is right ventricular-pulmonary vascular coupling defined as the ratio of end systolic elastance (Ees) to effective arterial elastance (Ea). We were the first to develop and validate measurement techniques for quantifying both Ees and Ea for the RV in mice (a) and have since used these techniques to determine the roles of collagen content and cross-linking in progressive right ventricular dysfunction, the impact of estrogen and sex differences, and correlations between Ees/Ea and myocyte mechanics (b) and genetic defects (c) in rodent models of disease. Furthermore, we have developed new approaches to assess coupling in clinical studies (d) and shared these broadly.

a) Tabima DM, Hacker TA, **Chesler NC**., (2010). *Measuring right ventricular function in the normal and hypertensive mouse hearts using admittance-derived pressure-volume loops.* Am J Physiol Heart Circ Physiol. 2010 Dec;299(6):H2069-75. PMID: 20935149
b) Liu A, Schreier D, Tian L, Eickhoff JC, Wang Z, Hacker TA, **Chesler NC**., (2014). *Direct and indirect protection of right ventricular function by estrogen in an experimental model of pulmonary arterial hypertension.* Am J Physiol Heart Circ Physiol. 2014 Aug 1;307(3):H273-83. PMID: 24906919
c) Golob MJ, Massoudi D, Tabima DM, Johnston JL, Wolf GD, Hacker TA, Greenspan DS, **Chesler NC** (2018) *Cardiovascular function and structure are preserved despite ablation of BMP1-related proteases.* Cellular and Molecular Bioengineering. DOI 10.1007/s12195-018-0534-y PMID: In Process.
d) Bellofiore A, Vanderpool R, Brewis MJ, Peacock AJ, **Chesler NC**. (2018) A novel single-beat approach to assess right ventricular systolic function. J Appl Physiol Feb 1;124(2):283-290. doi: 10.1152/japplphysiol.00258.2017. Epub 2017 Oct 12. PMID:29025899

4. Multiscale computational modeling

The significant advantage of a computational model-based approach to a scientific question is that modeling facilitates a rigorous cycle of hypothesis testing (quantitative comparison of model predictions to experimental observations), hypothesis refinement (redesign and reformulation of models in light of mismatches between predictions and data), and model-guided experimental design. Recently, we have made significant contributions to understanding cardiopulmonary disease through the application of multiscale models of cellular metabolic processes, calcium dynamics, cross-bridge kinetics, myocyte mechanics, bi-ventricular function and a simple model of whole-body circulatory dynamics (a) and (b). Moreover, we have previously used models to investigate the precision and accuracy of hemodynamic analysis techniques (c), the hemodynamic impact of heterogeneous vascular mechanics, and mechanisms of right ventricular failure that can be inferred from cardiopulmonary hemodynamics (d).

(a) Pewowaruk RJ, Philip JL, Tewari SG, Chen CS, Nyaeme MS, Wang Z, Tabima DM, Baker AJ, Beard DA, **Chesler NC**. (2018). *Multiscale Computational Analysis of Right Ventricular Mechanoenergetics.*

J Biomech Eng. 2018 Aug 1;140(8). doi: 10.1115/1.4040044. PMID: 30003251

(b) Philip JL, Pewowaruk RJ, Chen CS, Tabima DM, Beard DA, Baker AJ, **Chesler NC**. (2018). *Impaired Myofilament Contraction Drives Right Ventricular Failure Secondary to Pressure Overload: Model Simulations, Experimental Validation, and Treatment Predictions.* Front Physiol. 2018 Jun 27;9:731. doi: 10.3389/fphys.2018.00731. eCollection 2018. PMID: 29997518

(c) Qureshi MU, Colebank M, Schreier D, Tabima Martinez DM, Haider MA, **Chesler NC**, Olufsen MS. (2017). *Characteristic impedance: frequency or time domain approach?*. Physiol Meas. Nov 27. doi: 10.1088/1361-6579/aa9d60. PMID: 29176040

(d) Tewari SG, Bugenhagen SM, Wang Z, Schreier DA, Carlson BE, **Chesler NC**, Beard DA. (2013). *Analysis of cardiovascular dynamics in pulmonary hypertensive C57BL6/J mice.* Front Physiol. 2013 Dec 11;4:355. doi: 10.3389/fphys.2013.00355. eCollection 2013. PMID: 24376421

5. Mitochondrial changes in right ventricular failure

One of the major unresolved questions in cardiovascular pathophysiology is which steps in the cascade of carbon substrate preference, mitochondrial ATP production, ATP conduction, and ATP utilization ultimately contribute to the dysfunction of the failing heart. Many investigators are focused on the role of mitochondrial changes in left ventricular failure; we are at the forefront of investigations into the role of mitochondrial changes in right ventricular failure. Our contributions to this area of science include identifying structure-function correlations between mitochondrial respiration and hemodynamics in mild RV dysfunction (a), that increased numbers of small mitochondria be found in the failing RV (b), and mechanoenergetic relationships in the RV via computational modeling (c).

(a) Liu A, Philip J, Vinnakota KC, Van den Bergh F, Tabima DM, Hacker T, Beard DA, **Chesler NC.** (2017). *Estrogen maintains mitochondrial content and function in the right ventricle of rats with pulmonary hypertension*. Physiol Rep.2017 Mar;5(6). pii: e13157. doi: 10.14814/phy2.13157. PMID: 2832089

(b) Cheng TC, Philip JL, Tabima DM, Hacker TA, **Chesler NC.** (2018). *Multi-scale Structure-Function Relationships in Right Ventricular Failure Due to Pressure Overload.* Am J Physiol Heart Circ Physiol. 2018 Jun 8. doi: 10.1152/ajpheart.00047.2018. [Epub ahead of print] PMID: 29882684.

(c) Pewowaruk RJ, Philip JL, Tewari SG, Chen CS, Nyaeme MS, Wang Z, Tabima DM, Baker AJ, Beard DA, **Chesler NC**. (2018). Multiscale Computational Analysis of Right Ventricular Mechanoenergetics. J Biomech Eng. 2018 Aug 1;140(8). doi: 10.1115/1.4040044. PMID: 27011909.

6. Learning sciences and mentoring

My collaborator David Williamson Shaffer and I were the first to create engineering virtual internships, which are a novel paradigm for providing authentic engineering experiences to K-infinity learners based on the learning sciences theory of epistemic frames. We have shown that this approach can enable students to solve complex engineering problems in a mentored, collaborative environment; allow educators to assess engineering thinking; and provide an introductory experience that students enjoy and find valuable. Furthermore, we have shown that engineering virtual internships have been shown to increase students'—and especially women's—interest in and motivation to pursue engineering degrees. I have also designed, implemented and assessed mentoring programs based on the sociology of interpersonally- and institutionally generated gender roles and dynamics that make the construction and maintenance of mentoring relationships especially difficult for women in male-dominated fields.

(a) **Chesler NC**, Ruis AR, Collier W, Swiecki Z, Arastoopour G and Shaffer DW. A Novel Paradigm for Engineering Education: Virtual internships with individualized mentoring and automated assessment of engineering thinking. Journal of Biomechanical Engineering, 2015.

(b) Arastoopour, G, **Chesler, NC** and Shaffer, DW. Epistemic Persistence: A Simulation-Based Approach to Increasing Participation of Women in Engineering. Journal of Women and Minorities in Science and Engineering, 2014.

(c) **Chesler, NC** and Chesler, MA. Gender-informed mentoring strategies for women in engineering: On establishing a caring community. Journal of Engineering Education, Jan 91(1): 49-56, 2002.

http://www.ncbi.nlm.nih.gov/pubmed?term=Chesler%20N%5BAuthor%5D&cmd=DetailsSearch