BIOGRAPHICAL SKETCH

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NAME: Brown, Ashley Carson

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

POSITION TITLE: Assistant 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
Clemson University, Clemson, SC, USA	BS	08/2002	Biosystems Engineering
Georgia Institute of Technology, Atlanta, GA, USA	PhD	08/2011	Bioengineering
Georgia Institute of Technology, Atlanta, GA, USA	Postdoc	02/2014	Chem and Biochem/ Biomedical Engineering

A. Personal Statement

My long-term research goals are to understand mechanisms involved in coagulation and develop novel therapies that augment the body's native clotting and subsequent healing processes. My doctoral and postdoctoral training provided me with experimental and theoretical knowledge in the areas of coagulation, biomaterial design, fibrin mechanics, and cellular mechanotransduction mechanisms in fibrosis and wound healing, thus providing a firm foundation for the pursuit of my long-term research goals. A primary research focus in my group is the development of platelet-mimetic materials that participate in the natural coagulation cascade to promote hemostasis and enhance healing outcomes. I have extensive expertise evaluating fibrin polymerization and clot structure *in vitro* as well as evaluation of clotting *in vivo* in a variety of rodent injury and bleeding models and models of coagulopathy. I also have experience evaluating bleeding in a pig trauma model. Recent efforts in my group include the development of antimicrobial nanometal microgel composite platelet-like-particles that stop bleeding, fight infection, and improve healing outcomes. I have also become extremely interested in commercialization of hemostatic technologies resulting from our research efforts, particularly our platelet-like-particle technology. To this end, in cooperation with the Office of Technology Commercialization and New Ventures at NCSU we have started Selsym Biotech, Inc., an early-stage biotechnology company with the goal of developing novel hemostatic materials, for treating bleeding following trauma. The relevant publications are:

- Chee, E., Nandi, S., Nellenbach, K., Mihalko, E., Snider, D., Morrill, L., Bond, A., Sproul, E., Sollinger, J., Cruise, G., Hoffman, M. **Brown, A.C**.[+], Nanosilver composite pNIPAm microgels for the development of antimicrobial platelet-like-particles. *Journal of Biomedical Materials Research Part B*. 2020. Doi: 10.1002/jbm.b.34592.
- Nandi, S., Sproul, E., Gaffney, L., Freytes, D., **Brown, A.C**.[+], Platelet-like particles dynamically stiffen fibrin matrices and improve wound healing outcomes. *Biomaterials Science*, 2019, doi: 10.1039/C8BM01201F. *****Featured in the 2019 Biomaterials Science Emerging Investigators Collection***
- Sproul, E., Nandi, S**.**, Roosa, C., Schreck, L., **Brown, A.C[+].** Biomimetic microgels with controllable deformability improve healing outcomes. *Advanced Biosystems*, 2018, doi: 10.1002/adbi.201800042.
- **Brown, A.C.**[*], Stabenfeldt, S.E.[*], Ahn, B., Hannan, R., Dhada, K., Herman, E., Stefanelli, V., Guzzetta, N., Alexeev, A., Lam, W.A., Lyon, L.A., Barker, T.H. Ultrasoft microgels displaying emergent platelet-like behaviours. *Nature Materials*, 2014, **12**, 1108-14. doi:10.1038/nmat4066.

B. Positions and Honors

Positions and Employment

2014-2015 Research Scientist II, School of Chemistry and Biochemistry, Atlanta, GA
2015-present Assistant Professor, Joint Department of Biomedical Engineering, North Carolina State University, Raleigh, NC and University of North Carolina, Chapel Hill, NC

2016-present Affiliated Assistant Professor, Department of Materials Science and Engineering, North Carolina State University, Raleigh, NC
2019-present Founder and CEO, Selsym Biotech, Inc., Raleigh, NC

Honors and Awards

1. Tissue Engineering and Regenerative Medicine Society (TERMIS) AM Young Investigator Award (2020)
2. *Cellular and Molecular Bioengineering* Young Innovator (2020)
3. American Society for Matrix Biology Junior Investigator Award (2020)
4. North Carolina State University Faculty Scholar (2020)
5. National Science Foundation CAREER Award (2019)
6. American Heart Association Kenneth M. Brinkhous Young Investigator Prize in Thrombosis Finalist (2019)
7. *Biomaterials Science* Emerging Investigator (2019)
8. National Academy of Engineering Frontiers of Engineering Invitee (2018)
9. Biomaterials Gordon Research Conference Young Investigator Poster Award (2017)
10. American Heart Association Scientist Development Award Recipient (2016)
11. American Heart Association Postdoctoral Fellow (2012-2014)
12. American Society of Hematology Abstract Achievement Award (2012)
13. Society for Biomaterials Student Travel Achievement Recognition (STAR) Award (2011)
14. TERMIS-EU 50 Best Abstracts Award (2010)
15. NIH T32 Cell and Tissue Engineering Training Grant Awardee (2008-2010)
16. Georgia Institute of Technology Presidential Fellowship (2006-2010)

Recent Professional Activities and Memberships

2020, 2021 Ad hoc reviewer, NIH Oral, Dental, and Craniofacial Sciences (ODCS) Study Section
2020 Ad hoc reviewer, NIH NHBLI SBIR Phase IIB Study Section
2020-present Biomedical Engineering Society Student Affairs Subcommittee Chair
2019-present Society for Biomaterials Council Member
2019-present Society for Biomaterials Engineering Cells and Their Microenvironment Special Interest Group Chair
2018-present American Society for Matrix Biology Council Member
2016-present Biomedical Engineering Society Student Affairs Subcommittee Member
2008-present Member, American Society for Matrix Biology
2008-present Member, Society for Biomaterials
2010-present Member, Tissue Engineering and Regenerative Medicine International Society
2012-present Member, American Heart Association
2012-present Member, Biomedical Engineering Society
2012-present Member, American Society for Hematology
2014-present Member, International Fibrinogen Research Society
2018-present Member, International Society on Thrombosis and Haemostasis

C. Contribution to Science

1. **Designing bioresponsive platelet-like particles**: A major focus of my research is the development of fibrin-targeting platelet-like particles (PLPs) that interact specifically with nascent fibrin fibers at wound sites to augment clot formation and stop bleeding following traumatic injury. To maximize interactions with fibrin networks, we utilized highly deformable, ultra-low crosslinked (ULC) pNIPAm microgels with multiple sites for chemoligation as the base material for our hemostatic material. To impart fibrin specificity to the microgels, humanized synthetic single domain variable fragment (sdFv) antibodies with high affinity for fibrin were identified through molecular evolutionary techniques and then coupled to the microgels. Like natural platelets, these PLPs specifically target fibrin rather than fibrinogen, interactive extensively with fibrin networks, augment clotting *in vitro* and decrease bleeding times in rodent models of traumatic injury. Importantly, PLPs were found to actively collapse fibrin networks, an emergent behavior that mimics *in vivo* clot contraction. These studies demonstrate that this clot collapse feature was intimately related to 1) the high level of deformability of ULC particles and 2) the high affinity interactions of PLPs with the fibrin networks. I have shown the utility of these particles in treating bleeding following injury and in promoting healing. I have served as a primary investigator and PI in these studies.

a) **Brown, A.C.**[*]**,** Stabenfeldt, S.E.[*], Ahn, B., Hannan, R., Dhada, K., Herman, E., Stefanelli, V., Guzzetta, N., Alexeev, A., Lam, W.A., Lyon, L.A., Barker, T.H. Ultrasoft microgels displaying emergent platelet-like behaviours. *Nature Materials,* 2014, **12**, 1108-14. doi:10.1038/nmat4066.
b) Myers, D., Qiu, Y., Chester, D., Fay, M., Sakurai, Y., Tran, R., Ciciliano, J., Ahn, B., Mannino, R., Bunting, S., Bennett, C., Briones, M., Smith, M., **Brown, A.C.**, Sulchek, T., Lam, W. Single-platelet nanomechanics measured by high-throughput cytometry. *Nature Materials,* 2016, doi: 10.1038/nmat4772.
c) Sproul, E., Nandi, S., Chee, E., Sivadanam, S., Igo., B., **Brown, A.C**.[+], Development of antimicrobial platelet-like-particles comprised of microgel nanogold composites. *Regenerative Engineering and Translational Medicine,* 2019, doi: 10.1007/s40883-019-00121-6.
d) Nandi, S., Mohanty, K., Nellenbach, K., Erb, M., Muller, M., **Brown, A.C**.[+], Ultrasound enhanced synthetic platelet therapy for augment wound repair. *ACS Biomaterials Science and Engineering,* 2020. Doi: 10.1021/acsbiomaterials.9b01976

2. **Engineering cellular microenvironments to promote wound healing:** In a number of projects, where I have contributed as a primary investigator and corresponding author, I have utilized ECM biology principles to design environments for eliciting specific cellular responses to promote healing. This has included 1) designing fibrin-based colloids and fibrin-targeting colloids (i.e. PLPs) to enhance clot properties to promote wound healing and 2) utilizing integrin-specific recombinant fibronectin fragments coupled with biophysical cues to direct EMT responses for wound healing.

a) Nandi, S., Sommerville, L., Erb, M., Freytes, D., Hoffman, M., Monroe, D., **Brown, A.C**.[+]**,** Platelet-like particles improve clot properties in a hemophilic model of wound healing. *Journal of Colloid and Interface Sciences,* 2020. Doi: 10.1016/j.jcis.2020.05.088
b) Muhamed, I., Sproul, E., Ligler, F., **Brown, A.C.**[+] Fibrin nanoparticles coupled with keratinocyte growth factor enhance dermal wound healing rate. *ACS Applied Materials & Interfaces*, 2019, doi: 10.1021/acsami.8b21056.
c) **Brown, A.C.**, Dysart, M.M., Clarke, K.C., Stabenfeldt, S.E., Barker, T.H. Integrin $\alpha 3\beta 1$ binding to fibronectin is dependent on the 9th type III repeat. *Journal of Biological Chemistry*, 2015, Oct 16;290(42):25534-47. doi: 10.1074/jbc.M115.656702.
d) **Brown, A.C.**, Baker, S., Douglas, A., Keating, M., Alvarez, M., Botvinick, E., Guthold, M., Barker, T.H. Molecular interference of fibrin's divalent polymerization mechanism enables modulation of multi-scale material properties. *Biomaterials*, 2015, **9**, 27-36. doi: 10.1016/j.biomaterials.2015.01.010.

3. **Understanding the role of ECM mechanics and protein composition in tissue repair responses:** ECM mechanics and composition are dynamic during wound healing. During my doctoral studies, I demonstrated that increased tissue stiffness is a key regulator of disease associated epithelial to mesenchymal transitions (EMT) in pulmonary fibrosis. These studies identified matrix stiffness and/or cell contractility as critical targets for novel therapeutics for fibrotic diseases. These studies also demonstrated that the responses are dependent on integrin-specific interactions, which can be quite dynamic in the wound microenvironment. I was a primary investigator in these studies. In my independent group, I have focused on developing novel therapeutic strategies to combat fibrotic responses, including targeted delivery of cell contractility inhibitors to sites of fibrosis. I have also focused on developing novel colloidal based material platforms to further study the role of viscoelasticity in modulating cell contractility and downstream effects on fibrotic responses.

a) **Brown, A.C.**, Fiore, V.F., Sulchek, T.A., Barker, T.H. Physical and chemical microenvironmental cues orthogonally control the degree and duration of fibrosis associated epithelial to mesenchymal transitions. *J Pathol*. 229, 25-35, 2013.
b) **Brown, A.C.**[*], Qui, Y.[*], Myers, D.R., Sakurai, Y., Mannino, R., Tran, R., Ahn, B., Hardy, E., Kee, M., Kumar, S., Bao, G., Barker, T.H., Lam, W.A. Platelet mechanosensing of substrate stiffness during clot formation mediates adhesion, spreading and activation. *PNAS*, 2014, doi: 10.1073/pnas.1322917111.
c) Mihako, E., Huang, K., Sproul, E., Cheng, K.**, Brown, A.C**[+]**.** Targeted Treatment of Ischemic and Fibrotic Complications of Myocardial Infarction Using a Dual-Delivery Microgel Therapeutic. *ACS Nano,* 2018, doi: 10.1021/acsnano.8b01977.
d) Chester, D., Kathard, R., Nortey, J., Nellenbach, K. **Brown, A.C.**[+], Viscoelastic properties of microgel thin films control fibroblast modes of migration and pro-fibrotic responses. *Biomaterials*, 2018, doi: 10.1016/j.biomaterials.2018.09.012.

4. **Understanding coagulopathy in neonates following cardiopulmonary bypass:** Neonates have documented quantitative (concentration) and qualitative (functional) deficiencies of many coagulation proteins including both thrombin and fibrinogen. The consequences of fetal fibrinogen on clot structure in neonates, particularly in the context of surgery-associated bleeding, were not well characterized at the time of this investigation. In these studies, we examined the sequential changes in clotting components and resultant clot structure in a small sample of neonates undergoing cardiac surgery and cardiopulmonary bypass (CPB). We found that clots formed from neonatal plasma collected after CPB was more porous than baseline clots, and that the transfusion of adult fibrinogen component (current standard of care) did not result in a return to baseline structure. Further analysis with purified neonatal and adult fibrinogen demonstrated that the structure of neonatal and adult clots differed sustainably, and neonatal clots degraded significantly faster than adult clots. The two fibrinogen components did not integrate well when mixed clots (simulating transfusion conditions) were formed. Furthermore, mixed clots were found to have degradation properties similar to pure adult clots. Such properties could lead to adverse thrombotic events and these findings suggest that differential treatment strategies for neonates should be pursued to reduce the demonstrated morbidity of blood product transfusion. I was a primary investigator in these studies.

a) **Brown, A.C.**, Hannan, R., Timmins, L., Fernandez, J., Barker, T.H., Guzzetta, N. Fibrin network changes in neonates after cardiopulmonary bypass. *Anesthesiology,* 2016, 5, 124, pp 1021-1031. doi: 10.1097/ALN. 0000000000001058
b) Nellenbach, K., Guzzetta, N., and **Brown, A.C.**[+] Analysis of the structural and mechanical effects of procoagulant agents on neonatal fibrin networks following cardiopulmonary bypass. *Journal of Thrombosis and Haemostasis,* 2018, doi: 10.1111/jth.14280.
c) Nellenbach, K., Nandi, S., Kyu, A., Sivadanam, S., Guzzetta, N., and **Brown, A.C.**[+] Comparison of neonatal and adult fibrin clot properties between porcine and human plasma. *Anesthesiology,* 2020, doi: 10.1097/ALN.0000000000003165.
d) Nellenbach, K., Nandi, S., Peeler, C., Kyu, A., **Brown, A.C.**[+] Neonatal fibrin scaffolds promote enhanced cell adhesion, migration, and wound healing *in vivo* compared to adult fibrin scaffolds. *Cellular and Molecular Bioengineering.* 2020, doi: 10.1007/s12195-020-00620-5. *****Featured in the 2020 Young Innovators Collection.***

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Pq0z-9lmtoQc/bibliography/47877502/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

1R01HL146701 (PI: Brown) 08/15/2019-07/31/2024
NIH NHLBI
Targeted treatment of thrombotic occlusions using a dual-microgel therapeutic
The goal of this project is to develop fibrin-targeting core-shell microgels for delivery of tissue plasminogen activator and a ROCK inhibitor to treat thrombotic occlusions and ischemia reperfusion injury.
Role: PI

DMR-1847488 (PI: Brown) 04/01/2019-03/31/2024
NSF
CAREER: Dynamic microgels that mimic platelet behavior to promote healing
The goal of this project is to develop a platelet-mimetic particle that changes shape in response to wound triggers.
Role: PI

CMMI-1825398 (PI: Brown) 09/01/2018-08/31/2021
NSF
A multiscale material approach to understanding the effects of viscoelasticity on cell adhesion, migration, and TGFβ activation/signaling
The goal of this project is to utilize microgel based thin films in conjunction with DNA origami to understand the role of material viscoelasticity on directly cell adhesion, migration, and cytokine responses.
Role: PI

No Grant Number (PI: Brown) 07/01/2018-12/30/2020 (NCE)

NCSU Chancellor's Innovation Fund
Antimicrobial platelet-like-particles to stop hemorrhage and promote healing
The goal of this project is to evaluate the translational potential of antimicrobial PLPs.
Role: PI

R01HL130918-01A1 (MPIs: Barker, Lam) 07/01/2016-06/30/2021 (NCE)
University of Virginia Sub-award; NIH NHLBI
Platelet-like-particles for augmenting hemostasis
The goal of this project is to investigate the efficacy of hemostatic PLPs in various models of platelet deficiency.
Role: Co-I

W81XWH-15-1-0485 (PI: Barker) 09/15/2015-09/30/2020 (NCE)
University of Virginia Sub-award; DOD
Development of platelet-like particles for augmentation of hemostasis in congenital heart defect patients at high risk for bleeding during cardiac surgery
The goal of this study is to characterize the safety of synthetic hemostatic platelet-like particles in various animal models of bleeding.
Role: Co-I

1R01AR071985-01A1 (PI: Fisher, Co-Is Schnabel and Spang) 04/01/2018-03/31/2023
NIH NIAMS
Sex- and Age-dependent ACL Function in the Growing Knee Joint
The goal of this proposal is to determine how age and sex impact ACL maturation during skeletal growth and joint function after ACL injury and to assess if this knowledge can be applied to improve treatment.
Role: Co-I

No Grant Number (PI: Downey) 07/01/2019-12/31/2020 (NCE)
Emory University Sub-award; Society for Pediatric Anesthesia
In vivo effects of fibrinogen concentrate on the neonatal fibrin network
The goal of this project is to characterize the influence of fibrinogen concentrate on neonatal fibrin properties after cardiopulmonary bypass.
Role: Co-I

Completed Research Support (last three years)

R21AR071017 (PI: Brown) 07/01/2017-06/30/2020 (NCE)
NIH NIAMS
Ultrasound enhanced platelet-like particle therapy for accelerated wound repair
The goal of this project is to utilize ultrasound stimulation to enhance PLP deformation of fibrin networks to promote cell migration.
Role: PI

16SDG29870005 (PI: Brown) 07/01/2016-06/30/2020 (NCE)
AHA Scientist Development Grant (Mid-Atlantic Affiliate)
Development of anti-microbial platelet-like-particles for augmentation of hemostasis and advanced wound repair
The goal of this project is to develop anti-microbial platelet-like particles to promote hemostasis and wound repair following trauma
Role: PI

DMR-1726294 (PI: LeBeau) 08/15/2017-07/31/2019
NSF
MRI: Acquisition of a Transmission Electron Microscope for In-situ Studies of Soft and Hard Matter
This equipment grant seeks to acquire a Cryogenic TEM to facilitate in-situ studies of soft and hard materials.
Role: Co-PI

UL1TR001117 (PIs: Brown, Hoffman) 07/01/2017-06/30/2018
NIH: Duke/NCSU Translational Research Grant
Platelet-mimetic nanogels for augmentation of wound repair
This project investigated utility of platelet-mimetic nanogels in treating impaired wound healing in hemophilia.
Role: PI