BIOGRAPHICAL SKETCH

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NAME: Gao, Nan

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

POSITION TITLE: Professor of Cell Biology

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
Soochow Medical School, Suzhou	B. Med.	07/1997	Medicine
Vanderbilt University, Nashville	Ph. D.	12/2004	Cell & Developmental Biology
University of Pennsylvania, Philadelphia	Postdoc	12/2009	Genetics

A. Personal Statement

My interest in GI mucosal biology developed from postdoctoral research at University of Pennsylvania. After joining Rutgers, my lab used mouse genetics and cell biology to study how endosome and vesicular trafficking regulate host intestinal epithelial cell sensing and communication with commensal and pathogenic bacteria. These projects led to engineering of innovative mouse models for loss and gain of function studies of recycling endosome and Rho family small GTPase (*Rab11a, Rab11b, Cdc42),* and Paneth cell derived bacterial cell-wall processing enzyme (lysozyme*)*. With my long-term collaborator and a GI physiologist Dr. Ronaldo Ferraris (PI of this grant), we published on diverse topics related to host-microbe interaction, brush border development, epithelial junction maintenance, TLR trafficking, bacterial sensing, Paneth cell plasticity, stem cell injury, mucolytic commensal microbe regulation, and colitis susceptibility. We accumulated experiences in gnotobiotics, mucosal immunology, and intestinal epithelial biology that are relevant to this project. This renewal project is built on discovery made for LGG-regulated dietary tryptophan-dependent metabolites that may modulate host intestinal epithelial differentiation, barrier function, and pathobiont exclusion. The hypothesis supported by our preliminary data are novel and may open a door to precision probiotic treatment. Dr. Ferraris has 3 decades of research experience in dietary research, nutrient science, amino acid transport, and gut epithelial physiology. Our collaborators, Dr. Liping Zhao, the Center Director for Nutrition, Microbiome and Health at Rutgers, and Dr. Fang Yan, an expert of LGG biology will ensure sufficient microbiology and probiotics expertise in our team. Ongoing collaborations with Drs. Vivian Li and Xiaoyang Su allow us to properly design and interpretation of results related to metabolomics and bioinformatics. The parent R01 project has been completed by us, resulting in publications and manuscripts under revision, as well as a provisional patent.

Ongoing and recently completed projects that I would like to highlight include:

R01 DK132885
Gao (PI)
03/15/2022-01/31/2026
Paneth cell heterogeneity in infection and inflammation

R01 DK119198
Gao (PI)
07/01/2019-06/30/2024

Intestinal lysozyme regulates mucosal immune response to microbiota

R01 AT010243
Gao (PI, MPI-Ferraris)
09/20/2018-08/30/2022 (NCE)
Mucosal modulation by LGG and R. gnavus specific tryptophan metabolites

Citations:

1. Sakamori R, Das S, Yu S, Feng S, Stypulkowski E, Guan Y, Douard V, Tang W, Ferraris RP, Harada A, Brakebusch C, Guo W, Gao N. Cdc42 and Rab8a are Critical for Intestinal Stem Cell Division, Survival, and Differentiation in Mice. J Clin Invest. 2012 Mar 1;122(3):1052-65. PMCID: PMC3287229.

2. Zhang X, Bandyopadhyay S, Araujo LP, Tong K, Flores J, Laubitz D, Zhao Y, Yap G, Wang J, Zou Q, Ferraris R, Zhang L, Hu W, Bonder EM, Kiela PR, Coffey R, Verzi MP, Ivanov II, Gao N. Elevating EGFR-MAPK program by a nonconventional Cdc42 enhances intestinal epithelial survival and regeneration. JCI Insight. 2020 Aug 20;5(16):e135923. PMCID: PMC7455142.

3. Yu S, Tong K, Zhao Y, Balasubramanian I, Yap GS, Ferraris RP, Bonder EM, Verzi MP, Gao N. Paneth Cell Multipotency Induced by Notch Activation following Injury. Cell Stem Cell. 2018 Jul 5;23(1):46-59. PMCID: PMC6035085

4. Yu S, Balasubramanian I, Laubitz D, Tong K, Bandyopadhyay S, Lin X, Flores J, Singh R, Liu Y, Macazana C, Zhao Y, Béguet-Crespel F, Patil K, Midura-Kiela MT, Wang D, Yap GS, Ferraris RP, Wei Z, Bonder EM, Häggblom MM, Zhang L, Douard V, Verzi MP, Cadwell K, Kiela PR, Gao N. Paneth cell-derived lysozyme defines the composition of mucolytic microbiota and the inflammatory tone of the intestine. Immunity. 2020 Aug 18;53(2):398-416.e8. PMCID: PMC7461615

B. Positions, Scientific Appointments, and Honors

Positions & Scientific Appointments

2022-	Professor, Cell and Molecular Biology, Rutgers University
2016- 2022	Associate Professor, Cell and Molecular Biology, Rutgers University.
2010- Present	Assistant Professor, Cell and Molecular Biology, Rutgers University.
2010- Present	Member, Rutgers Cancer Institute of New Jersey, NCI comprehensive cancer center.
2016- Present	Member, Rutgers University Genome Editing Core Advisory Committee
2017- Present	Member, Rutgers Gnotobiotics Core Advisory Committee
2020	Organizing Committee Member, Rutgers Microbiome Program (RUMP)
2022	Standing member, DNPD Study Section.
2021	ZAT1 PS (02) NCCIH Training and Education Review Panel, ZRG1 DNPD-A Study Section (ad hoc)
2020	Allergies and Mucosal Inflammation Special Emphasis Panel (HAMI/IMM-T57), GMPB Study Section, ZRG1 DKUS P-02 Topics in Gastroenterology Special Emphasis Panel
2019	GMPB Study Section (ad hoc), Special Emphasis Panel/Scientific Review Group 2019/05 ZDK1 GRB-K (M1), Hypersensitivity, Allergies and Mucosal Inflammation Special Emphasis Panel (HAMI/IMM-T57), ZRG1 DKUS M04 GI Special Emphasis Panel
2018	NIH ZRG1 DKUS-H (54) Special Emphasis Panel, GMPB Study Section (ad hoc), Special Emphasis Panel (CIMG Conflicts)
2018-2021	Standing member, ACS Tumor Biochemistry & Endocrinology Review Panel
2017	ACS Tumor Biochemistry & Endocrinology Review Panel; NIDDK Digestive Diseases and Nutrition C (DDK-C) Study Section (ad hoc); ZRG1 DKUS-H (54) Special Emphasis Panel; CIMG Study Section (ad hoc); ZDK1 GRB-8 J1 Special Emphasis Panel; ZDK1 GRB-7 M6 Special Emphasis Panel
2016	NIH/NIDDK ZDK1 GRB-8 M2 Special Emphasis Panel
2015	NIH/NIDDK Digestive Diseases and Nutrition C (DDK-C) Study Section (ad hoc)
2014	NIH/NCI ZCA1 RPRB-O M1 P Special Emphasis Panel

2010 US Department of Agriculture; NSF Integrative Organismal Systems - BIO Directorate; Broad Medical Research Program-Inflammatory Bowel Disease; Busch Biomedical Grant Advisory Committee; UK Medical Research Council; UK Biotechnology and Biological Sciences Research Council; Diabetes UK

Honors

2022 Rutgers Presidential Outstanding Faculty Scholar
2015 American Cancer Society Research Scholar.
2015 Rutgers Newark Chancellor's IMRT Award.
2011 Charles and Johanna Busch Biomedical Award.
2011 Rutgers Faculty Research Award.
2008 Beta Cell Biology Consortium Domestic Scholarship.
2007-9 Juvenile Diabetes Research Foundation Postdoctoral Fellowship.

C. Contributions to Science

1. My early postdoctoral research at Penn centered on understanding the mechanism of intestinal epithelial cell fate commitment, differentiation, and polarization. By generating Cdx2 and Foxa1 conditional mice, we reported their regulation of early intestinal and pancreatic cell fate determination and how these factors control the physiological functions in adult life.

a. **Gao N**, White P, Doliba N, Golson ML, Matschinsky FM, Kaestner KH. Foxa2 controls vesicle docking and insulin secretion in mature Beta cells. *Cell Metab.* 2007 Oct;6(4):267-79. PMID: 17908556.
b. **Gao N**, Le Lay J, Vatamaniuk MZ, Rieck S, Friedman JR and Kaestner KH. Dynamic regulation of Pdx1 enhancers by Foxa1 and Foxa2 is essential for pancreas development. *Genes & Development* (2008); 22:3435-3448. PMCID: PMC2607077
c. **Gao N**, White P, Kaestner KH. Establishment of Intestinal Identity and Epithelial-Mesenchymal Signaling by Cdx2. *Developmental Cell* (2009); 16(4): 588-599. PMCID: PMC2673200
d. **Gao N** and Kaestner KH. Cdx2 regulates endo-lysosomal function and epithelial cell polarity. *Genes & Development* (2010); 24(12):1295-305. (COVER). PMCID: PMC2885664

2. My team in Rutgers developed experiences using mouse genetics to study intestinal stem cell function and enterocyte development, which are relevant to this proposal. Our published work contributed to understanding the molecular pathogenesis of microvillus inclusion disease, a lethal form of enteropathy. We described the molecular machinery required for the proper assembly of apical brush border in enterocytes. By loss-of-function approach and by developing a new Cdc42 gain-of-function allele, we reported the necessity and sufficiency of Cdc42 in intestinal stem cells to drive epithelial renewal after genotoxic injury.

a. Sakamori R, Das S, Yu S, Feng S, Stypulkowski E, Guan Y, Douard V, Tang W, Ferraris RP, Harada A, Brakebusch C, Guo W, **Gao N**. Cdc42 and Rab8a are Critical for Intestinal Stem Cell Division, Survival, and Differentiation in Mice. *J Clin Invest.* 2012 Mar 1;122(3):1052-65. PMCID: PMC3287229.
b. Sakamori R, Yu S, Zhang X, Hoffman A, Sun J, Das S, Vedula P, Li G, Fu J, Walker F, Yang CS, Yi Z, Hsu W, Yu DH, Shen L, Rodriguez AJ, Taketo MM, Bonder EM, Verzi MP, **Gao N**. CDC42 Inhibition Suppresses Progression of Incipient Intestinal Tumors. *Cancer Res.* 2014 Oct 1;74(19):5480-92. PMCID: PMC4184946
c. Zhang X, Ren J, Wang J, Li S, Zou Q, **Gao N**. Receptor-mediated endocytosis generates nanomechanical force reflective of ligand identity and cellular property. *J Cell Physiol.* 2018 Aug;233(8):5908-5919. PubMed PMID: 29243828. PMCID: PMC7274725
d. Zhang X, Bandyopadhyay S, Araujo LP, Tong K, Flores J, Laubitz D, Zhao Y, Yap G, Wang J, Zou Q, Ferraris R, Zhang L, Hu W, Bonder EM, Kiela PR, Coffey R, Verzi MP, Ivanov II, **Gao N**. Elevating EGFR-MAPK program by a nonconventional Cdc42 enhances intestinal epithelial survival and regeneration. *JCI Insight.* 2020 Aug 20;5(16):e135923. PMID: 32686657; PMCID: PMC7455142.

3. We developed expertise in establishing various genetic and disease-relevant mouse models related to intestinal inflammation and colonic epithelial injury and healing, which are related to this project. We made the first mouse Rab11a conditional allele. Intestinal epithelial cell-specific Rab11a-deficient mice develop chronic and progressive mucosal inflammation and show exacerbated inflammatory response to microbial agonists of TLRs and abnormal NFκB activation in enterocytes at steady states. We further developed a Rab11b knockout mouse model and delineated a mechanism of redundant regulation by Rab11a and Rab11b to control YAP-Areg and Stat3-IL6 signaling pathways in mature enterocytes. Molecular characterization of these mouse models in

vivo and in primary organoid cultures identified important Rab11 cargos, including Syntaxin 3 for brush border morphogenesis, Glut5 for glucose transport and sensing, as well as Merlin, a scaffolding protein enhancing Hippo kinase activity at junction to suppress YAP activity.

a. Yu S, Nie Y, Knowles B, Sakamori R, Stypulkowski E, Patel C, Das S, Douard V, Ferraris RP, Bonder EM**,** Goldenring JR, Ip YT, **Gao N**. TLR sorting by Rab11 endosomes maintains intestinal epithelial-microbial homeostasis. *EMBO J.* 2014 Sep 1;33(17):1882-95. PMCID: PMC4195784
b. Feng Q, Bonder EM, Engevik AC, Zhang L, Tyska MJ, Goldenring JR, **Gao N**. Disruption of Rab8a and Rab11a causes formation of basolateral microvilli in neonatal enteropathy. *J Cell Sci.* 2017 Aug 1;130(15):2491-2505. PMCID: 5558269
c. D'Agostino L, Nie Y, Goswami S, Tong K, Yu S, Bandyopadhyay S, Flores J, Zhang X, Balasubramanian I, Joseph I, Sakamori R, Farrell V, Li Q, Yang CS, Gao B, Ferraris RP, Yehia G, Bonder EM, Goldenring JR, Verzi MP, Zhang L, Ip YT, **Gao N**. Recycling Endosomes in Mature Epithelia Restrain Tumorigenic Signaling. *Cancer Res.* 2019 Aug 15;79(16):4099-4112. PubMed PMID: 31239271; PubMed Central PMCID: PMC6726494.
d. Goswami S, Balasubramanian I, D'Agostino L, Bandyopadhyay S, Patel R, Avasthi S, Yu S, Goldenring JR, Bonder EM, **Gao N**. RAB11A-mediated YAP localization to adherens and tight junctions is essential for colonic epithelial integrity. *J Biol Chem.* 2021 Jul;297(1):100848. PMID: 34058200; PMCID: PMC8254046.

4. We developed substantial genetic tools and expertise in studying Paneth cells. Our lab derived several knockin and knockout mouse models to study Paneth cell plasticity and immunity. We reported that radiation injury that ablates intestinal stem cells induces Paneth cell plasticity upon Notch activation. We also used Lyz1 knockout and overexpressing mouse models to demonstrate that Paneth cells regulate ileal and colonic mucosal immunology via secreting the bacterial cell wall processing enzyme lysozyme. The absence of intestinal lysozyme diminished NOD-like receptor signaling, while abnormal production of this enzyme drives the inflammatory response in experimental colitis. By collaboration, we contributed to the understanding of microbial metabolite-supported stem cell development. These studies demonstrated our capability of carrying out the proposed work to elucidate cross-talks between epithelia and microbiome.

a. Das S, Yu S, Sakamori R, Vedula P, Feng Q, Flores J, Hoffman A, Fu J, Stypulkowski E, Rodriguez A, Dobrowolski R, Harada A, Hsu W, Bonder EM, Verzi MP, **Gao N.** Rab8a vesicles regulate Wnt ligand delivery and Paneth cell maturation at the intestinal stem cell niche. *Development* (Cambridge, England). 2015; 142(12):2147-62. PMCID: PMC4483769.
b. Lee YS, Kim TY, Kim Y, Lee SH, Kim S, Kang SW, Yang JY, Baek IJ, Sung YH, Park YY, Hwang SW, O E, Kim KS, Liu S, Kamada N, **Gao N**, Kweon MN. Microbiota-Derived Lactate Accelerates Intestinal Stem-Cell-Mediated Epithelial Development. *Cell Host Microbe.* 2018 Dec 12;24(6):833-846.e6. PubMed PMID: 30543778.
c. Yu S, Tong K, Zhao Y, Balasubramanian I, Yap GS, Ferraris RP, Bonder EM, Verzi MP, **Gao N**. Paneth Cell Multipotency Induced by Notch Activation following Injury. *Cell Stem Cell* 2018 Jul 5;23(1):46-59. PubMed PMID: 29887318; PubMed Central PMCID: PMC6035085.
d. Yu S, Balasubramanian I, Laubitz D, Tong K, Bandyopadhyay S, Lin X, Flores J, Singh R, Liu Y, Macazana C, Zhao Y, Béguet-Crespel F, Patil K, Midura-Kiela MT, Wang D, Yap GS, Ferraris RP, Wei Z, Bonder EM, Häggblom MM, Zhang L, Douard V, Verzi MP, Cadwell K, Kiela PR, **Gao N**. Paneth cell-derived lysozyme defines the composition of mucolytic microbiota and the inflammatory tone of the intestine. *Immunity.* 2020 Aug 18;53(2):398-416.e8. PMCID: PMC7461615

5. Through ongoing projects in the lab and several important collaborative projects, we developed solid foundation in studying intestinal growth factor signaling as well as innate immune signaling pathways. We contributed to the study of intestinal epithelial endocytosis and delivery of commensal bacterial antigens from the epithelial cells to lamina propria T cells, and how diet-mediated diurnal regulation of mucosal and microbial homeostasis through intestinal epithelial cell MHC class 2 molecules.

a. Sun J, Yu S, Zhang X, Capac C, Aligbe O, Daudelin T, Bonder EM, **Gao N**. Wntless-Sec12 complex on ER membrane regulates early Wnt secretory vesicle assembly and mature ligand export. *J Cell Sci.* 2017 Jul 1;130(13):2159-2171 PMCID: PMC5536887.
b. Ladinsky MS, Araujo LP, Zhang X, Veltri J, Galan-Diez M, Soualhi S, Lee C, Irie K, Pinker EY, Narushima S, Bandyopadhyay S, Nagayama M, Elhenawy W, Coombes BK, Ferraris RP, Honda K, Iliev ID, **Gao N**, Bjorkman PJ, Ivanov II. Endocytosis of commensal antigens by intestinal epithelial cells regulates mucosal T cell homeostasis. *Science.* 2019 Mar 8;363(6431). PubMed PMID: 30846568. PMCID IN PROCESS.

c. Tuganbaev T, Mor U, Bashiardes S, Liwinski T, Nobs SP, Leshem A, Dori-Bachash M, Thaiss CA, Pinker EY, Ratiner K, Adlung L, Federici S, Kleimeyer C, Moresi C, Yamada T, Cohen Y, Zhang X, Massalha H, Massasa E, Kuperman Y, Koni PA, Harmelin A, **Gao N**, Itzkovitz S, Honda K, Shapiro H, Elinav E. Diet Diurnally Regulates Small Intestinal Microbiome-Epithelial-Immune Homeostasis and Enteritis. *Cell.* 2020 Sep 17;182(6):1441-1459.e21. PMID: 32888430.
d. Das S, Feng Q, Balasubramanian I, Lin X, Liu H, Pellón-Cardenas O, Yu S, Zhang X, Liu Y, Wei Z, Bonder EM, Verzi MP, Hsu W, Zhang L, Wang TC, **Gao N**. Colonic healing requires Wnt produced by epithelium as well as Tagln+ and Acta2+ stromal cells. *Development*. 2022 Jan 1;149(1). PMID: 34910127; PMCID: PMC8881740.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/nan.gao.1/bibliography/public/