CURRICULUM VITAE

Name: John Edgar French, Ph.D.

Position Professor

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EDUCATION

1975-1978	Post-doctoral research in radiation biology and cancer. NCI-NNMC, 9000 Wisconsin Ave., Bethesda, MD (Mentor: Dr. Sigmund J. Baum, NNMC)
1970-1975	Ph.D., Physiology and Cell Biology; North Carolina State University, Raleigh, NC (Mentors: Prof. J. Roberts and Prof. E. Hodgson)
1967-1968	Environmental Physiology, Colorado State University, Ft. Collins, CO (Mentor: Dr. W. Marquardt)
1965-1967	M.S., Physiology and Immunology; Mississippi State University, State College, MS (Mentors: Prof. R. Sadler and B. Glick)
1961-1965	B.S., Zoology and Chemistry, Mississippi State University, State College, MS

PROFESSIONAL EXPERIENCE

7/1/19-Present Professor, University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Nutrition Research Institute (Prof. S. Zeisel, Director, Kannapolis, NC 28081) and Nutrition Department (Prof. Beth Mayer-Davis, Chapel Hill, North Carolina 27599).
Research is focused on pre-clinical genetically-diverse models for translation to nutrition and health outcomes related to diet-induced obesity, calorie restriction, concomitant environmental toxic chemical exposures, and associated co-morbidities (cancer, type 2 diabetes, metabolic syndrome, etc. Translation of risk from the mouse model to human populations is carried out through collaborations with nutrition experts mining SNP GWAS of the same co-morbidities. Using bioinformatics of functional gene and intergenic sequence variants identified in the mouse model and human studies we use binary interactions based on gene

ontologies in multiple gene sets extracted from large agnostic databases to predict networks and associations based on canonical pathways that aid explain similar magnitude of selected phenotype variance between the species. Additional service is being provided by invited lectures and serving on student academic (M.S. and Ph.D.) research committees.

9/1/2017- 6/30/2019 Visiting Professor, University of North Carolina at Chapel Hill, Gilling School of Global Public Health, Nutrition Research Institute, Kannapolis, North Carolina 27599. *Responsibilities have included development and implementation of pre-clinical mouse models and infrastructure for precision nutrition using genetically-diverse Collaborative Cross Recombinant Inbred Lines (CC RIL) and Diversity Outbred mice (DO). Experimental models developed with UNC faculty for nutritional intervention in fetal alcohol syndrome disorder, obesity heterogeneity and associated diseases (atherosclerosis, diabetes, salt sensitivity, and basic studies of host genetics on inter-individual differences in metabolomics and gut microbiota.*

2013-Present Adjunct Associate Professor, Center for Pharmacogenetics and Individualized Therapy (Dr. Tim Wiltshire, Director), Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599. *Responsibilities have included interacting with faculty and students, participating in lecture courses focusing on inter-individual differences in serious adverse reactions by providing invited lectures and serving on student academic and research committees*.

2007-2013 Branch Chief, Host Susceptibility, National Toxicology Program (John Bucher, Ph.D., Associate Director, NTP), National Toxicology Program, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina 27709 USA. *Responsibilities included supervision of a team of Ph.D. level scientists to develop and manage a multidisciplinary research and testing program focused on developing our understanding of the genetic basis for population-level differences for both toxicant exposures and/or disease susceptibility. This multidisciplinary research initiative will aid understanding of how and why substances in our environment are hazardous to some individuals and not to others. Asthma, cardiovascular disease, cancer, diabetes, and obesity are a few examples of diseases associated with multiple interacting genes and their allelic variants that are induced or influenced by environmental exposure to toxins and xenobiotic chemicals. Specific research projects included the use of population-based panels of laboratory and wild-derived inbred mice linking exposure to genetic susceptibility, population variation in ADME and toxicokinetics, and genome wide linkage and mapping studies for toxicity phenotypes, mouse aging and spontaneous disease profiles for the Collaborative Cross and DO mice founder stains for reference, DNTP/DIR mouse methylome reference using C57BL/6, C3H/He, and their F1 hybrid to establish within and between strain differences in methylation marks and parent of origin effects using DNA-Seq, Bis-Seq, and RNA-Seq under NTP*

standard dietary and environmental conditions. The Host Susceptibility Branch supports the NIEHS & NTP mission by planning, designing, conducting, and analyzing a multi-model assessment of the xenobiotic chemicals that are associated with human diseases or disease processes (e.g., cytotoxicity, tissue regeneration, DNA damage and repair, nuclear receptor-based hormonal signaling, immunosuppression, mitochondrial energetics, xenobiotic metabolism, etc.) resulting from gene-environment interactions.

2001-2007 Group and NTP Discipline Leader, Transgenic Carcinogenesis, Laboratory of Molecular Toxicology (John Pritchard, Ph.D., Acting Chief), Environmental Toxicology Program, Division of Intramural Research, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina, USA. *Genetically modified rodent models of cancer were developed and used for short-term cancer bioassays to complement conventional studies for the identification and characterization of presumptive genotoxic or immunosuppressive human carcinogens. Genes and their allelic variants associated with susceptibility to chemical and physical carcinogens that induced the loss of tumor suppressor gene function and increased tumor progression were investigated using molecular biology and genetic analysis through hypothesis-based research.*

1996 to 2001 Unit and Discipline Leader, Transgenic Carcinogenesis, Laboratory of Environmental Carcinogenesis and Mutagenesis (Raymond W. Tennant, Ph.D., Chief), Environmental Toxicology Program, Division of Intramural Research, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina, USA. *Genetically modified mouse models of carcinogen and nutrient-gene interactions that modulate the cellular redox state, mitogenesis, and apoptosis were investigated to identify modes of action and predictivity for human carcinogens.*

1990 to 1996 Research Physiologist, Laboratory of Environmental Carcinogenesis and Mutagenesis (Raymond W. Tennant, Ph.D., Chief), Environmental Carcinogenesis Program, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina USA. *Investigated p53 tumor suppressor gene function in chemically induced mutagenesis and carcinogenesis were investigated for the identification of carcinogens using p53 haploinsufficient mice carrying a λlizα transgene for rapid in vivo mutagenesis for short-term cancer and mutagenesis.*

1989 to 1990 Senior Scientist, US Public Health Service Foreign Work/Study Fellowship; Combined Nordic Studies, Project on Molecular Genetics, Institute of Occupational Health, Helsinki, Finland. *RAS proto-oncogene mutations and chromosomal abnormalities associated with a loss of heterozygosity at known sites of tumor suppressor genes were investigated in asbestos and smoking related human lung and pleural membrane tumors from occupational exposed workers.*

1984 to 1989 Physiologist, Carcinogenesis and Toxicology Evaluation Branch (James K. Selkirk, Ph.D., Chief), Division of Toxicology Research and Testing, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina USA. *Study design, data evaluation and interpretation, and reporting (technical reports/scientific literature) on NTP/NIEHS toxicology and carcinogenesis studies. Management and administration of NTP contracted studies at a major contract laboratory. Technical evaluation and monitoring of study conduct, costs, and laboratory performance by site visit evaluation and reports are essential elements.*

1982 - 1984 Physiologist, Carcinogenesis and Toxicology Evaluation Branch (Bernard Schwetz, DVM, Ph.D., Chief), Division of Toxicology Research and Testing, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina USA. *Study director, Carcinogenesis Bioassays; Independent research on chemically induced lesions in the hematopoietic system of rats and mice.*

1978 - 1982 Supervisory Research Physiologist (Blood and Blood Products Branch (Joseph Fratantoni, M.D., Chief), Division of Blood and Blood Products, National Center for Drugs and Biologics, NIH and Food and Drug Administration, Building 29, NIH, 8800 Rockville Pike, Bethesda, Maryland USA. *Cell physiology of inflammatory cells and stem cells isolated from leukapheresis and counter flow centrifugal pheresis before and after cryopreservation for transplantation was investigated. In addition, I was responsible for review of investigational and new drug applications related to therapeutic uses of blood, stem cells, and associated products*.

1976 - 1978 Supervisory Research Physiologist, Department of Experimental Hematology (Sigmund Baum, Ph.D., Director), Radiobiology Research Institute, National Naval Medical Center, Bethesda, Maryland USA. *Research focused on radiation biology and physiology of cell transfusion therapy for immunosuppression, septicemia, and shock.*

1973 - 1975 Post-Doctoral Fellow in Radiation Biology and Toxicology of Mammalian Systems (Sigmund Baum, Ph.D., Mentor), Department of Experimental Pathology, Radiobiology Research Institute, National Naval Medical Center, Bethesda, Maryland USA. *Radiation biology and the dysregulation of cell function in hematopoietic stem cells and inflammatory cells and xenobiotic metabolism was the focus of this training program.*

1970 - 1973 NIEHS Pre-doctoral Student in Molecular Toxicology and Comparative Biochemistry (Drs. John F. Roberts and E. Hodgson), Inter-Departmental Graduate Program in Toxicology, North Carolina State University, Raleigh, North Carolina USA. *Drug metabolism, reactive intermediates and DNA damage response and replication in prokaryotes and eukaryotes were investigated.*

1968 - 1970 Instructor of Biology & Physiology (Howard Erikson, Ph.D., Chairman), Department of Biological Sciences, Towson State University, Baltimore, Maryland USA. *Taught immunology and physiology courses to* undergraduate students in Biology Department and Nursing programs.

HONORS, AWARDS, and FELLOWSHIPS

Visiting Professorship, Precision Nutrition, UNC Nutrition Research Institute, Kannapolis, NC 2017 –2018.

NIH Merit Award for demonstrating the importance of genetically diverse mouse models in understanding how and why environmental substances are hazardous to some individuals and not to others. February 13, 2013.

President and President-Elect, The Genetics and Environmental Mutagenesis Society, Research Triangle Park, North Carolina, USA, 2008—2010.

NIH Merit Award for development of the NTP Host Susceptibility Initiative, 2008.

President, Carcinogenesis Specialty Section, Society of Toxicology, 2005—2006.

Visiting Professor, Department of Environmental Sciences & Engineering, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, 2004-2005.

President, Carcinogenesis Specialty Section, Society of Toxicology, 2005—2006.

NIH Merit Award for Genetically Modified Mouse Models for Carcinogenesis Research, 2001.

NIH Intramural Research Award: Antioxidants and Cancer, 1998.

NIH Intramural Research Award: IGF-1 and Urinary Bladder Cancer, 1996.

Sustained Performance Award, Laboratory of Environmental Carcinogenesis and Mutagenesis, Environmental Carcinogenesis Program, NIEHS, Research Triangle Park, North Carolina, USA, 1996

US PHS Foreign Work/Study Fellowship: Combined Nordic Ministries Project on Human Molecular Genetics, Helsinki, Finland (Sponsor: Drs. Richard Griesemer, DTRT, NIEHS and Phil Chen, NIH), 1989 to 1990

PHS NIH Special Achievement Award: Providing Direction and Guidance in Branch Use of Computers for Meeting Program Goals and Office Automation (Sponsor: Dr. James Selkirk), 1988.

Outstanding Employee, Radiobiology Research Institute, National Naval Medical Center, 1977 and 1978 (Sponsor: Dr. S. Baum).

NIEHS Traineeship in Molecular Toxicology and Comparative Biochemistry, (Mentors: Drs. John Roberts and Ernest Hodgson), 1970-1975.

Post-Graduate Training and Education in Mammalian Genetics:

Short Course on Complex Trait Analysis and Statistical Genetics, The Jackson Laboratory, 2007, High Seas, Bar Harbor, ME

Short Course on Experimental Genetics of The Laboratory Mouse in Cancer Research, The Jackson Laboratory, 1996, High Seas, Bar Harbor, ME

Short Course on Medical and Experimental Mammalian Genetics, The Jackson Laboratories, 1988, Bar Harbor, ME

Intramural/Extramural Committees/Faculties Service:

NTP Bimolecular Screening Faculty 2009-2013 (Kristine Witt, Chair)

NTP Toxicogenomics Faculty 2008-2013 (Nigel Walker, Chair)

NIEHS Conferences and Distinguished Lecture's Committee 2009-2013

External Advisory Board for UNC-CH-MIT Bioengineering Research Partnership in Toxicology, 2007-2012

NCI-Mouse Models of Human Cancer Consortium – Ad hoc Prevention Advisory Committee (Cory Abate-Shen, Chair) 2011

NTP/NIEHS Management Committee 2009-2010 (Nigel Walker, Chair)

NIEHS Bioinformatics Search Committee 2008-2009 (Tom Kunkel, Chair)

External Advisory Board for Systems Genetics Program, Oak Ridge National Laboratories, Oak Ridge, TN 2007-2009

Planning and Development of the NTP Host Susceptibility Initiative (Lead, October 2006 – October 2007) (John Pritchard, Chair)

Review of the Use of Transgenic Rodent Models for the Environmental Toxicology Program (John Pritchard, Chair), 2001-2002

p53 Model Assay Working Group, Alternatives to Carcinogenicity Testing Committee, International Life Sciences Institute, Health and Environmental Sciences, Washington, DC, 1998-2002

Transgenic Models Faculty, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, 1996-2001

Animal Use and Care (Robert Chapin, Chairman) Division of Intramural Research, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, 1993-1998

Career Development and Training (Paul Nettesheim, Chairman) Division of Intramural Research, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, 1998

Transgenic Technology and Use Committee (Mitch Eddy, Chairman) Division of Intramural Research, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, 1994-96

Special Emphasis Review Panel, CSR, NIGMS, NIH for RO1 Grant Reviews, 1996, 1998, 2001, 2002

Society Memberships

American Association for Cancer Research
American Society of Nutrition

Complex Traits Community (Population Genetics)

Genetics and Environmental Mutagenesis Society

Journal Referee

Archives of Toxicology, Cancer Research, Carcinogenesis, Chemico-Biological Interactions, Environmental Health Perspectives, Frontiers in Genetics, International Journal for Cancer, Nature Genetics, NIEHS Intramural Manuscript Review, Nutrition & Cancer, Oncogene, PLoS One, PLoS Biology, PLoS Genetics, Science, Toxicological Pathology, and Toxicological Sciences

Chair and Organizer for NIH, Regional, National, and International Meetings

1. Population based animal models for discovery of complex traits, American Society of Human Genetics, October 22-26, 2013, Boston, MA.

2. NextGen Mouse Models: The Use of Population Based Mouse Models in Toxicology, Toxicology Forum, July 8-11, 2013, Aspen, CO.
3. Genetics & Epigenetics – The Link Between Individual Genomes-Environment Interaction and Toxicity, International Congress of Toxicology 2013, June 30-July 4, Seoul, Korea.
4. Genetics: The Link Between Exposure, Gene X Environment Interaction, and Toxicity, Society of Toxicology, March 7-11, 2010, Salt Lake City, UT, USA.
5. Dissecting Genome Structure, Genetic Traits, and the Basis for Complex Diseases, Genetics and Environmental Mutagenesis Society, October 5, 2009, The Friday Center, UNC-Chapel Hill, Chapel Hill, NC.
6. Genome Architecture: The Role for Copy Number and Structural Variation, Genetics and Environmental Mutagenesis Society, April 13, 2009, Research Triangle Park, NC.
7. Genetic Susceptibility – The Link between Environmental Exposure and Human Disease, NIH Research Festival, October 14, 2008, Bethesda, MD
8. Host Susceptibility and Chemical Safety Testing: New Approaches to Estimate Risks in The Human Population, Co-Chair with Ivan Rusyn, M.D., Ph.D., 47th Annual Meeting of the Society of Toxicology, March 18, 2008, Seattle, WA.
9. 5th Complex Traits Consortium, Chapel Hill, NC, Co-Chair with David Threadgill, UNC-CH, May 6-9, 2006, Chapel Hill, NC.
10. Alternatives to Carcinogenicity Testing Using Genetically Altered Rodent Models for Carcinogen Identification and Determining Mechanisms of Action, American College of Toxicology, November 3, 2003,Washington, DC.
11. *p53 and RasH2 Mouse Models*, International Workshop on Genotoxicity, Plymouth, England, June 27-29, 2002.

Invited Symposia/Workshop Presentations:

1. How does genetic diversity affect metabolism and cancer risk? Cancer and Metabolism Symposium, Turku Center for Disease Models, December 13-14, 2016, Turku, Finland.

2. Using Diversity Outbred Mice to Identify the Genetic Basis for Toxicity Thresholds and Susceptibility, Genetics and Environmental Mutagenesis Society, April 15, 2015, USEPA, Research Triangle Park, NC.
3. Identifying G X E Interactions and Thresholds for Toxicity in Diversity Outbred Mice. Population-based Rodent Resources for Environmental Health Sciences Meeting, March 18-19, 2015, NIEHS, Research Triangle Park, NC.
4. Integrating pathology and toxicology with genetics using MAGIC Mice, American College of Veterinary Pathology, November 7-12, 2014, Atlanta, GA, USA.
5. Mapping Susceptibility QTLs for GEI and Environmental Toxicity, American Society of Human Genetics, October 13-16, 2013, Boston, MA.
6. Population Based Mouse Models for Toxicology and Carcinogenesis, International Congress of Toxicology, July 3, 2013, Seoul, Korea.
7. A new genetically diverse mouse population model reveals individual susceptibilities to benzene genotoxicity, Mouse Models for Human Cancer Consortium, June 18, 2013, Bethesda, MD.
8. The Use of Population-Based Inbred Panels and Diversity Outbred Mouse Models to Explore Individual Variability and Toxicity to Benzene, Society of Toxicology, March 14, 2013, San Antonio, TX.
9. Using Population-based Models to Explore Individual Variability and Susceptibility to Toxicity, Michigan Society of Toxicology, December 1, 2012, Ann Arbor, MI.
10. *Genetic Basis of the Response to Drugs and Chemicals*, STP Mechanisms of Toxicity, Annual Meeting, June 24-28, 2012, Boston, MA USA.
11. *DNA damage phenotypes in diversity outbred (J:DO) mice are associated with QTLs demonstrating allele specific resistance and susceptibility*, Complex Trait Community, The Pasteur Institute, June 12-15, 2012, Paris, France,
12. *Using In Vivo Animal Models to Explore Individual Variability in Toxicity, Biological Factors that Underlie Individual Susceptibility to Environmental Stressors, and Their Implications for Decision-Making*. National Academy of Sciences, April 18-19, 2012, Washington, DC.
13. *Ionizing Radiation Induced DNA Damage, Strand Break (DSB) Repair and Lymphohematopoietic Disease In Vivo and In Vitro*, Mouse Genetics 2011, June 24, 2011, Washington, DC.
14. *The Host Susceptibility Initiative: A new NTP research and testing strategy and paradigm for hazard characterization and risk assessment*, Society of Toxicology, March 7-11, 2010, Salt Lake City, UT.
15. *Benzene Mode of Action, Hazard, and Risk Characterization in Genetically-Defined and Modified Mouse Models*, Benzene 2009: Health Effects and Mechanisms of Bone Marrow Toxicity, September 10, 2009, Munich, Germany.
16. *Genetically Modified Mouse Models for Hazard Identification and Risk Assessment in Toxicology and Carcinogenesis: Strengths and Weaknesses*, Society of Toxicologic Pathology, June 23, 2009, Washington, DC.

17. *Genetic Susceptibility: The Link Between Exposure and Disease*, ICCA-LRI Workshop, June 16, 2009, Charleston, SC.
18. *Genetic susceptibility to DNA strand break damage, loss of heterozygosity (genomic instability), and cancer*, NIH Research Festival, October 14, 2008, Bethesda, MD.
19. *The radiation induced tumor and DNA strand break repair phenotype in p53 deficient and wildtype mouse hematopoietic stem cells (HSC) in vivo and in vitro is genetic background dependent,* Phenotyping of Model Organisms, CTC/QTRN Satellite Conference, May 31, 2008, Montreal, Quebec, Canada.
20. *Host susceptibility and individual susceptibility to environmental agents and diseases,* Host Susceptibility and Chemical Safety Testing: New Approaches to Estimate Risks in The Human Population, Co-Chair, 47th Annual Meeting of the Society of Toxicology, March 18, 2008, Seattle, WA.
21. *Genetically-Engineered Mouse Models for Hazard Identification and Risk Extrapolation: A Brief Overview on the 20th Anniversary,* CEA-TAC Symposium, 47gh Annual Meeting of the Society of Toxicology, March 17, 2008, Seattle, WA.
22. *Identification of Presumptive Human Carcinogens and their Mode of Action using Toxicogenetics.* Approaches to determining whether a carcinogen is acting via a genotoxic mode of action, 46th Annual Meeting of the SOT, March 25, 2007, Charlotte, NC .
23. *NTP Host Susceptibility Initiative: Genetic Variation and Susceptibility to Toxicity*, Toxicology Forum, July 10, 2007, Aspen, CO**.**
24. *Gene-Environment Interaction in a Mouse Model for Susceptibility to Carcinogen Induced DNA Damage.* Second Annual Conference CRG - Unveiling Genome-Wide DNA Variation in 15 Diverse Mouse Strains, September 25, 2006, Research Triangle Park, NC.
25. *Genetic Susceptibility to Ionizing Radiation Induced Loss of Heterozygosity in Mouse and Human Hematopoietic Stem Cells, 5th Annual Complex Traits Consortium Meeting, May 7, 2006, Chapel Hill, NC.*
26. *Signaling pathways for DNA damage and repair, apoptosis, and lymphoid progenitor survival are deregulated by N-acetyl-L-cysteine*. DNA Evaluation and Repair, Co-Chair and presenter, 44th Annual Meeting of the SOT, March 8, 2005, New Orleans, LA.
27. *Genotoxic stress and genomic instability in the p53 haploinsufficient mouse*. C.L. Davis Symposium, Hoffman-La Roche, December 10, 2004, Nutley, NJ.
28. *The role of the p53 haploinsufficient mouse model in toxicology and cancer studies.* American College of Toxicology, November 3, 2003, Washington, DC.
29. *Alternative carcinogenicity testing with the FVB/N-TgN^{Led} (v-Ha-Ras) and the B6;129-Trp53^{tm1Brd} (N5) genetically altered mouse models*. DIA, June 16, 2003, San Antonio, TX.
30. *An overview of selected transgenic models used for carcinogen identification*. NTP Workshop, February 20, 2003, Washington, DC.
31. *p53 and Ras function in cancer*. Japanese Society for Animal Models of Human Disease, November 6 & 7, 2002, Tokyo, Japan.

32. *New Models for Toxicology and Carcinogenesis*. Food Safety Symposium, American Chemical Society, August 18 & 19, 2002, Boston, MA.
33. *Alternative models for identification of potential human carcinogens*. Fourth International Congress for Alternatives, August 14 & 15, 2002, New Orleans, LA.
34. *p53 and RasH2 mouse models for identification of carcinogens*. UK Environmental Mutagen Society, July 3, 2002, Plymouth, England.
35. *The application of mechanistic information from transgenic animal studies for identification and characterization of presumptive human carcinogens.* Workshop on Mechanistic Considerations in the Molecular Epidemiology of Cancer, International Agency for Research on Cancer, November 14-17, 2001, Lyon, France.
36. *The development, characterization, and use of the TSG-p53 haploinsufficient and the Tg.AC (v-Ha-Ras) mouse models for rapid identification of carcinogens*. Eighth International Conferences on Environmental Mutagenesis. October 24, 2001, Shizuoka, Japan.
37. *p53 and Hras2 transgenic tumor models working group.* Eighth International Conferences on Environmental Mutagenesis. October 22, 2001, Shizuoka, Japan.
38. *Application of transgenic models in toxicology* (A CE Course Sponsored by the IUTOX). Chinese Toxicology Society, October 15-16, 2001, Nanjing, China.
39. *The development, characterization, and use of genetically altered mouse models for identification of carcinogens.* American College of Laboratory Animal Medicine, April 3, 2001, Point Clear, AL.
40. *The nature of the p53 haploinsufficient mouse model*. ILSI/HESI Evaluation of Alternative Methods for Carcinogenicity Testing, November 1-3, 2000, Leesburg, VA.
41. *p53 Haploinsufficiency, genetic susceptibility, and environmental Carcinogenesis*. Thirty-Eighth Hanford Symposium on Health and the Environment, October 19-20, 2000, Richland, WA.
42. *Immune suppression and immunomodulation in genetically altered mouse models*. Mechanisms of Immunomodulation, September 23, 1999, Bethesda, MD.
43. *Benzene leukemogenesis: an environmental carcinogen induced tissue specific model of neoplasia using genetically altered mouse models*. Benzene State of the Science Workshop, December 15-17, 1998, University of Ottawa, Ottawa, Canada.
44. *Genetically altered mouse models for rapid identification and investigation of carcinogens*. Alternative Toxicological Methods for the 21st Century: Protecting Human Health and Advancing Animal Welfare, December 3, 1998, Bethesda, MD.
45. *Identification and investigation of mutagenic carcinogens using the heterozygous p53 deficient mouse model.* American College of Toxicology, November 11, 1998, Orlando, FL.
46. *Identification and investigation of mutagenic carcinogens using the heterozygous p53 deficient mouse model*. 1st Rodent Models of Modern Risk Assessment Meeting, The Jackson Laboratory, , September 8-12, 1998, Bar Harbor, ME.

47. *Studies in the heterozygous p53 deficient mouse model.* NTP Board of Scientific Counselors, NIEHS, NIH, February 5, 1998, Research Triangle Park, NC, USA.
48. *The use of transgenic animals in cancer testing*. Colloquium on scientific advances and the future in toxicologic risk assessment: 50th Anniversary of the National Research Council's Committee on Toxicology, December 4-5, 1997, Washington, DC.
49. *Genetically altered mouse models for predicting mutagenicity and carcinogenicity.* American College of Toxicology, November 10, 1997, Washington, DC.
50. *The heterozygous p53 deficient mouse model for cancer endpoints in safety assessment.* Drug Information Association Workshop, October 26 & 27, 1997, Noordwijk, The Netherlands.
51. *Transgenic models for mutagenesis and carcinogenesis: testing of xenobiotics*. Eighth Annual North American ISSX Meeting, October 26-30, 1997, Hilton Head, SC.
52. *Evaluation of transgenic mouse models for drug and chemical safety assessment.* Second Annual Conference on Molecular Toxicology, IBC, April 28-30, 1997, Rockville, MD
53. *Applications of transgenic models in toxicology*. Monsanto Annual Toxicology Symposium, May 5, 1997, Creve Coeur, St. Louis, MO.
54. *Susceptibility of Tg.AC (v-Ha-Ras) and p53 deficient transgenic mouse lines to environmental carcinogens identified in long-term bioassays.* US-Japan Workshop: Genetic and Environmental Actions in Cancer, Susceptibility in Animal Models, NIH, March 27-28, 1997, Bethesda, MD.
55. *Update of benzene studies in transgenic mouse models.* The 22nd Winter Toxicology Forum, February 22-27, 1997, Washington, DC.
56. *Rapid identification of mutagenic carcinogens in tumor suppressor gene p53 deficient (+/-) mice.* December 4-6, 1996, Barton Creek, TX.
57. *Alternative in vitro and in vivo assays using genetically altered mice for predicting carcinogenicity.* American College of Toxicology, November 10, 1996, Valley Forge, PA.
58. *Rapid identification of in vivo mutagenic carcinogens using the p53 deficient (+/-) mouse with a lacI neutral reporter gene*. 14th Annual GEMS Fall Meeting, October 11, 1996, Research Triangle Park, NC.
59. *Short-term mutagenesis and carcinogenesis assays in genetically altered mice.* Genetic Toxicology of Pharmaceuticals, American Society of Industrial Microbiology, August 6, 1996, Research Triangle Park, NC.
60. *Indirect Mechanisms of Carcinogenesis.* Food and Drug Administration Workshop, March 4-5, 1996, Bethesda, MD.
61. *Correlation between mutagenic carcinogens induced mutant frequency and tumorigenesis in* λliz_a*:*$p53^{def}$ *(+/-) F1 transgenic mice*. Transgenic Mice in Mutation Research, March 20-23, 1996, Sidney, BC, Canada.
62. *Validation of the p53 deficient mouse carcinogenesis model*. 1995 Toxicology Fall Workshop; Pharmaceutical Research and Manufacturing Association, October 5-6, 1995, Rockville, MD.

63. *The bi-transgenic lacIq:p53def mouse model for mutagenesis and carcinogenesis studies*. Mini-Symposium on the Use of Transgenic Mice for Short Term Bioassays, National Institute of Public Health and Environmental Protection, November 10, 1995, Utrecht, The Netherlands.
64. *Chemical effects in transgenic mice* In Vivo Transgenic Models, International Congress of Toxicology-VII, July 2-6, 1995, Seattle, WA.
65. *Short-term chemical carcinogenesis studies in Big Blue™TSG-p53™deficient mice.* Midwest Society of Toxicology, May 20, 1994, Chicago, IL.
66. *The p53 deficient mouse model for mutagenesis and carcinogenesis studies. Potential use of transgenic mouse models for in vivo mutagenesis and carcinogenesis studies.* Gene Therapy Symposium, Glaxo, November 9, 1993, Research Triangle Park, NC.
67. *Chemical effects in transgenic mice*. Environmental Carcinogens and Risk Assessment, November 30, 1993, Barton Creek, TX.
68. *Short-term carcinogenesis studies in mice haploinsufficient for the wildtype p53 tumor suppressor gene*. Use of Transgenetic Animal Models in Biomedical Research. American College of Toxicology, October 5, 1993, New Orleans, LA.
69. *US NTP summary results on organic solvent toxicology and carcinogenesis studies in rats and mice*. Toxicology of Industrial Chemicals Symposium, 11th Annual Meeting of the Finnish Society of Toxicology, May 25-26, 1990, Tampere, Finland.

Selected Invited Seminars

Forward and Reverse Genetic Analysis of Metabolic Syndrome in a Mouse to Human Model. November 5, 2020, UNC Nutrition Research Institute, Kannapolis, NC.

1. Forward and Reverse Genetic Analysis of Metabolic Syndrome in a Mouse to Human Model. November 5, 2020 UNC Nutrition Research Institute, Kannapolis, NC.
2. Interindividual Genetic Variation and Biological Relevance: The Collaborative Cross and Diversity Outbred Mice: New Models for Gene x Environment Interaction (GEI) Investigations. May 4, 2017, UNC Nutrition Research Institute, Kannapolis, NC.
3. Mapping susceptibility QTLs for gene-environment interactions and environmental toxicity**.** January 14, 2014, University of North Carolina at Chapel Hill, Chapel Hill, NC.
4. Using Population-based Models to Explore Individual Variability and Susceptibility to Toxicity in Environmental Health Research. University of North Carolina at Greensboro, March 20, 2013, Greensboro, NC.
5. Using Population-based Models to Explore Individual Variability and Susceptibility to Toxicity in Environmental Health Research, November 30, 2012, Center for Molecular Toxicology and Carcinogenesis, Pennsylvania State University, State College, PA.
6. GWAS in Diversity-Outbred mice exposed to benzene reveals candidate genes for resistance and susceptibility alleles to genotoxicity. September 11, 2012, National Advisory Environmental Health Sciences Council, Research Triangle Park, NC.
7. *Mouse GWAS in diversity outbred mice reveals resistance and susceptibility alleles to benzene hematotoxicity and genotoxicity*, July 2, 2019, ILS, RTP, NC.
8. *Host susceptibility: Why some people might get cancer and others don't*! May 29, 2012, DNTP Post-Doctoral IRTA Seminar, NIEHS, RTP, NC.

9. *The CC/DO mice in toxicology*. May 23, 2012, The NIH Deputy Directors, Bethesda, MD.
10. *ADME & HAM*, November 20, 2009, The DNTP Forum, RTP, NC.
11. *Genetic Susceptibility - The Link between Exposure, Toxicity, and Disease*, January 29, 2009, University of Arizona, Tucson, AZ.
12. *Genetic Susceptibility – The Link between Exposure, Toxicity, and Disease,* October 15, 2008, CDER, USFDA, White Oak, MD.
13. *Genetic Susceptibility to LOH and Cancer*. LPC/LMT Seminars, October 12, 2006, NIEHS, RTP, NC.
14. *Genetically altered mouse models for carcinogens of presumptive risk to humans.* January 18, 2005, NCEA, USEPA, Washington, DC.
15. *Genotoxic stress and genomic instability in the p53 haploinsufficient mouse.* LPC/LMT Seminars, NIEHS, October 7, 2004, RTP, NC.
16. *Genetically altered rodent models and mechanisms of carcinogenesis.* April 16, 2004, Pfizer, Kalamazoo, Michigan.
17. *The role of tumor suppressor gene haploinsufficiency in genomic instability and cancer.* February 25, 2003, NHERRL, Triangle Park, NC.
18. *p53 Haploinsufficiency, LOH, and Genomic Instability.* November 11, 2002, National Cancer Research Center, Tokyo, Japan.
19. *p53/Tg.AC/RasH2 transgenic mouse models for carcinogen identification.* November 6, 2002. IBL, Tokyo, Japan.
20. *The application of transgenic mouse models to toxicology and cancer.* April 24, 2002, University of North Carolina at Chapel Hill, Chapel Hill, NC.
21. *The role of p53 haploinsufficiency in tumorigenesis*. November 1, 2001, Laboratory of Molecular Carcinogenesis, NIEHS, RTP, NC.
22. *Use of genetically altered mouse models for pharmaceutical safety assessment*. February 12, 200, Glaxo Smith Kline.
23. *Potential roles of p53, p16Ink4a, and p19ARF in urinary bladder cancer*. December 6, 1999, NIEHS Transgenics Faculty, RTP, NC.
24. *Use of transgenic mice to identify carcinogens of potential human risk*. November 12, 1999, Department of Pathobiology, University of Illinois, Champaign-Urbana, Illinois, USA.
25. *Benzene leukemogenesis in transgenic mouse models*. February 19, 1998, Environmental and Occupational Health Institute, University of Medicine and Dentistry of New Jersey and Rutgers University, New Brunswick, NJ.
26. *Chemical carcinogenesis in the p53 haploinsufficient mouse*. January 5, 1998, Chemical Industries Institute for Toxicology, Research Triangle Park, NC.
27. *The p53 mouse model*. October 28, 1997, The National Institute of Public Health and the Environment, Bilthoeven, The Netherlands.
28. *The potential for transgenic mouse models in toxicology and carcinogenesis.* June 9, 1997, NIEHS, Molecular Oncology Faculty,

29. *The TP53 gene suppresses cancer by regulating critical signaling pathways for DNA damage and repair, apoptosis,* and gene-environment interactions. May 20, 1997, US EPA, Research Triangle Park, NC.
30. *The potential for p53 and Tg.AC mouse models in safety assessment of pharmaceuticals.* May 7, 1997, Boehringer-Ingelheim Pharmaceuticals Inc., Ridgefield, CT.
31. *Carcinogen-induced genomic instability in the p53 deficient mouse*. May 5, 1997, GD Searle and Monsanto Symposium, St. Louis, MO.
32. *p53 Mouse model for cancer*. December 2, 1996, Triangle Carcinogenesis Club, CIIT, RTP, NC.
33. *Conduct of carcinogenesis bioassays using transgenic mouse models*. November 22, 1996, Integrated Laboratory Systems, RTP, NC.
34. *Induction of LOH in the p53 deficient mouse.* May 10, 1996, Baylor College of Medicine, Houston, TX.
35. *Mutagenesis and carcinogenesis in transgenic mouse models*. May 12, 1994, Wallenberg Laboratory, Stockholm University, Stockholm, Sweden.
36. *Modeling environmental exposures in transgenic mouse models.* February 11, 1994, Swedish Institute of Occupational Health, Division of Toxicology, Stockholm, Sweden.
37. *Investigation of tumorigenesis mechanisms in transgenic mouse models*. December 12, 1993, Karolinska Institute, Department of Tumor Biology, Solna, Sweden.
38. *Mechanisms of tumorigenesis in the p53 deficient mouse.* Karolinska Institute, Department of Nutrition and Toxicology, Huddinge, Sweden, December 18, 1993.
39. *Mechanisms of mutagenesis and carcinogenesis.* September 7, 1993, North Carolina State University, Department of Toxicology, Raleigh, NC.
40. *Role of folate deficiency in mutation frequency*. September 2, 1993, University of North Carolina at Chapel Hill, Chapel Hill, NC.

MENTORING AND TEACHING

2013-Present Invited Lectures in Exposure Assessment ENVR770 (Prof. Nylander-French)
Department of Environmental Science and Engineering, UNC-CH

Research Fellows/Trainees

2004-2007 Hengning Ke, M.D., Ph.D. (IRTA) (Pleiotropic functions of *BCL2 in apoptosis, cell adhesion and migration in mouse and human cells*

1998–2003 Keith Martin, Ph.D. (IRTA Fellow, Intramural Research Award on Antioxidant/Pro-oxidant Modulation of Apoptosis, Cell Proliferation and Cancer)

2000-2002 Janis Hulla, Ph.D., Senior Research Fellow. (The *Trp53* tumor suppressor gene and suppression of tumorigenesis. Co-mentor with Ken Tindall, Ph.D., NIEHS, NIH)

1998-2000 Muriel Saulnier, DVM, Ph.D. (Ph.D. student, NCSU-Raleigh) Interaction between the *Hras* proto-oncogene and the *Trp53* tumor suppressor gene in benzene induced leukemogenesis.

1985-1988 S. Gangjee, Ph.D. (The role of *Csf1 (cFms)* proto-oncogene activity in the origin and development of F344 rat mononuclear cell leukemia.)

Student Trainees & Advisory Committees

2018-2020 Laura W. Taylor, Ph.D., Department of Environmental Sciences & Engineering, Ph.D. student, UNC-CH, Chapel Hill, North Carolina (Leena A. Nylander-French, Ph.D., CIH; Thesis Director)

2009–2013 Michelle Disimone, Department of Genetics, Ph.D. student, UNC-CH & NCSU, Raleigh, North Carolina (David W. Threadgill, Ph.D.; Thesis Director)

2007–2012 Rong Jiang, Department of Environmental Sciences & Engineering, Ph.D. student, UNC-CH, Chapel Hill, North Carolina (Leena A. Nylander-French, Ph.D., CIH; Thesis Director)

2006–2010 Connie Kang, Department of Environmental Sciences & Engineering, Ph.D. student, UNC-CH, Chapel Hill, North Carolina (Leena A. Nylander-French, Ph.D., CIH; Thesis Director)

2005–2006 Thembekile Dube, Biological Science Laboratory Technician (SIS), Earned BS (Genetics) at NCSU-Raleigh, North Carolina (NIH Bachelor of Science Trainee)

2003–2005 Matthew Smith, Biological Science Laboratory Technician (SIS), Earned BS (Genetics) at NCSU-Raleigh. Biologist, Cellzdirect, Inc., Pittsboro, NC (NIH Bachelor of Science Trainee)

1998–2003 Hayden Honeycutt, Matthew Smith, Biological Science Laboratory Technician (SIS), Earned BS (Biochemistry) at NCSU-Raleigh and PharmD. (Nuclear Pharmacy) at UNC-CH. Managing Director, Nuclear Pharmacy, Lubbock, TX. (NIH Bachelor of Science Trainee)

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Refereed research papers/articles (reverse order)

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2. Taylor LW, **French JE**, Robbins ZG, Boyer JC, Nylander-French LA Influence of Genetic Variance on Biomarker Levels After Occupational Exposure to 1,6-Hexamethylene Diisocyanate Monomer and 1,6-Hexamethylene Diisocyanate Isocyanurate. Front Genet. 2020 Aug 19;11:836. doi: 10.3389/fgene.2020.00836. eCollection 2020. PMID: 32973864
3. Grimm SA, Shimbo T, Mav D, Takaku M, **French, JE** et al. Genetics, sex, and life experience-based influences on DNA methylation in mice. Nat Comm doi: 10.1038/s41467-018-08067-z, 10(1):305, 2019**.**

4. Rusyn I, Kleeberger SR, McAllister KA, **French JE**, Svenson KL. Introduction to mammalian genome special issue: the combined role of genetics and environment relevant to human disease outcomes. Mamm Genome. 29:1-4, 2019.
5. R Vermeulen, I Linhart, O Raaschou-Nielsen, P Gunel, A Seidler, R Andreoli, F Belpoggi, S Fustinoni, Y Hirabayashi, H Tsuda, D-H Koh, J Kirkeleit, N B Hopf, P Vineis, W A Chiu, **J E French,** J Huff, J Jinot, D M Reif, D B Richardson, D Ross,N Rothman, K Salazar, S Silver, E Symanski, R Thomas, L Zhang. Carcinogenicity of Benzene, Lancet Oncology 18:274-5, 2017.
6. Gatti, D, **French, JE**, Schughart, K. QTL Mapping and Identification of Candidate Genes in DO mice: A Use Case Model Derived from a Benzene Toxicity Experiment. Methods Mol Biol.1488:265-281, 2017.
7. Morgan DL, Dixon D, King DH, Travlos GS, Herbert RA, **French JE**, Tokar EJ, Waalkes MP, Jokinen MP. NTP Research Report on Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation: Research Report 3 [Internet]. Durham (NC): National Toxicology Program; 2017 Aug. PMID: 30016014
8. **French JE**, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA: Diversity Outbred mice identify population-based exposure thresholds and genetic factors that influence benzene-induced genotoxicity. *Environ Health Perspect* 123(3):237-45, 2015. [PMCID: PMC4348743].
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12. Leena A. Nylander-French, Michael C. Wu, **John E. French**, Jayne Boyer, Lisa Smeester, Alison P. Sanders, Rebecca C. Fry. DNA Methylation Modifies Urine Biomarker Levels in 1,6-Hexamethylene Diisocyanate Exposed Workers: A Pilot Study. Toxicol Lett. 2014 Dec 1;231(2):217-26, Letters, doi: 10.1016/j.toxlet.2014.10.024.

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3R35CA197627 NIH/NCI French (PI) 08/01/2018 – 07/31/2020
Genetic and Dietary Influence on Carboplatin Efficacy and Resistance in a Population-Based Mouse Model of Basal-Like Breast Cancer. The goal of this project is to determine the role of diet-induced obesity on inter-individual differences in carboplatin toxicokinetics and correlation with carboplatin DNA damage as a basis for resistance to its efficacy in basal-like breast cancer.
Role: PI

R21-OH011562 CDC/NIOSH (Nylander-French, PI) 09/01/2018 – 08/31/2020
Population-based Genetic Model for Diisocyanate-induced Asthma
The goal of this project is to test the difference in skin-airway sensitization potential between two commonly used diisocyanates to determine a benchmark-dose response and to demonstrate inter-individual differences in their relative sensitization potential using a new genetically-diverse Collaborative Cross mouse model that will allow investigation of exposure-outcome relationships while controlling potential confounding variables.
Role: Co-Investigator

Supplement to 5P30DK056350-19 NIDDK NORC Zeisel and Mayer-Davis (Co-PIs)
08/01/2019 – 07/31/2020
Using DO mice to establish inter-individual differences with pure EPA and DHA
The goal for this project is to test the role of polyunsaturated fatty acids to suppress systemic inflammation in obese Diversity Outbred male and female mice, a population based genetically diverse preclinical mouse model.
Role: Co-Investigator

CAREER FOCUS STATEMENT (Five-Year)

Dr. French is Professor in the Department of Nutrition, the Nutrition Research Institute, Gillings School of Global Public Health, and Adjunct Associate Professor, Center for Pharmacogenomics & Individualized Therapy, Eshelman School of Pharmacy, The University of North Carolina, Chapel Hill, North Carolina. Previously, he was Visiting Professor in the UNC-CH Nutrition Research Institute and the Department of Environmental Science and Engineering. He has focused his research and mentoring students and faculty on the development and use of the Collaborative Cross recombinant inbred lines (CCRIL) and Diversity Outbred Mice (DO) used for population-based genetics research focused on precision nutrition and cancer, nutritional intervention and host genetics in diet-induced obesity (cancer susceptibility, type 2 diabetes, metabolic syndrome, cardiovascular disease, etc.) and outcome followed by calorie restriction paradigms in formerly obese mice to investigate and model the inter-individual differences based on the genetics of weight loss. These eight-way multiparental advanced generation intercross CCRIL and DO mouse models have more than 45 million single nucleotide polymorphisms (SNP) and structural variants (SV) that show an average 12% minor allele frequency (MAF) distributed randomly. Their genomic architecture provides a powerful model for genotype-phenotype analysis via genome-wide associations in complex diseases (asthma, cancer, diabetes, obesity, etc.). The genetic diversity, fine meiotic recombination intervals, and a balanced 12% minor allele frequency enable genome-wide association or linkage analysis research on complex polygenic phenotypes for health and disease.

At the UNC NRI, Dr. French and colleagues have developed an active collaborative research program to establish the CC RIL and DO pre-clinical mouse models for precision nutrition research to complement clinical research. Precision Nutrition research focuses on two primary areas: 1) the inter-individual differences in the heterogeneity of obesity phenotypes and the population genetics of diet-induced obesity weight gain followed by different calorie restriction paradigms. Dr. French's previous research experience was focused on gene x environment interactions (GEI) and toxicogenetics at the National Institute of Environmental Health Sciences, NIH. Dr. French has extensive research experience and publications in genetically-engineered mouse models for investigation of host-genetic mechanisms of chemical stressors, nutrient/chemical antioxidants, and carcinogenicity as well as population-based genetically diverse Diversity Outbred (DO) mice derived from the incipient lines of the Collaborative Cross Recombinant Inbred Lines (CCRIL) to quantitatively measure host responses to nutritional and environmental insults. Most diseases are polygenic complex traits that require our understanding of inter-individual differences in disease mechanisms and treatment. Mouse models for preclinical research have been limited by investigation of the one gene at a time research paradigm using inbred mouse strains with limited genetic diversity resulting in poor translation to human research. New genetically-diverse mouse models like the CCRIL and DO offer the possibility of experimental pre-clinical studies based upon multiple interacting genes, their allelic variants, and other genomic modifiers (e.g., methylome, gut microbiota) to improve reliability and reproducibility between preclinical and clinical research. The DO and CCRIL models enable both candidate-gene and genome-wide association studies to identify quantitative trait loci and haplotype intervals for identification of DNA coding and non-coding (regulatory) sequences and assessing quantitative potential causal relationships associated with susceptibility or resistance based on exposure-response measurements. The forward genetics approach uses SNPs (to identify associated founder haplotypes) as genetic markers that are unbiased and provide a physical location for a quantitative trait locus (QTL) and the haplotype of origin. Sanger Institute in-depth and high coverage

sequences for each of the founder homozygous inbred lines provides the basis for an informatics approach to analyze both coding and non-coding DNA sequences that contain genetic or epigenetic risk variants. Candidates sequences with significant effect size can thus be investigated using reverse genetic methodologies using CCRIL founders, consomics, congenics, and CRISPR/Cas9 technology based on predicted networks and pathways associated with the interacting QTLs (candidate risk variants) and tested for proof of biological plausibility. These predictive tools are based on large-scale databases cataloging gene-gene, gene-protein, and protein-protein interactions observed in mouse and/or human cells. Predicted networks and pathways are based on significant statistical size effects that reduce the risk for false positive outcomes and can be used to guide mechanistic research to substantiate causality and better understand disease etiology based on the NRI Precision Nutrition paradigm.

To carry out this research program Dr. French focus is on the Collaborative Cross (CC) and Diversity Outbred (DO) mouse populations that are powerful preclinical models for complex multigenic disease or treatment phenotypes. These models have shown the power to increase our understanding of the heterogeneity of obesity and the potential for investigation of the role of obesity in cancer and other diseases. Most animal studies have capitalized upon standardized genomic backgrounds that are homogeneous (homozygous inbred). Further, animal studies have typically only interrogated variation at a single locus. Thus, single locus studies provide a poor model for human variation relative to complex multigenic diseases, like obesity. In contrast, novel heterogeneous mouse populations, like the DO and CC, better approximate human populations in terms of genetic diversity and thus have more power for investigating complex disease biology (1).

Homozygous inbred lines of mice have been a useful preclinical experimental research model with success in basic and biomedical research with qualifications (2). To aid quantitative research similar to human genome-wide association studies (GWAS), new mouse models and approaches have been created to use quantitative trait genetic analysis (3-8). Hybrid mouse diversity panels, the Collaborative Cross Recombinant Inbred Lines (CCRIL) and DO mice are representative of haplotype association mapping and linkage analysis approaches in preclinical experimental population-based mouse models. Hybrid mouse diversity panels are a powerful tool with more than 8 million SNPs but are limited by significant intervals that are identical by descent (IBD) in some or all laboratory derived homozygous inbred lines (9-10). This approach may be limited for robust quantitative trait loci (QTL) analysis for some phenotypes if a risk variant is located in an IBD sequence.

The CCRIL and the DO mice have different strengths and potential limitations. The CCRIL mice were created through a multiple advanced generation intercross using eight homozygous inbred lines of mice selected based on particular attributes (11). The DO mice were created from early progenitors of the early CCRIL in two steps starting from a founding population of 150 sister-brother pairs of partially inbred CC lines sampled at the 6^{th} filial generation from the second generation (G2F6) (12). Simulated rounds of mating in which females and males were paired at random with the constraint that sib-mating was prohibited were used (12). The final inbred lines of the CCRIL and the randomized DO mating contain more than 50 million SNP and structural variants (deletions, insertions, chromosome duplications or losses, etc.) and an average 12% minor allele frequency (MAF). Together, these models represent powerful tools for quantitative genetics and identifying QTL based on the variance contributed by one or more founder haplotype of origin (13-14). The eight-founder lines contributed significant genetic diversity and a high MAF for genetics to aid quantitative trait analysis to identify genes and bioinformatic analysis to explain

significant variance associated with phenotype and gene ontology. These discovery tools further enable reverse genetics studies to demonstrate causal relationships using the founder lines (congenics, consomics, etc.) or the CCRILs. The genetic sequence and identification of phenotype associated QTL identified candidate gene SNP or structural variants and tools to aid mouse to human translation are available on the Mouse Genome Informatics database at The Jackson Laboratories (15-16). For further information, please refer to The Jackson Laboratory Mouse Genome Informatics (MGI; http://www.informatics.jax.org) and Mouse Phenome Database (MPD; mouse phenome).

It is important to note that the creation of loss and/or gain of function mutants based on "single locus" of origin (homozygous inbred strain) used in genetically-altered mouse models for pre-clinical research does not apply to the CCRIL and DO mice models. Each CCRIL or DO mouse has 8 different alleles (haplotypes) at each genetic locus. Each CCRIL is isogenic (>95% homozygosity at each locus) allowing for co-isogenic controls in experimental balanced block design.

Many homozygous inbred strains derived in the laboratory, principally from the *Mus musculus domesticus* subspecies, have significant IBD. IBD limits genetic diversity at specific loci and significantly decreases the statistical ability to identify phenotype specific protocol driven QTLs based on non-synonymous SNPs, regulatory sequences, and/or CNV. Thus, our understanding and accounting for the multigenic basis of the phenotypic trait to explain phenotype variance can be decreased. Depending upon study design, the randomly bred genetically-diverse DO mice and the isogenic inbred CCRILs capture a similar magnitude of genetic diversity. Together, they provide increased opportunities to develop methods necessary to extrapolate between these genetically-diverse mouse models and humans based on similar phenotype and genotype/haplotype.

Weight gain and loss risk variants identified in DO mice studies can be tested in selected CCRIL lines mice with CRISPR/Cas9 modifications to investigate specific allelic variants and their mechanisms to demonstrate proof of causality. For example, population-based genetically diverse mouse models can be used to dissect complex traits related to nutrient overload (3,17). Several studies in CCRIL and DO mice have demonstrated the use of these population-based models to identify QTLs that may help to explain human phenotypic variation (18-22).

Taken together, we consider the randomized DO mice as forward genetics or discovery model approach and the isogenic CCRILs for corroborating phenotypes and QTLs leading to a hypothesis based research approach with isogenic controls as well as traditional comparisons of phenotypic responder and non-responder phenotypes in F1 and F2 outcrosses. For instance, we are using DO mice as a discovery model to determine why some mice have improved hyperinsulinemia and hyperglycemia with select dietary interventions and others do not in the context of obesity. To further demonstrate, our DO mice studies have focused on the heterogeneity of obesity based on specific operational paradigms. We are using series of independent DO mice cohorts (50-100 of each sex) over time to gain power for linkage analysis to discover candidate sequences that explain the haplotype(s) of origin and a majority of the operationally defined phenotypic variance (research paradigm dependent). Once a haplotype is identified that explains significant phenotypic variance, we can use the CCRIL with and without the genetic locus specific haplotype and retest to compare and contrast outcomes. This also allows for use of the appropriate CCRIL, individual CC Founder Lines, and CC founder congenics and consomics lines or CRISPR/Cas9 genetically modified CCRIL for creating defined haplotype specific controls and experimental groups to test for fidelity of the genetic basis for quantitative trait gene x diet interactions. We are working toward using experimental clinical designs and phenotypic and genetic analysis outcomes and incorporating the

elements of those designs based on the features of the CCRIL and DO mouse models to test complementarity between SNP based GWAS or family linkage analysis approaches.

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Research In Progress Summary Description(s)

I. Heterogeneity of Obesity in the DO and CC Founder Mouse Models with Human Translation Potential for Precision Nutrition

In the past 3 years we have conducted 3 independent cohort studies in Diversity Outbred (DO) mice using 50 females and 50 males per cohort to gain sufficient power to identify quantitative trait genes of relevance to the human biology of diet-induced obesity. From many quantitative trait loci, we have acquired significant preliminary data to demonstrate the similarity in phenotype between the mouse model and human. We are poised to move from the phenotyping and forward genetics (discovery) phase to the reverse genetics phase (etiology and causality) of the major obesity phenotypes and establish the relevance between the experimental model and the human condition. My first priority is to further develop a finding observed after 12-wks diet induced obesity that revealed a quantitative trait locus (QTL)on mouse chromosome 12 at 12.75 megabases. This QTL contains a possible quantitative trait gene involving a potassium channel gene *Kcnh5* product (Kv10.2) in the DO mice with haplotype variants with interacting candidate gene products that may have a critical role in modulating dopamine activity associated with obesity in the VHFD (60% fat kcal) diet treated mice. We propose to initially test this observation in reverse genetics protocols by inducing obesity in each of the 8 founder CC mice compared to low fat (10% fat kcal) normal protein isogenic controls. We will collect brain, liver, pancreas, brown fat, and visceral fat for weight, preparation in RNALater® for quantitative rt-PCR, and flash freezing tissue proteomics and metabolomics for targeted or untargeted methodologies.

Hypothesis: The genetic basis for inter-individual differences in weight-gain and adiposity in female and male DO mice is due to dopamine salience in a genetic network based on the Chr 12.75 Mb dominant haplotype (*Kcnh5, Ppp2r5e, Syn2e2, Pcdh2, and Cd44;* FDR 7.68 x 10^{-11}).

Specific Aims: 1) As proof of the phenomena observed in quantitative studies in DO mice (derived from the intercross of the CCRIL eight different founder strains) we will test homozygous inbred founder male mice under the same experimental conditions of the DO mice for 12-wks. **2)** We will dissect the brains of euthanized DIO mice and their isogenic diet controls to isolate protein and mRNA to quantify and correlate inter-individual strain differences in the potassium channel (Kv10.2; formed from KCNH5) and dopamine receptor modulation (DRD1-5).

Summary basis for Specific Aims: Using 12-wks VHFD DO mice data for 4-hr fasted glucose and insulin levels we were able to calculate the 4-hr fasted HOMA-IR. HOMA-IR is associated with the development of insulin resistance and other metabolic (lipid dysregulation, inflammation, etc.) phenotypes leading to type 2 diabetes, etc. Using RQTL/2 haplotype linkage analysis we observed a mouse HOMA-IR phenotype associated QTL at Chr12.75Mb quantitative trait locus (LOD > 20). Kari North investigated human SNP based GWAS studies and found fasted glucose and HOMA-IR human phenotype based highly significant variants on CHR14, that overlapped with mouse genes on mouse Chr12.75Mb haplotype linkage analysis QTL potential candidate genes. Human SNP GWAS significant variants were observed on Chr14, 13, and 11. The potential candidate genes must be validated using functional assays to demonstrate functional relationships. We observed potential candidate genes in the mouse genomes (Kcnh5, Ppp2r5e, Syne2, Pcdh9, and Cd44) and in the human genomes (KCNH5, PPP2R5E, SYNE2, PCDH9, CD44). Using bioinformatics and gene ontology we observe a connection between inter-

individual outcomes from high-fat diet that demonstrate a potential salient links between the potassium channel gated gene and dopamine metabolism. Both the human and mouse genes may be associated with inter-individual differences in the dysregulation of dopamine effects on obesity related addiction.

II. Precision Nutrition, Heterogeneity of Obesity, and Host Genetics Impact on Carboplatin Resistance in the CCRIL x B6.FVB/N-Tg(C3-1-TAg) Recombinant Intercross (RIX) Mouse Model of Human Basal-like (Triple-Negative) Breast Cancer/Prostate Cancer

The prevalence of obesity, an established risk and prognostic factor for basal-like breast cancer (BLBC), has risen dramatically in the US and many other countries. Obesity is also associated with an increased resistance to several classes of cancer chemotherapeutic agents, including carboplatin. This direct acting platinum-based chemotherapeutic agent is often used as part of first-line treatment for advanced BLBC. Unfortunately, resistance to carboplatin treatment occurs at a high rate, particularly in obese women, and the mechanisms underlying carboplatin resistance and the interactions of obesity and resistance mechanisms are incompletely understood. The impact of **host genetics along with diet and precision nutritional interventions, including intermittent caloric restriction, have not been investigated in an experimental population-based genetics model for carboplatin treatment efficacy and inter-individual differences in host pharmacokinetics and adaptive responses to chemotherapy for BLBC in obese and normoweight individuals**.

Hypothesis: Host genetics impacts diet and nutritional intervention response to carboplatin cancer treatment, treatment-related adverse events, cancer prognosis and related health outcomes

Specific Aims: (1) We will create and tumor phenotype (tumor incidence and progression) the progeny from 10 different randomly selected genetically-diverse Collaborative Cross recombinant inbred lines (CC RIL) female mice outcrossed with B6.FVB/N-Tg(C3-1-TAg) congenic male mice to produce co-isogenic CCRIL.B6.FVB/N-Tg(C3-1-TAg) recombinant inbred crossed (RIX) female and male mice. **(2)** Using a balanced block design of co-isogenic RIX with and without specified treatments, we will test precision nutrition intervention diets against obesogenic diets to determine tumor penetrance and susceptibility with different body compositions. (3) Using same design, we will test RIX specific tumor susceptible phenotypes (BLBC and Prostate) for resistance to clinical treatment relevant carboplatin treatment regimens.

The C3-1TAg transgene expression drives a human basal-like breast cancer subtype. Carboplatin treatment efficacy or resistance compared to untreated controls will be examined in obese or normal weight mice following calorically-restricted (CR) in 10 selected genetically-diverse CC RIL.B6.FVB-C3-1-TAg RIX inbred mice. To date, we have determined a significant differences between the CCRIL RIX in terms of tumor penetrance and tumor growth. Also, we will determine differences between RIX inbred mice for carboplatin tissue concentrations and DNA damage and repair in peripheral red blood cells, bone marrow, liver, and mammary gland tissue in both obese and normoweight following CR. This data will identify relevant outlier phenotypes in the CC RIL sampled. Using haplotype association mapping, both candidate and unknown gene associations can be tested for these quantitative phenotypes. Further, identification of CC RIL outlier phenotypes will aid design of haplotype linkage analysis to identify quantitative trait loci

intervals and candidate genes and/or regulatory sequences in the CC RIL that modulate diet and platinum chemotherapy efficacy and outcome in this population-based mouse model. This research paradigm has the potential improve our understanding and guide research on host genetics, chemotherapeutic drug regimens, pharmacokinetics, and precision nutrition using genetically-diverse mouse models relevant to human translation.

Expected Outcomes: We anticipate observing inter-individual differences between the homozygous inbred CC founder haplotypes in both the DO and CCRIL mice, and have the ability to investigate the quantitative candidate genes using several approaches to validate the role and impact of dopamine salience that drives high-fat diet weight gain, adiposity, and insulin resistance based on dopamine associated networks.

Relevance to precision nutrition: Amino acids are known to play a role in neurotransmitter signaling. We speculate that this research may lead to a precision nutrition focus and dietary intervention to modulate neurotransmitter impact and improve health outcomes.

Enhancing grant competitiveness for funding: Funding to date has been provided via Prof. Hursting's R35, NRI intramural funds, and UNC Heterogeneity of Obesity funds. Preliminary data that moves the research findings from observational to specific outcomes relating to etiology and causality will greatly improve research opportunities and funding to obtain quantitative proof of these summarized findings

I**dentify the target agency and RFA/NOSI for which you plan to submit this grant to in FY 2021 or 2022:** We anticipate being positioned to participate in both NIH RFA and Commons funding of Precision Nutrition research.

Summary – In Progress

Publications (submitted, in preparation)

Gordon-Larsen, P, **French JE,** Moustaid-Moussa, N, Voruganti, VS, Mayer-Davis, EJ, Bizon, CA, Cheng, Z, Stewart, DA, Meyer, KA, Easterbrook, JW, Shaikh, SR. **Synergizing mouse and human studies to understand the heterogeneity of obesity**. Advances in Nutrition (in revision for resubmission) 2021.

VerHague, M, Albright, J. Bennett, B, **French, JE**, and Hursting, SD. **Diet-induced Diversity Outbred mice weight gain and calorie restriction induced weight loss quantitative traits. In preparation. 2020**

Grant submissions and/or pending resubmissions

RFA CA-18-024. 2019. NCI SPORE P50 AWARD Investigator Initiated: Genetics of Basal-like Mammary Cancer Resistance to Carboplatin (CBDNA) Chemotherapy. PI: Stephen D. Hursting; Co-I: John E. French. Scored: 38. Unfunded. Resubmission planned with additional data in FY21 3rd Quarter PA-19-056.

NORC P&F. 2019 Defining in utero suboptimal nutrition metabotypes using population genetics (Diversity Outbred mice). Unscored. Preliminary data required for submission as R01.

NIEHS R21 Investigator Initiated: Susceptibility to Environmental Stressor-Induced Metabolic Syndrome. PI: John E. French. Not reviewed. Revision planned. Resubmission in FY21 3rd or 4th Quarter FY21.

NIEHS R01 PA 19-053 1 R01 ES0322452-01Investigator Initiated: *Pregnancy, Inflammation and Environmental Exposure*. Multi-PI: John E. French & Melissa Troester. Reviewed & Scored: 35. Unfunded. Pending resubmission based on obtaining additional preliminary data for an R01 submission FY21 or 22.

Timeline for achieving targets and goals

Quantitative trait locus (QTL) analysis and the identification of risk variants for diet-induced obesity and resistance to calorie restricted weight loss research papers is targeted for completion in FY 21 4th Quarter. *2-3 papers planned.

Quantitative trait locus (QTL) analysis and the identification of risk variants for diet-induced obesity and resistance to calorie restricted weight loss research papers focused on extrapolation of preclinical mouse variants to clinical variant outcomes in humans is anticipated for completion in FY 22 1st Quarter. *at least 2 papers planned.

Initial analysis on Precision Nutrition, Heterogeneity of Obesity, and Host Genetics Impact on Carboplatin Resistance in the CCRIL x B6.FVB/N-Tg(C3-1-TAg) Recombinant Intercross (RIX) Mouse Model of Human Basal-like (Triple-Negative) Breast Cancer/Prostate Cancer are expected in FY22 3rd-4th Quarter.