BIOGRAPHICAL SKETCH

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NAME: Tracy G. Anthony

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

POSITION TITLE: Professor

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
Virginia Tech University, Blacksburg, VA	B.S.	08/1993	Human Nutrition & Foods
University of Illinois, Urbana, IL	M.S.	05/1995	Nutritional Sciences
University of Illinois, Urbana, IL	Ph.D.	05/1998	Nutritional Sciences
Penn State College of Medicine, Hershey, PA	Postdoctoral	07/2001	Cellular & Molecular Physiology

A. Personal Statement

The broad aim of my research program is to understand how altering the supply of amino acids, in total or individually, regulates metabolism and protein homeostasis in the whole animal. I have expansive training in biochemistry, endocrinology, immunology, kinesiology, metabolism, molecular biology and physiology, and I hold deep experience in the design and use of experimental diets, exercise modes and animal models to reflect the human condition. Over the years I have published numerous high impact publications which delineate mechanisms of metabolic and proteostasis control by diet, drugs, genetics and environmental stressors in multiple organ systems. I am especially interested in nutrient sensing and how signal transduction networks are coordinated to protect and preserve tissue and organ function in response to nutritional or environmental stress. I have been continuously funded by the NIH since 2010 to examine mechanisms by which amino acid insufficiency impacts health and disease outcomes. The mechanisms I study are foundational to cellular operations but also work to guide inter-organ metabolism and homeostasis.

Ongoing project that I would like to highlight:

5 R01DK109714 NIH/NIDDK Anthony/Wek (MPI; Anthony lead) 07/01/2016–06/30/2025
Homeostatic Responses to Amino Acid Insufficiency
Define the contribution of the integrated stress response to the early molecular and physiological responses that function to maintain proteostasis during dietary amino acid insufficiency.
Role: Lead PI

B. Positions and Honors
Positions and Employment

2018-current Professor, Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ
2012-2018 Associate Professor, Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ
2010-2012 Associate Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine-Evansville, Evansville, IN
2005-2010 Assistant Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine-Evansville, Evansville, IN
2001-2005 Assistant Scientist/Assistant Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine-Evansville, Evansville, IN
1998-2001 American Diabetes Association Postdoctoral Research Fellow, Department of Cellular and Molecular Physiology, Penn State College of Medicine, Hershey, PA

Other Experience and Professional Memberships

2019 – 2020 Visiting Scholar (sabbatical), laboratory of Josh Rabinowitz, Lewis-Sigler Institute for Integrative Genomics, Carl Icahn Laboratory, Princeton University, Princeton, NJ
2019 Attendee: 12th Annual Course on Isotope Tracers in Metabolic Research, Nashville, TN, October 21-25
2017-current Editorial Board, *Journal of Biological Chemistry*
2016-current Editorial Board, *Annual Reviews in Nutrition*
2015-current Editorial Board, *Advances in Nutrition*
2004-current Member, American Society for Biochemistry and Molecular Biology
1997-current Member, American Physiological Society
1994-current Member, American Society for Nutrition

Honors

2021 *Editor's Pick*, Research article (doi: 10.1093/jn/nxaa396) selected in *The Journal of Nutrition* with an accompanying Commentary (https://doi.org/10.1093/jn/nxaa457.)
2020 *Invited Session Chair,* FASEB Summer Research Virtual Conference "Nutrient Sensing and Metabolic Signaling", Aug 10-11
2019 *Editor's Pick*, Research article (J. Biol. Chem. doi: 10.1074/jbc.RA119.009864) awarded to the top 2 percent of manuscripts reviewed in a year in significance and overall importance. This article was also selected for inclusion in the August 2020 Virtual Issue: Women in biological chemistry, honoring women in science and celebrating progress made in regards to the participation of women in science: *https://www.jbc.org/site/vi/women_in_jbc/*
2019 *Fellow*, Higher Education Resource Services (HERS) academic leadership institute for women, Bryn Mawr, PA July 8-20
2019 *Fellow*, Higher Education Resource Services (HERS) academic leadership institute for women, Bryn Mawr, PA July 8-20
2019 *Fellow*, Higher Education Resource Services (HERS) academic leadership institute for women, Bryn Mawr, PA July 8-20
2018 Research article (J. Nutr. 130:2413-2419, 2000) highlighted in *The Journal of Nutrition* 90th Anniversary supplement issue as one of the most cited and impactful papers published in the journal's history.
2017 *Editor's Pick,* Research article [doi: 10.3945/jn.116.246710] selected in *The Journal of Nutrition*
2017 *Invited Co-chair*, NIH/NIDDK Workshop on "Emerging Role of Branched-Chain Amino Acids in Human Diseases", May 25-26, 2017
2014 *Fellow*, Dannon Institute Academic Mid-Career Nutrition Leadership Institute
of amino acids in protein metabolism
2013-2018 *Standing Member*, Integrative Nutrition and Metabolic Processes Scientific Review Group, NIH
2003 American Society for Nutritional Sciences *Peter J. Reeds Young Investigator Award* for recognition of research which focuses on the regulation of somatic growth and the unique roles

C. Contributions to Science

1. Identified mechanisms of metabolic toxicities by the anti-cancer drug L-asparaginase. Asparaginase is used to treat acute lymphoblastic leukemia, the most common childhood cancer, but unpredictably causes adverse metabolic toxicities that lead to treatment failure. My group was the first to show that asparaginase activates the amino acid response/integrated stress response via GCN2 in mammalian tissues. We also revealed the protective function of GCN2 during asparaginase treatment and described the mechanism by which loss of GCN2 predisposes to immunosuppression (PMID: 20861212), hepatic failure (PMID: 24002574) and pancreatitis (PMID: 26968207), providing the first mechanistic explanation for adverse events by asparaginase. We all detailed the role of obesity and the effect of age on the liver transcriptome. This latter work was highlighted as an "Editor's Pick" for its high quality and impact (**marked below).

a. Bunpo P, Dudley A, Cundiff JK, Cavener DR, Wek RC, **Anthony TG**. GCN2 protein kinase is required to activate amino acid deprivation responses in mice treated with the anti-cancer agent L-asparaginase. J Biol Chem. 2009 Nov 20;284(47):32742-9. doi: 10.1074/jbc.M109.047910. Epub 2009 Sep 25. PMID: 19783659
b. Wilson GJ, Lennox BA, She P, Mirek ET, Al Baghdadi RJ, Fusakio ME, Dixon JL, Henderson GC, Wek RC, **Anthony TG**. GCN2 is required to increase fibroblast growth factor 21 and maintain hepatic triglyceride homeostasis during asparaginase treatment. Am J Physiol Endocrinol Metab. 2015 Feb 15;308(4):E283-93. doi: 10.1152/ajpendo.00361.2014. Epub 2014 Dec 9. PMID: 25491724; PMC4329494
c. Nikonorova IA, Al-Baghdadi RJT, Mirek ET, Wang Y, Goudie MP, Wetstein BB, Dixon JL, Hine C, Mitchell JR, Adams CM, Wek RC, **Anthony TG**. Obesity challenges the hepatoprotective function of the integrated stress response to asparaginase exposure in mice. J Biol Chem. 2017 Apr 21;292(16):6786-6798. doi: 10.1074/jbc.M116.768408. Epub 2017 Feb 27. PMID: 28242759, PMC5399125
d. **Nikonorova IA, Zhu Q, Signore CC, Mirek ET, Jonsson WO, Kong B, Guo GL, Belden WJ, **Anthony TG**. (2019) Age modulates liver responses to asparaginase-induced amino acid stress in mice. J Biol Chem. 2019 Sep 20;294(38):13864-13875. doi: 10.1074/jbc.RA119.009864. Epub 2019 Aug 14. PMID: 31413113

2. Identified role of GCN2 and TORC1 during different states of amino acid insufficiency. Our group uncovered early and seminal evidence revealing how dietary amino acid insufficiency is sensed by GCN2 and signals via phosphorylation of eIF2 to inhibit protein synthesis and mTORC1 signaling in tissues of mammals. Loss of GCN2 unleashes mTORC1 inappropriately and correlates with maladaptive physiological responses *in vivo*.

a. **Anthony TG**, McDaniel BJ, Byerley RL, McGrath BC, Cavener DR, McNurlan MA, Wek RC. Preservation of liver protein synthesis during dietary leucine deprivation occurs at the expense of skeletal muscle mass in mice deleted for eIF2 kinase GCN2. J Biol Chem. 2004 Aug 27;279(35):36553-61. Epub 2004 Jun 22. PMID: 15213227
b. Hao S, Sharp JW, Ross-Inta CM, McDaniel BJ, **Anthony TG**, Wek RC, Cavener DR, McGrath BC, Rudell JB, Koehnle TJ, Gietzen DW. Uncharged tRNA and Sensing of Amino Acid Deficiency in Mammalian Piriform Cortex. Science. 2005 Mar 18;307(5716):1776-8. PMID: 15774759
c. Nikonorova IA, Mirek ET, Signore CC, Goudie MP, Wek RC, **Anthony TG**. Time-resolved analysis of amino acid stress identifies eIF2 phosphorylation as necessary to inhibit mTORC1 activity in liver. J Biol Chem. 2018 Apr 6;293(14):5005-5015. doi: 10.1074/jbc.RA117.001625. Epub 2018 Feb 15. PMID: 29449374
d. Misra J, Holmes MJ, T Mirek E, Langevin M, Kim HG, Carlson KR, Watford M, Dong XC, **Anthony TG**, Wek RC. Discordant regulation of eIF2 kinase GCN2 and mTORC1 during nutrient stress. Nucleic Acids Res. 2021 Jun 4;49(10):5726-5742. doi: 10.1093/nar/gkab362. PMID: 34023907

3. Uncovered regulatory events that guide physiological responses to dietary sulfur amino acid restriction (SAAR). Dietary SAAR leads to physiological responses that extend lifespan and confer protection against metabolic diseases by reducing visceral fat, increasing insulin sensitivity, and altering lipid metabolism. Our group explored the role of GCN2 and the integrated stress response in regulating changes in body composition during dietary SAAR in mice. We found that hepatic phosphorylation of eIF2 did not correlate with long term changes in fat or lean mass, suggesting that auxiliary or redundant control mechanisms not

previously appreciated are unique to SAAR. Two of these papers (**marked below) were selected as an "Editor's Pick" for its scientific quality and impact.

a. Wanders D, Stone KP, Forney LA, Cortez CC, Dille KN, Simon J, Xu M, Hotard EC, Nikonorova IA, Pettit AP, **Anthony TG**, Gettys TW. Role of GCN2-Independent Signaling Through a Noncanonical PERK/NRF2 Pathway in the Physiological Responses to Dietary Methionine Restriction. Diabetes. 2016 Jun;65(6):1499-510. doi: 10.2337/db15-1324. Epub 2016 Mar 2. PMID: 26936965, PMCID: PMC4878423
b. **Pettit AP, Jonsson WO, Bargoud AR, Mirek ET, Peelor FF 3rd, Wang Y, Gettys TW, Kimball SR, Miller BF, Hamilton KL, Wek RC, **Anthony TG**. Dietary Methionine Restriction Regulates Liver Protein Synthesis and Gene Expression Independently of Eukaryotic Initiation Factor 2 Phosphorylation in Mice. J Nutr. 2017 Jun;147(6):1031-1040. doi: 10.3945/jn.116.246710. Epub 2017 Apr 26. PMID: 28446632, PMCID: PMC5443467
c. Jonsson WO, Margolies NS, **Anthony TG**. (2019) Dietary Sulfur Amino Acid Restriction and the Integrated Stress Response: Mechanistic Insights. Nutrients. 2019 Jun 15;11(6). pii: E1349. doi: 10.3390/nu11061349. PMID: 31208042 – Invited Review
d. **Jonsson WO, Margolies NS, Mirek ET, Zhang Q, Linden MA, Hill CM, Link C, Bithi N, Zalma B, Levy JL, Pettit AP, Miller JW, Hine C, Morrison CD, Gettys TW, Miller BF, Hamilton KL, Wek RC, **Anthony TG**. Physiologic Responses to Dietary Sulfur Amino Acid Restriction in Mice Are Influenced by Atf4 Status and Biological Sex. J Nutr. 2021 Jan 29:nxaa396. doi: 10.1093/jn/nxaa396. PMID: 33512502. ****Article highlighted in a Commentary: https://doi.org/10.1093/jn/nxaa457**

4. Identified and characterized key regulatory elements within the integrated stress response. Activation of eIF2 kinases to environmental stress triggers the integrated stress response to promote cellular adaptation. Our group described novel and key features of the integrated stress response and specifically the role of eIF2 kinases and ATF4 in regulating selective mRNA translation, antioxidant stress responses and cell fate decisions with novel applications to human diseases such as cancer, hepatic injury and leukodystrophy.

a. Teske BF, Wek SA, Bunpo P, Cundiff JK, McClintick JN, **Anthony TG**, Wek RC. The eIF2 kinase PERK and the integrated stress response facilitate activation of ATF6 during endoplasmic reticulum stress. Mol Biol Cell. 2011 Nov;22(22):4390-405. doi: 10.1091/mbc.E11-06-0510. Epub 2011 Sep 14. PMID: 21917591; PMC3216664
b. She P, Bunpo P, Cundiff JK, Wek RC, Harris RA, **Anthony TG**. General control nonderepressible 2 (GCN2) kinase protects oligodendrocytes and white matter during branched-chain amino acid deficiency in mice. J. Biol. Chem. 2013 Oct 25;288(43):31250-60. doi: 10.1074/jbc.M113.498469. PMID: 24019515; PMC3829435
c. Jonsson WO, Mirek ET, Wek RC, **Anthony TG**. Activation and execution of the hepatic integrated stress response by dietary essential amino acid deprivation is amino acid specific. FASEB J. 2022 Jul;36(7):e22396. doi: 10.1096/fj.202200204RR. PMID: 35690926
d. Cordova RA, Misra J, Amin PH, Klunk AJ, Damayanti NP, Carlson KR, Elmendorf AJ, Kim HG, Mirek ET, Elzey BD, Miller MJ, Dong XC, Cheng L, Anthony TG, Pili R, Wek RC, Staschke KA. GCN2 eIF2 kinase promotes prostate cancer by maintaining amino acid homeostasis. Elife. 2022 Sep 15;11:e81083. doi: 10.7554/eLife.81083. PMID: 36107759

5. Discovered mechanisms by which dietary protein or leucine after exercise or fasting stimulates recovery of muscle protein synthesis and mRNA translation initiation *in vivo*. Our group was the first to show that the feeding protein after endurance exercise stimulates muscle protein synthesis recovery via activation of mRNA translation initiation and then described how the leucine content of a complete meal is a determining factor for initiating but not sustaining the anabolic response to dietary protein. Our group was also the first to show that the branched chain amino acid leucine was unique in its potency to stimulate mechanistic/mammalian target of rapamycin complex 1 (mTORC1) in vivo and were the first to show control of mRNA translation initiation by leucine in mammalian tissue. One of these papers (**marked below) was highlighted in 2018 by the journal as one of the most impactful in its 90 year history.

a. **Gautsch TA**, Anthony JC, Kimball SR, Paul GL, Layman DK, Jefferson LS. Availability of eIF4E regulates skeletal muscle protein synthesis during recovery from exercise. Am J Physiol. 1998 Feb;274(2 Pt 1):C406-14. PMID: 9486130

b. Anthony JC, **Anthony TG**, Kimball SR, Vary TC, Jefferson LS. Orally administered leucine stimulates protein synthesis in skeletal muscle of post-absorptive rats in association with increased eIF4F formation. J Nutr. 2000 Feb;130(2):139-45. PMID: 10720160
c. **Anthony JC, Yoshizawa F, **Anthony TG**, Vary TC, Jefferson LS, Kimball SR. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. J Nutr. 2000 Oct;130(10):2413-9. PMID: 11015466
d. **Anthony TG**, Anthony JC, Yoshizawa F, Kimball SR, Jefferson LS. Oral administration of leucine stimulates ribosomal protein mRNA translation but not global rates of protein synthesis in the liver of rats. J Nutr. 2001 Apr;131(4):1171-6. PMID: 11285321

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