UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELYSIUM HEALTH, INC.
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

U.S. Patent No. 8,383,086 B2

DECLARATION OF JOSEPH A. BAUR, PH.D.

I, Joseph A. Baur, hereby declare as follows:

I. INTRODUCTION

1. I have been retained by Elysium Health, Inc. ("Elysium"). I am being paid for my time regardless of the outcome of this case. Beyond the compensation I received for my time in this matter, I will not be affected in any way, positively or negatively, by the outcome of this case.

II. QUALIFICATIONS

2. I am an Associate Professor of Physiology and the Director of the Mouse Phenotyping, Physiology, and Metabolism Core at the Perelman School of Medicine, the medical school of the University of Pennsylvania.

3. I hold a Bachelor's degree in Chemistry with honors from Acadia University (Wolfville, NS, Canada) and received a Ph.D. from the program in Integrative Physiology at the University of Texas Southwestern Medical Center at Dallas.

4. As a postdoctoral researcher, I trained with David Sinclair at Harvard Medical School, who is a world-renowned expert in sirtuins – a class of enzymes that require nicotinamide adenine dinucleotide (NAD+) as a co-substrate. My research particularly focused on strategies to activate these enzymes and the primary research paper resulting from this work is one of the most highly cited in

the field, with over 3000 citations to date (Baur et al., "Resveratol improves health and survival of mice on a high-calorie diet," *Nature*, 444(7117):337-42 (2006)).

5. As an independent researcher, I have won a number of competitive awards, including a New Scholar Award from the Ellison Medical Foundation and the Joseph A. Pignolo, Sr. Award in Aging Research.

6. One of my major research interests has been in the metabolism and potential benefits of NAD+ precursors, including nicotinamide riboside. I have received a research grant from the National Institutes of Health to study NAD+ metabolism, and have recently published three papers on the subject in top journals (*Cell Metabolism*, *Hepatology*, and the *Journal of Biological Chemistry*), with several more manuscripts in preparation for publication.

7. I am regularly invited to give lectures at the national and international level and sought out as a peer reviewer for grant applications and manuscripts related to sirtuins and NAD+. Thus, I believe I am well qualified to evaluate the patents and relevant literature discussed in this Declaration.

8. My CV is attached to this Declaration as Appendix A.

III. MATERIALS CONSIDERED

9. I have read U.S. Patent No. 8,383,086 (the "'086 patent") (Ex. 1001) and reviewed its prosecution history. I have also reviewed pieces of prior art that

are relevant in my opinion to the '086 patent, including the following, which are discussed below:

- Joseph Goldberger et al., "A Study of the Blacktongue-Preventative Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man," *Public Health Reports*, 43(23):1385-1454 (1928) ("Goldberger et al.") (Ex. 1005); and
- Joseph Goldberger and W.F. Tanner, "A Study of the Treatment and Prevention of Pellagra," *Public Health Reports*, 39(3):87-107 (1924) ("Goldberger and Tanner") (Ex. 1006).

I have also reviewed other references that illuminate the inherent properties of the prior art, including the following, which are discussed below:

- Samuel A.J. Trammell et al., "Nicotinamide Riboside is a Major NAD+ Precursor Vitamin in Cow Milk," *J. of Nutrition*, 146(5):965-963 (2016) ("Trammell I") (Ex. 1007);
- Samuel A.J. Trammell et al., "Nicotinamide Riboside is Uniquely and Orally Bioavailable in Mice and Humans," *Nature Communications*, Vol. 7, Art. No. 12948 (2016) ("Trammell II") (Ex. 1008);
- Joseph Goldberger et al., "A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventative in Yeast,"

Public Health Reports, 43(12):657-694 (1928) ("A Further Study of Experimental Blacktongue") (Ex. 1009);

- Laurent Mouchiroud et al., "NAD^+ Metabolism, a Therapeutic Target for Age-Related Metabolic Disease," *Crit. Rev. Biochem Mol Biol.*, 48(4):397-408 (2013) ("Mouchiroud et al.") (Ex. 1010);
- Texas Agricultural Extension Service, "Good Milk for Good Meals," *Texas Agricultural Experiment Station*, Bulletin No. 807 (1956) ("Good Milk") (Ex. 1011);
- William Douglas McFarlane and Hugh Lehman Fulmer, "The Colorimetric Determination of the Tyrosine and Tryptophan Content of Various Crude Protein Concentrates," *Biochemical Journal*, 24(6):1601-1610 (1930) (Ex. 1012);
- Krishna S. Tummala, et al., "Inhibition of De Novo NAD+ Synthesis by Oncogenic URI Causes Liver Tumorigenesis through DNA Damage," *Cancer Cell*, 26:826-839 (2014) ("Tummala") (Ex. 1017);
- Carles Cantó et al., "The NAD+ Precursor Nicotinamide Riboside Enhances Oxidative Metabolism and Protects against High-Fat Diet-Induced Obesity," *Cell Metabolism*, 15:838-847 (2012) ("Cantó") (Ex. 1018);

- Bing Gong et al., "Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-y coactivator 1α regulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models," *Neurobiol. Aging*, 34:1581-1588 (2013) ("Gong") (Ex. 1019);
- Joseph Goldberger et al., "The Prevention of Pellagra: A Test of Diet Among Institutional Inmates," *Public Health Reports*, 30(43):3117-3131 (1915) ("The Prevention of Pellagra") (Ex. 1020); and
- Joseph Goldberger et al., "A Study of the Relation of Diet to Pellagra Incidence in Seven Textile-Mill Communities of South Carolina in 1916," *Public Health Report*, 35(12):648-713 (1920) ("Relation of Diet to Pellagra Incidence") (Ex. 1021).

IV. BACKGROUND

A. NAD+ Biosynthesis

10. NAD+ is a coenzyme associated with various biological activities. It is synthesized in eukaryotes through four major pathways: 1) Nicotinamide is phosphoribosylated by the enzyme nicotinamide phosphoribosyltransferase (NAMPT) to generate nicotinamide mononucleotide, which is subsequently converted to NAD+ by the action of nicotinamide mononucleotide adenylyltransferases (NMNATs). 2) Nicotinic acid is phosphoribosylated by a

distinct phosphoribosyltransferase (NAPRT) to generate nicotinic acid mononucleotide, which is subsequently converted to nicotinic acid adenine dinucleotide by the action of NMNATs, and finally, is converted to NAD+ by NAD synthase. This is known as the Preiss-Handler pathway. 3) Tryptophan is converted to NAD+ through a complex, but well-defined series of enzymatic reactions known as the de novo (kynurenine) pathway. 4) Nicotinamide riboside and nicotinic acid riboside are incorporated into NAD+ synthesis pathways by the action of nicotinamide riboside kinases (NRKs), which convert them to the corresponding mononucleotides.

B. Natural Sources of Nicotinamide Riboside

11. Nicotinamide riboside (NR) is a form of vitamin B3 that has been carefully and clearly documented to be present at a substantial level in milk. Trammell I determined that the NR concentration in milk typically falls in the range of 4.3 +/- 2.6 micromolar (excluding one atypical sample in which 27 micromolar NR was detected) in raw cow's milk, 1.9 +/- 1.0 micromolar in organic skim milk and 3.1 +/- 1.6 micromolar in conventional skim milk. (Ex. 1007, Trammell I, at 3, 5.) Trammell I states that the data presented in the article show that approximately 40% of niacin equivalents (excluding tryptophan) in cow's milk are present as NR, with the remainder present as nicotinamide. (*Id*. at 6.)

12. While Trammell I did not directly measure NR in buttermilk, it is my opinion that NR is present in buttermilk. Based on the disclosure of Trammell I, it is clear that raw milk and skim milk both contain NR. Skim milk is the product that remains when almost all of the cream is removed from whole milk. (Ex. 1011, Good Milk, at 6.) Traditional buttermilk, such as that which was consumed by the test subjects in Goldberger and Tanner (discussed below), is the product that remains after butter has been churned from whole milk or cream. (*Id*.) Because NR is a water-soluble molecule that is stable in milk (Ex. 1007, Trammell I, at 3-5), the majority of NR originally present in the churned whole milk or cream remains in the aqueous buttermilk when the fat-rich butter is removed. Thus, the removal of butter from whole milk or cream to make buttermilk necessarily results in an increase in the concentration of any NR originally present in the whole milk or cream from which it was made. This is consistent with Goldberger and Tanner's finding that the pellagra-preventing activity of buttermilk is significantly higher than that of butter and with their proposal that "...fresh milk and buttermilk may be assumed to be quantitatively interchangeable". (Ex. 1006, Goldberger and Tanner, at 95.)

C. Oral Bioavailability of Nicotinamide Riboside

13. Nicotinamide riboside taken orally contributes to NAD+ synthesis. This has been documented in numerous studies, including Tummala (Ex. 1017),

Cantó (Ex. 1018), and Gong (Ex. 1019) showing that NR is sufficient to increase the concentration of NAD+ in various mammalian tissues. (Ex. 1017, Tummala, at 832-33; Ex. 1018, Cantó, at 842-43; Ex. 1019, Gong, at 1583 and Figure 1.) Moreover, several studies, including Trammell II, have taken the additional step of incorporating stable isotopes into the NR before dosing, allowing a definitive demonstration that the orally administered NR is ultimately incorporated into NAD+ molecules, rather than causing an increase indirectly. (Ex. 1008, Trammell II, at 5-7 and Figure 7.)

14. The bioavailability of NR taken orally is as great or greater than that of nicotinic acid or nicotinamide. Trammell II reports the consequences of oral administration of equal molar amounts of each of these precursors. NR administration results in a greater peak concentration of the product, NAD+, in the liver than does either of the other two precursors. (Ex. 1008, Trammell II, at 4-5 and Figure 5.) The area under the curve over 12 hours, reflecting the total increase in NAD+ synthesis caused by the administered compound, was greater for NR than for nicotinic acid, with an intermediate value for nicotinamide. (Ex. 1008, Trammell II, at 4-6 and Figure 5.) Similarly, in the declaration of Charles Brenner, dated January 16, 2016, and submitted on January 17, 2016 during prosecution of Application No. 11/912,400, it is disclosed that oral administration of NR to a human subject is more effective than oral administration of an equal molar dose of

nicotinamide for increasing white blood cell NAD+ concentration, and these data were later published in Trammell II. (Ex. 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 132-35.) Thus, NR is orally bioavailable, and its bioavailability appears to be greater than that of other NAD+ precursors.

D. The Goldberger Studies

15. The disease pellagra in humans and a similar condition known as blacktongue in dogs are caused by deficiency in NAD+. Pellagra is characterized by dermatitis, diarrhea, and dementia, and is often fatal if untreated. It was prevalent in the American South in the early part of the twentieth century. The primary forms of the disease are curable by provision of any precursor molecule that can be used to synthesize NAD+, i.e., nicotinamide, nicotinic acid, tryptophan, or nicotinamide riboside (or nicotinic acid riboside). Although symptomatic cases today would be treated with purified precursors in addition to diet modification, a diet rich in milk and meat is sufficient to prevent and in many cases treat pellagra, and improvement in diet quality with particular attention to these components is the primary recommendation for at-risk populations.

16. The utility of milk as a means to prevent pellagra was demonstrated almost one hundred years ago by the pioneering studies of Goldberger and colleagues. Goldberger, Waring, and Willets published a study in 1915 in which they reported that an improvement in the quality of the diet provided to

institutional inmates was sufficient to completely prevent pellagra. (Ex. 1020, The Prevention of Pellagra.) Meat and milk were suspected to be the active ingredients, but the design of the study did not conclusively test this hypothesis. (*Id*.) A subsequent observational study by Goldberger, Wheeler, and Syndenstricker, which was reported in 1920, revealed that households receiving a pint of milk or 30 grams of fresh meat per adult were at a substantially reduced risk of pellagra, and that the risk further decreased with increased access to either of these foods. (Ex. 1021, Relation of Diet to Pellagra Incidence, at 687-88.)

17. In 1924, Goldberger and Tanner reported the outcome of experiments designed specifically to test whether milk could prevent pellagra. (Ex. 1006, Goldberger and Tanner.) Twenty-nine patients from the Georgia State Sanitarium were given a diet supplemented with 40 ounces of buttermilk per day, selected because this was the primary form of milk consumed in the South at the time. (*Id*. at 93.) (In an article regarding pellagra in South Carolina households, Goldberger noted that "home-churned buttermilk was the predominating form in which milk was used" by the participants in the study. (Ex. 1021, Relation of Diet to Pellagra Incidence, at 681.)) As noted above, buttermilk is the product that remains when butter is removed from milk or cream in the process of churning. (Ex. 1011, Good Milk, at 6.)

18. Of these patients, 19 were pellagrins (i.e., known to have periodic episodes of pellagra symptoms) and 16 of those completed a full year of observation. (Ex. 1006, Goldberger and Tanner, at 93.) No patient developed symptoms of pellagra during the observation period. (*Id*.) Because their prior experience with similar patients suggested that "upward of 40 or 50 per cent of the group would with certainty have developed pellagra within a period of from three to seven or eight months", the authors concluded that, "…the complete absence of any indication of the disease in any of this group is, in our judgment, conclusive evidence of the preventive action of the buttermilk." (*Id*.) The authors further concluded that "milk contains the essential pellagra preventive factor or factors." (*Id*.)

19. In their discussion, Goldberger and Tanner raise a number of points that are relevant to their study. First, they describe unpublished work demonstrating that butter is insufficient to prevent pellagra, and therefore conclude that, "as the treatment and prevention of pellagra (in the specific sense) is concerned, fresh milk and buttermilk may be assumed to be quantitatively interchangeable." (*Id*. at 95.) They further point out that milk is likely to be more valuable than beef for the treatment of pellagra because it can be taken without chewing or even by tube, and the condition of the mouth can cause eating to become painful or impossible over the course of the disease. (*Id*. at 96.) The failure

of gelatin to prevent pellagra is discussed as evidence that something in milk and meat beyond protein per se is active in the prevention of disease, and the failure of a vitamin and mineral enriched diet led the authors to suggest that the pellagra preventive factor must be an unrecognized vitamin or mineral complex, or might reflect some quality of the specific proteins in milk and meat, such as the specific mix of amino acids. (*Id*.) These statements proved extremely prescient.

20. In a 1928 report, Goldberger, Wheeler, Lillie, and Rogers presented their findings on dietary factors that can ameliorate or prevent blacktongue in dogs, a condition that they correctly believed to be a canine form of pellagra. (Ex. 1005, Goldberger et al., at 1385-86, 1446-47.) Sixteen specific factors, including milk, were tested, with varying degrees of success. (*Id*. at 1447-48.) In this study, the milk employed was fresh skim milk, given orally at a dose of approximately 30 c.c. per kg of body weight daily along with "diet No. 123," a diet that otherwise produced blacktongue within approximately two months. (*Id*. at 1403.) (Goldberger showed that diet No. 123 produced blacktongue in A Further Study of Experimental Blacktongue (Ex. 1009 at 659-61).)

21. Five dogs were tested, with one developing a clear attack of blacktongue in 37 days, one developing "slight transient evidence of an attack" at the end of one year, and three others surviving 9-12 months with no evidence of blacktongue. (Ex. 1005, Goldberger et al., at 1404.) The authors noted that

"feeding with basic diet No. 123 has regularly resulted in an attack of blacktongue within a period only exceptionally longer than about two months" and summarized their results by stating, "It may be concluded, therefore, that milk contains the blacktongue preventive, but that somewhat more than 30 c.c. daily per kilogram of body weight, at least of skim milk, may be needed to secure complete protection when used to supplement such a basic diet as our No. 123." (*Id*.) Thus, in both humans and in dogs, milk alone was established to improve the course of or prevent pellagra through the action of an unknown preventive substance.

V. LEGAL STANDARDS

22. I have been informed of certain legal principles that impact the interpretation and analysis of the claims in this patent. My understanding of these principles is set forth below.

23. I understand that, for purposes of forming the opinions expressed in this Declaration, claim terms should be given their broadest reasonable interpretation in light of the specification, as understood by a person of ordinary skill in the art.

24. I understand that several factors are to be considered in determining who would have been a person of ordinary skill in the art. These factors include: the type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and

educational level of active workers in the field. In my opinion, a person of ordinary skill in the art in the relevant timeframe (i.e., the mid-2000s) would have had a Ph.D. in biology, biochemistry, or a similar field.

25. I also understand that claim terms generally should be given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art.

26. I understand that claim 1 of the ’086 patent is an “independent” claim and claims 2-5 are “dependent” claims that depend from claim 1. Dependent claims include all of the elements of the claims upon which they depend. Likewise, an independent claim encompasses the subject matter of its dependent claims. Accordingly, I understand that the term “pharmaceutical composition” in independent claim 1 of the ’086 patent encompasses the formulations specified in dependent claim 3, including food.

27. I understand that the ’086 patent defines “an isolated molecule” as follows:

> As used herein, an isolated molecule . . . means a molecule separated or substantially free from at least some of the other components of the naturally occurring organism, such as for example, the cell structural components or other polypeptides or nucleic acids commonly found associated with the molecule.

(Ex. 1001, ’086 patent, at 9:3-9:10.) Accordingly, I understand the phrase “is isolated” as used in claim 2 should be understood to mean “is separated or substantially free from at least some of the other components of the naturally occurring organism.”

28. I have been advised by Elysium’s attorneys that a claim is anticipated when a single prior art patent or publication discloses, either expressly or inherently, every limitation of the claim in the claimed arrangement.

29. I understand that a prior art reference will anticipate a claim by inherent disclosure only when the reference must *necessarily* include unstated limitation(s). I have also been advised that with respect to inherent disclosures, it is not necessary that people skilled in the art actually recognized that a reference inherently made such disclosures at the time the reference was created in order to establish anticipation.

VI. SPECIFIC ANALYSES OF ANTICIPATION

A. Overview of the Claims of the ’086 Patent

30. Claim 1 claims a pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration. In claim 2, the NR is isolated from a natural or synthetic source. Claim 3 specifies different forms the NR-containing formulation can take, including an elixir, suspension, or food. Claim 4 requires that the

composition also contain tryptophan, nicotinic acid, and/or nicotinamide. Finally, claim 5 specifies that the pharmaceutical composition increases NAD+ biosynthesis upon oral administration.

B. Disclosures by Goldberger et. al

1. Claim 1

31. All of the elements of claim 1 are disclosed in Goldberger et al. (Ex. 1005.) Goldberger et al. teaches the administration of a pharmaceutical composition (which is understood to include food, based on the legal standard outlined above in paragraph 26) to prevent blacktongue. While it was not known at the time that Goldberger and colleagues performed their work that cow's milk inherently contained NR, that fact is mentioned in the '086 patent and later described in detail, including with respect to skim milk, in Trammell I. (Ex. 1005, Goldberger et al., at 1402-05; Ex. 1001, '086 patent, at 3:9-12; Ex. 1007, Trammell I, at 3, 5, 6.)

32. The NR in skim milk is in admixture with other components of the milk, including components that are demonstrated in Trammell I to bind and stabilize the compound. (Ex. 1007, Trammell I, at 5-6.) The skim milk in Goldberger et al. was administered orally. (Ex. 1005, Goldberger et al., at 1403.) Thus, Goldberger et al. teaches the administration of a pharmaceutical composition

that inherently contains NR in admixture with a carrier and is suitably formulated for oral administration.

2. **Claim 2**

33. Given the understanding of the term "is isolated" described above in paragraph 27, the element added by claim 2 is disclosed in Goldberger et al. because the NR in skim milk is isolated from a natural source, first, from the cow and later from the whole milk when the fat elements of whole milk are separated from the non-fat elements, including the NR. (Ex. 1005, Goldberger et al., at 1403; Ex. 1011, Good Milk, at 6.)

3. **Claim 3**

34. Goldberger et al. discloses the element added in claim 3 because milk is a food.

4. **Claim 4**

35. As is documented in Trammell I, skim milk contains nicotinamide in addition to NR. (Ex. 1007, Trammell I, at 5.) (Trammell I also notes that "[i]t has long been known that the NAD+ precursors in milk include nicotinamide and tryptophan." (*Id*. at 1.)). Thus, the skim milk in Goldberger et al. necessarily is a composition containing NR and nicotinamide, satisfying the requirement added in claim 4.

5. **Claim 5**

36. As it is now known that blacktongue in dogs is a disease caused by NAD+ deficiency, it follows that the resolution or prevention of blacktongue by milk supplementation, as shown in Goldberger et al., is direct evidence that the milk stimulated greater NAD+ biosynthesis upon oral administration. (Ex. 1005, Goldberger et al., at 1404.) This conclusion is confirmed by later studies, discussed above in paragraphs 13-14, directly demonstrating that oral intake of NR increases NAD+ concentration in multiple tissues. Thus, Goldberger et al. teaches the oral administration of a composition containing NR that necessarily increases NAD+ biosynthesis upon oral administration, as required by claim 5.

C. Disclosures by Goldberger and Tanner

1. **Claim 1**

37. All of the elements of claim 1 are disclosed in Goldberger and Tanner. Goldberger and Tanner teaches the administration of a pharmaceutical composition (which is understood to include food, based on the legal standard outlined above in paragraph 26) to prevent pellagra. While it was not known at the time that Goldberger and Tanner performed their work that buttermilk contained NR and buttermilk was not the form of milk in which NR was directly assayed in Trammell I, it is my opinion that NR is present in buttermilk, for the reasons given above in paragraph 12. The NR in buttermilk is in admixture with other soluble components of the milk, including components that are demonstrated in Trammell I to bind and

stabilize the compound. (Ex. 1007, Trammell I, at 5-6.) The buttermilk in Goldberger and Tanner was administered orally. (Ex. 1006, Goldberger and Tanner, at 93.) Thus, Goldberger and Tanner teaches the administration of a pharmaceutical composition that inherently contains NR in admixture with a carrier that is suitably formulated for oral administration.

2. **Claim 2**

38. Given the understanding of the term "is isolated" described above in paragraph 27, the element added by claim 2 is disclosed in Goldberger and Tanner because the NR in buttermilk is isolated from a natural source, first, from the cow, and later from the whole milk or cream, when the fat elements that are churned into butter are separated from the water-soluble elements, including NR. (Ex. 1006, Goldberger and Tanner, at 93; Ex. 1011, Good Milk, at 6.)

3. **Claim 3**

39. Goldberger and Tanner discloses the element added in claim 3 because milk is a food.

4. **Claim 4**

40. As explained above in paragraph 35, Trammell I documents that milk contains nicotinamide in addition to NR and notes that "[i]t has long been known that the NAD+ precursors in milk include nicotinamide and tryptophan." (Ex. 1007, Trammell I, at 1, 3.) Nicotinamide, like NR, is water soluble and therefore present in buttermilk, as explained above in paragraph 12. That is, because

nicotinamide is a water-soluble molecule, it remains in the aqueous buttermilk when the butter is removed.

41. Moreover, McFarlane and Fulmer's testing of dried buttermilk powder, among other proteins, establishes that tryptophan is present in buttermilk powder. (Ex. 1012, McFarlane and Fulmer, at, e.g., 1602, 1604, 1608-09.) Indeed, the researchers concluded that "The tyrosine and tryptophan content of buttermilk powder has been found to be much higher than that of other crude protein materials investigated." (*Id*. at 1609.) Tryptophan must therefore be present in the liquid buttermilk from which the buttermilk power is directly derived.

42. Thus, the buttermilk in Goldberger and Tanner is a composition containing nicotinamide and tryptophan, satisfying the requirement added by claim 4.

5. **Claim 5**

43. As it is now known that pellagra is a disease caused by NAD+ deficiency, it follows that the prevention of pellagra by buttermilk supplementation demonstrated in Goldberger and Tanner is direct evidence that the buttermilk stimulated greater NAD+ biosynthesis upon oral administration. (Ex. 1006, Goldberger and Tanner, at 93.) This conclusion is confirmed by later studies, discussed above in paragraphs 13-14, directly demonstrating that oral NR increases NAD+ concentration in multiple tissues. Thus, although the authors did not know

it at the time, Goldberger and Tanner inherently discloses an NR-containing composition that can be orally administered and increases NAD+ biosynthesis upon oral administration.

44. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVII of the United States Code.

July 16, 2017

Joseph A. Baur

APPENDIX A

CURRICULUM VITAE

Joseph Anthony Baur, Ph.D.

July, 2017

Institute for Diabetes, Obesity, and Metabolism, Department of Physiology
Perelman School of Medicine, University of Pennsylvania
Smilow Center for Translational Research, 3400 Civic Center Blvd., Room 12-114
Tel: (215) 746 4585 • Fax: (215) 898 5408
Baur@mail.med.upenn.edu

Education

Acadia University, Wolfville, NS, Canada	B.Sc.H.	1998	Chemistry
UT Southwestern Medical Center, Dallas, TX	Ph.D.	2003	Integrative Biology
Harvard Medical School, Boston, MA	Postdoctoral Fellow	2008	Molecular Biology of Aging

Professional Experience

1998-2003	Ph.D. (Integrative Biology), Department of Cell Biology, UT Southwestern Medical Center, Dallas, Texas (UTSW)
2003-2008	Post-Doctoral Fellow, Dr. David Sinclair, Department of Pathology Harvard Medical School
2008-2009	Instructor, Institute for Diabetes, Obesity and Metabolism and Department of Physiology, Perelman School of Medicine, University of Pennsylvania
2009-2017	Assistant Professor, Institute for Diabetes, Obesity and Metabolism and Department of Physiology, Perelman School of Medicine at the University of Pennsylvania
2016-Present	Director, Mouse Phenotyping, Physiology, and Metabolism Core of the Diabetes Research Center, Perelman School of Medicine at the University of Pennsylvania
2017-Present	Associate Professor, Institute for Diabetes, Obesity and Metabolism and Department of Physiology, Perelman School of Medicine at the University of Pennsylvania

Honors and Awards

1994	Gold level Duke of Edinburgh's Award (Citizenship)
1995	Manning Scholarship, Acadia University
1995	NSPI Scholarship, Nova Scotia Power Inc.
1995	Dr. Leverett Chipman Dev. Scholarship, Acadia University
1996	Chester W. Small Scholarship, Acadia University
1996-1997	Clarke K. McLeod Scholarship, Acadia University
1997	Malcolm W. Orchard Memorial Scholarship, Acadia University
1997	Colville Award/Huggins Scholarship, Acadia University
1998	NSERC Post-Graduate Fellowship, National Science and Engineering Research Council (declined)
1999	Honorary Mention for the Howard Hughes Fellowship, Howard Hughes Research Institute
2001	New Opportunities Award NO-0005-00, Ellison Medical Foundation
2001-2003	Breast Cancer Research Program Pre-doctoral Fellowship DAMD17-01-1-0419, US Department of Defense
2001	Sigma Xi and GSO Poster Awards
2003	Finalist for the Nominata Award (top UTSW Graduate Student)
2004-2006	Post-doctoral Fellowship 0425834T, American Heart Association
2008-2012	K99/R00 Pathway to Independence Award

2010-2014 New Scholar Award, Ellison Medical Foundation
2013 Joseph A. Pignolo, Sr. Award in Aging Research

Lectures by Invitation

Jul, 2004 "Resveratrol activates SIRT1 and mimics caloric restriction in mammalian cells", American Institute for Cancer Research Conference, Washington, DC
Nov, 2005 "Sirtuins, caloric restriction, and the regulation of longevity", Longevity Consortium Symposium, San Diego, CA
Oct, 2007 "Resveratrol in health and longevity", 2nd Bruce Ames International Symposium on Nutritional Genomics, Davis, CA
Apr, 2008 "Physiological and transcriptional effects of long-term resveratrol treatment in mice", FASEB Experimental Biology Meeting, San Diego, CA
Dec, 2008 "Metabolic effects of sirtuin activation", Regional DERC Meeting, Columbia University, New York, NY
May, 2009 "SIRT1 and Mitochondrial Biogenesis in the Regulation of Longevity", NIA New Investigators Forum, Bethesda, MD
Oct, 2009 "SIRT1 and lifespan extension: more than just red wine", mini-symposium entitled "Aging: is the end inevitable?" within Renal Week 2009, San Diego, CA
Nov, 2009 "Resveratrol alters global patterns of gene regulation and improves physiology", Cal Poly Pomona Nutrigenomics Conference, Pomona, CA
Aug, 2010 "Can we mimic caloric restriction to delay aging?", XVII Yrjo Jahnsson Medical Symposium, Porvoo, Finland
Sep, 2010 "Resveratrol and life extension", Resveratrol 2010: 1st international conference of resveratrol and health, Elsinore, Denmark
Oct, 2010 "Metabolic effects of resveratrol and sirtuins", Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN
Jun, 2011 "Caloric restriction in a pill? Insights from mouse models", American Diabetes Association 71st Scientific Sessions, San Diego, CA
Sep, 2011 "Rapamycin-induced hepatic insulin resistance is mediated by mTORC2 and uncoupled from longevity", Target Meeting's 1st world cardiovascular, diabetes, and obesity online conference.
Jun, 2012 "The science behind the hype: resveratrol, wine & chocolate", New York Academy of Sciences, NY, NY (Science & the City seminar series)
Aug, 2012 "Small molecules that influence mammalian aging", Roskilde University, Roskilde, Denmark
Aug, 2012 "Regulation of mitochondrial biogenesis by caloric restriction and resveratrol", Workshop: Resveratrol and other anti-inflammatory compounds in human health, Copenhagen, Denmark
Sep, 2012 "Is aging inevitable?", Big Ideas @Penn (GAPSA-sponsored event), University of Pennsylvania
Oct, 2012 "mTOR signaling, insulin, and ageing", 2012 Louis-Jeantet Symposium, Centre Medical Universitaire, Geneva, Switzerland.
Dec, 2012 "Regulation of mitochondrial biogenesis by caloric restriction and aging", Resveratrol 2012: 2nd International Scientific Conference on Resveratrol and Health, Leicester, UK
Feb, 2013 "Regulation of insulin sensitivity and mitochondrial biogenesis by mTOR", Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, NJ
Jun, 2013 "Inhibiting mTOR Signaling: A Strategy to Mimic Caloric Restriction?", American Aging Association (AGE) Meeting, Baltimore, MD
Jul, 2013 "Regulation of insulin sensitivity and adipocyte fate by mTOR", Obesity Research Special Interest Group, Thomas Jefferson University, Philadelphia, PA
Oct, 2013 "Resveratrol, Sirtuins, and NAD", Resveratrol 2013, Tokyo, Japan

Nov, 2013 "Rapamycin: A small molecular that mimics caloric restriction?", Naomi Berrie Diabetes Center, Columbia University, NY

Feb, 2014 "Rapamycin: A small molecular that mimics caloric restriction?", Department of Microbiology and Molecular Genetics, Rutgers University, Newark, NJ

May, 2014 "ROS, resveratrol, and rapamycin", Connecting the Biological Principles of Mammalian Aging Workshop, Arlington, VA

May, 2014 "Rapamycin: A small molecular that mimics caloric restriction?", Molecular and Cell Biology and Genetics Program, Drexel University College of Medicine, Philadelphia, PA (Student-invited speaker)

Oct, 2014 "Metabolic effects of rapamycin, a mammalian longevity drug", ICGEB Symposium, University of Chile, Santiago, Chile

Dec, 2014 "Resveratrol, sirtuins, and mitochondria in critical injury", Resveratrol 2014, Hilton Waikoloa Village, Hawaii.

Mar, 2015 "Metabolic Effects of Rapamycin, a Mammalian Longevity Drug", Albert Einstein College of Medicine, Bronx, NY

Oct, 2015 "NAD metabolism influences skeletal muscle function and integrity", Einstein-Mt Sinai Diabetes Research Center, Bronx, NY

Feb, 2016 “NAD salvage plays an essential role in aging muscle”, Huffington Center on Aging, Baylor College of Medicine, Houston, TX

Mar, 2016 “NAD metabolism in the long-term health of mammalian tissues”, Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI

Apr, 2016 "Modulating NAD Metabolism in Mammals", Pfizer's Ninth Annual Frontiers in Human Disease Symposium subtitled "Senescence, Aging, and Human Disease", Boston, MA

Sep, 2016 "Metabolism and Aging", Summer School on Diabetes and Metabolism, sponsored by the Danish Diabetes Academy, Sinatur Hotel Gl. Avernaes, Ebberup, Denmark

Nov, 2016 "Loss of NAD Triggers Progressive Muscle Degeneration", Thomas Jefferson University, Philadelphia, PA

Nov, 2016 "Loss of NAD Homeostasis Triggers Progressive Muscle Degeneration", State Key Laboratory of Reproductive Medicine, Nanjing Medical University, Nanjing, China

Nov, 2016 "Resveratrol and NAD in Hemorrhagic Shock", Resveratrol 2016, Taipei Medical University, Taipei, Taiwan

June, 2017 “Loss of NAD Homeostasis Triggers Progressive Muscle Degeneration”, École Polytechnique Fédérale De Lausanne, Lausanne, Switzerland

June, 2017 “Celastrol and Hypothalamic mTORC2 Modulate Leptin Resistance”, Aging & Sleep, meeting of the International Association of Sleep Research in Gerontology, Lyon, France

Publications

1. Holt, S.E., Aisner, D.L., **Baur, J.**, Tesmer, V.M., Dy, M., Ouellette, M., Trager, J.B., Morin, G.B., Toft, D.O., Shay, J.W., Wright, W.E. and White, M.A. Functional requirement of p23 and hsp90 in telomerase complexes. *Genes & Development*. **13**: 817-826 (1999).

2. Yi, X., White, D.M., Aisner, D.L., **Baur, J.A.**, Wright, W.E., Shay, J.W. An alternate splicing variant of human telomerase catalytic subunit inhibits telomerase activity. *Neoplasia*. **2**(5): 433-440 (2000).

3. Wood, L.D., Halvorsen, T.L., Dhar, S., **Baur, J.A.**, Pandita, R.K., Vikram, B., Wright, W.E., Hande, M.P., Calaf, G., Levine, F., Shay, J.W., Wang, J.Y., Pandita, T.K. Characterization of ataxia telangiectasia fibroblasts with extended life-span through telomerase expression. *Oncogene*. **20**: 278-288 (2001).

4. **Baur, J.A.**, Zou, Y., Shay, J.W., Wright, W.E. Telomere position effect in human cells. *Science*. **292**: 2075-2077 (2001).

5. **Baur, J.A.**, Wright, W.E., and Shay, J.W. Analysis of mammalian telomere position effect. In *Methods in Molecular Biology*, Humana Press, Totowa, NJ. **287**: 121-136 (2004).

6. **Baur, J.A.**, Shay, J.W., and Wright, W.E. Spontaneous reactivation of a silent telomeric transgene. *Chromosoma.* **112**: 240-246 (2004).

7. **Baur, J.A.**, Sinclair, D.A. Therapeutic potential of resveratrol: the *in vivo* evidence. *Nature Reviews in Drug Discovery*. **5**(6): 493-506 (2006).

8. Yang, H., **Baur, J.A.**, Chen, A., Miller, C., Sinclair, D.A. Design and synthesis of compounds the extend yeast replicative lifespan. *Aging Cell*. **6**(1): 35-43 (2006).

9. **Baur, J.A.***, Pearson, K.J.*, Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D.A. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. **444**(7177): 337-342 (2006).

10. Kim, D., Nguyen, M.D., Dobbin, M.M., Fischer, A., Sananbenesi, F., Rodgers, J.T., Delalle, I., **Baur, J.A.**, Sui, G., Armour, S.M., Puigserver, P., Sinclair, D.A., Tsai, L.H. SIRT1 deacetylase protects against age-dependent neurodegeneration. *EMBO Journal*. **26**(13):3169-3179 (2007). PMCID: PMC1914106

11. **Baur, J.A.** Obesity: do grapes hold the answer? *Pediatric Research* **61**(6):633 (2007).

12. Yang, H., Yang, T., **Baur, J.A.**, Perez, E., Matsui, T., Carmona, J.J., Lamming, D.W., Souza-Pinto, N.C., Bohr, V.A., Rosenzweig, A., de Cabo, R., Sauve, A.A., Sincalir, D.A. Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. *Cell*. **130**(6):1095-107 (2007). PMCID: PMC3366687

13. Pearson, K.J.*, **Baur, J.A.***, Lewis, K.N., Peshkin, L., Price, N.L., Labinskyy, N., Swindell, W.R., Kamara, D., Minor, R.K., Perez, E., Jamieson, H.A., Zhang, Y., Dunn, S.R., Sharma, K., Pleshko, N., Woolett, L.A., Csiszar, A., Ikeno, Y., Le Couteur, D., Elliott, P.J., Becker, K.G., Navas, P., Ingram, D.K., Wolf, N.S., Ungvari, Z., Sinclair, D.A., and de Cabo, R. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metabolism*. **8**(2):157-68 (2008). PMCID: PMC2538685

14. **Baur, J.A.**, and Sinclair, D.A. What is xenohormesis? *American Journal of Pharmacology and Toxicology*. **3**(1):152-159 (2008).

15. **Baur, J.A.** Metabolic effects of caloric restriction. In *Encyclopedia of Life Sciences*, John Wiley & Sons, Ltd, Chichester, UK. (2009).

16. Armour, S.M., **Baur, J.A.**, Hsieh, S.N., Land-Bracha, A., Thomas, S.N., Sinclair, D.A. Inhibition of mammalian S6 kinase by resveratrol suppresses autophagy. *Aging (Albany, NY).* **1**(6):515-528 (2009). PMCID: PMC2806030

17. Lou, Z., Wei, J., Riethman, H., **Baur, J.A.**, Voglauer, R., Shay, J.W., and Wright, W.E. Telomere length regulates ISG15 expression in human cells. *Aging* **1**(7):515-525 (2009). PMCID: PMC2806043

18. **Baur, J.A.** Biochemical effects of SIRT1 activators. *Biochimica and Biophysica Acta* **1804**(8):1626-34 (2010). PMCID: PMC2886178

19. **Baur, J.A.** Resveratrol, sirtuins, and the promise of a DR mimetic. *Mechanisms of Ageing and Development.* **131**(4):261-9 (2010). PMCID: PMC286768

20. **Baur, J.A.**, Chen, D., Chini, E.N., Chua, K., Cohen, H.Y., de Cabo, R., Deng, C., Dimmeler, S., Gius, D., Guarente, L.P., Helfand, S.L., Imai, S., Itoh, H., Kadowaki, T., Koya, D., Leeuwenburgh, C., McBurney, M., Nabeshima, Y., Neri, C., Oberdoerffer, P., Pestell, R,G., Rogina, B., Sadoshima, J., Sartorelli, V., Serrano, M., Sinclair, D.A., Steegborn, C., Tatar, M., Tissenbaum, H.A., Tong, Q., Tsubota, K., Vaquero, A., and Verdin, E. Dietary restriction: standing up for sirtuins. *Science.*

329(5995):1012-3 (2010).

21. **Baur, J.**A. Sirtuins and oxidative stress. *Pathways* (Qiagen). 12 (2010).

22. Miller, R.A., Harrison, D.E., Astle, C.M., **Baur, J.A.**, Boyd, A.R., de Cabo, R., Fernandez, E., Flurkey, K., Javors, M.A., Nelson, J.F., Orihuela, C.J., Pletcher, S., Sharp, Z.D., Sinclair, D.A., Starnes, J.W., Wilkinson, J.E., Nadon, N.L., and Strong, R. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci.* **66**(2):191-201 (2011). PMCID: PMC3021372

23. Agarwal, B., and **Baur, J.A.** Resveratrol and life extension. *Ann NY Acad Sci.* **1215**:138-43 (2011).

24. Varamini, B., and **Baur, J.A**. The Polyphenol Resveratrol Alters Global Patterns of Gene Regulation and Improves Physiology through Multiple Potential Pathways. In *The Impact of Dietary Regulation of Gene Function on Human Disease*, CRC Press, Boca Raton, FL. 185-196 (2011).

25. Ungvari, Z., Sonntag, W.E., de Cabo, R., **Baur, J.A.**, and Csiszar, A. Mitochondrial protection by resveratrol. *Exerc Sport Sci Rev.* **39**(3):128-32 (2011).

26. Smoliga, J.M., **Baur, J.A.**, and Hausenblas, H.A. Resveratrol and health – a comprehensive review of human clinical trials. *Mol Nutr Food Res.* **55**(8):1129 (2011).

27. Vang, O., Ahmad, N., Baile, C.A., **Baur, J.A.**, Brown, K., Csiszar, A., Das, D.K., Delmas, D., Gottfried, C., Lin, H.Y., Ma, Q.Y., Mukhopadhyay, P., Nalini, N., Pezzuto, J.M., Richard, T., Shukla, Y., Surh, Y.J., Szekeres, T., Szkudelski, T., Walle, T., Wu, J.M. What is new for an old molecule? Systematic review and recommendations on the use of resveratrol. *PLoS One*. **6**(6):e19881 (2011). PMCID: PMC3116821

28. Smoliga, J.M., Vang, O., **Baur, J.A.** Challenges of Translating Basic Research Into Therapeutics: Resveratrol as an Example. *J Gerontol A Biol Sci Med Sci*. **67**(2):158 (2012). PMCID: PMC3261440

29. Minor, R.K., **Baur, J.A.**, Gomes, A.P., Ward, T.M., Csiszar, A., Mercken, E.M., Abdelmohsen, K., Shin, Y.-K., Canto, C., Scheibye-Knudsen, M., Krawczyk, M., Irusta, P.M., Martin-Montalvo, A., Hubbard, B.P., Zhang, Y., Lehrmann, E., White, A.A., Price, N.L., Swindell, W.R., Pearson, K.J., Becker, K.G., Bohr, V.A., Gorospe, M., Egan, J.M., Talan, M.I., Auwerx, J., Westphal, C.H., Ellis, J.L., Ungvari, Z., Vlasuk, G.P., Elliott, P.J., Sinclair, D.A., and de Cabo, R. SRT1720 improves survival and healthspan of obese mice. *Sci. Rep.* **1**:70 (2011).

30. Xie, H.M., Perin, J.C., Schurr T.G., Dulik, M.C., Zhadanoy, S.I., **Baur, J.A**,. King, M.P., Place, E., Clarke, C., Grauer, M., Schug J., Santani, A., Albano, A., Kim, C., Procaccio, V., Hakonarson, H., Gai, X., and Falk, M.J. Mitochondrial genome sequence analysis: a custom bioinformatics pipeline substantially improves Affymetrix MitoChip v2.0 call rate and accuracy*. BMC bioinformatics* **12**: 402, (2011).

31. Strong R., Miller R.A., Astle C.M., **Baur J.A.**, de Cabo R., Fernandez E., Guo W., Javors M., Kirkland J.L., Nelson J.F., Sinclair D.A., Teter B., Williams D., Zaveri N., Nadon N.L., and Harrison D.E. Evaluation of Resveratrol, Green Tea Extract, Curcumin, Oxaloacetic Acid, and Medium-Chain Triglyceride Oil on Life Span of Genetically Heterogeneous Mice. *J Gerontol A Biol Sci Med Sci.* (2013). PMCID: PMC3598361

32. Lamming, D.W.*, Ye, L.*, Katajisto, P., Goncalves, M.D., Saitoh, M., Stevens, D.M., Davis, J.G., Salmon, A.B., Richardson, A., Ahima, R.S., Guertin, D.A., Sabatini, D.M., and **Baur, J.A.** Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science* **335**(6076):1638-43, 2012. PMCID: PMC3324089

33. Price, N.L., Gomes, A.P., Ling, A.J., Duarte, F.V., Martin-Montalvo, A., North, B.J., Agarwal, B., Ye, L., Ramadori, G., Teodoro, J.S., Hubbard, B.P., Varela, A.T., Davis, J.G., Varamini, B., Hafner, A., Moaddel, R., Rolo, A.P., Coppari, R., Palmeira, C.M., de Cabo, R., **Baur, J.A.**, Sinclair, D.A. SIRT1

Is Required for AMPK Activation and the Beneficial Effects of Resveratrol on Mitochondrial Function. *Cell Metab*. **15**(5):675-90 (2012).

34. **Baur, J.A.**, Ungvari, Z., Minor, R.K., Le Couteur, D.G., de Cabo, R. Are sirtuins viable targets for improving healthspan and lifespan? *Nat Rev Drug Discov*. **11**(6):443-61 (2012).

35. Ye, L., Varamini, B., Lamming, D.W., Sabatini, D.M., **Baur, J.A.** Rapamycin has a biphasic effect on insulin sensitivity in C2C12 myotubes due to sequential disruption of mTORC1 and mTORC2. *Front Genet*. **3**:177 (2012). PMCID: PMC3438685

36. Guarente, L., **Baur, J.A.,** Mai, A. Revelations into resveratrol's mechanism. *Nature Medicine.* **18**(4):500-1 (2012). (Community Corner)

37. Agarwal, B.*, Campen, M.J.*, Channell, M.M., Wherry, S.J., Varamini, B., Davis, J.G., **Baur, J.A**., Smoliga, J.M. Resveratrol for primary prevention of atherosclerosis: Clinical trial evidence for improved gene expression in vascular endothelium. *Int J Cardiol.* **166**(1):246-8 (2013). PMCID: PMC3646959

38. Lamming, D.W., Ye, L., Sabatini, D.M., **Baur, J.A.** Raplogs and mTOR inhibitors as anti-aging therapeutics. *J Clin Invest.* **123**(3):980-989 (2013). PMCID: PMC3582126

39. Lamming, D.W., Ye, L., Astle, C.M., **Baur, J.A.**, Sabatini, D.M., Harrison, D.E. Young and old genetically heterogeneous HET3 mice on a rapamycin diet are glucose intolerant but insulin sensitive. *Aging Cell*. **12**(4):712-8 (2013). PMCID: PMC3727050

40. Chellappa, K., **Baur, J.A.** mTOR pathways in aging. *Experimental Medicine (Japanese)*. **31**:37-44 (2013).

41. Zhang, Z., Tsukikawa, M., Peng, M., Polyak, E., Nakamaru-Ogiso, E., Ostrovsky, J., McCormack, S., Place, E., Clarke, C., Reiner, G., McCormick, E., Rappaport, E., Haas, R., **Baur, J.A.**, Falk, M.J. Primary respiratory chain disease causes tissue-specific dysregulation of the global transcriptome and nutrient-sensing signaling network. *PLoS One*. **8**(7):e69282 (2013). PMCID: PMC3722174

42. Ye, L., Widlund, A.L., Sims, C.A., Lamming, D.W., Guan, Y., Davis, J.G., Sabatini, D.M., Harrison, D.E., Vang, O., **Baur, J.A.** Rapamycin doses sufficient to extend lifespan do not compromise muscle mitochondrial content or endurance. *Aging* **5**(7): 539-550 (2013). PMCID: PMC3765582

43. Widlund, A.L., **Baur J.A.**, Vang. O. mTOR: more targets of resveratrol? *Expert Rev Mol Med*. **15**:e10 (2013).

44. Jimenez-Gomez, Y., Mattison, J.A., Pearson, K.J., Martin-Montalvo, A., Palacios, H.H., Sossong, A.M., Ward, T.M., Younts, C.M., Lewis, K., Allard, J.S., Longo, D.L., Belman, J.P., Malagon, M.M., Navas, P., Sanghvi, M., Moaddel, R., Tilmont, E.M., Herbert, R.L., Morrell, C.H., Egan, J.M., **Baur, J.A.**, Ferrucci, L., Bogan, J.S., Bernier, M., de Cabo, R. Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on high-fat, high-sugar diet. *Cell Metab*. **18**(4):533-45 (2013). PMCID: PMC3832130

45. Naidoo, N., Davis, J.G., Zhu, J., Yabumoto, M., Singletary, K., Brown, M., Galante, R., Agarwal, B., **Baur, J.A**. Aging and sleep deprivation induce the unfolded protein response in the pancreas: implications for metabolism. *Aging Cell*. **13**(1):131-41 (2014). PMCID: PMC4009977

46. Zhang, J., Zhu, Y., Zhan, G., Fenik, P., Panossian, L., Wang, M.M., Reid, S., Lai, D., Davis, J.G., **Baur, J.A.**, Veasey, S. Extended wakefulness: compromised metabolics in and degeneration of locus ceruleus neurons. *J Neurosci*. **34**(12):4418-31 (2014). PMCID: PMC3960479

47. Mattison, J.A., Wang, M., Bernier, M., Zhang, J., Park, S., Maudsley, S., An, S.S., Santhanam, L., Martin, B., Faulkner, S., Morrell, C., **Baur, J.A.**, Peshkin, L., Sosnowska, D., Csiszar, A., Herbert, R.L., Tilmont, E.M., Ungvari, Z., Pearson, K.J., Lakatta, E.G., de Cabo, R. Resveratrol Prevents High Fat/Sucrose Diet-Induced Central Arterial Wall Inflammation and Stiffening in Nonhuman Primates. *Cell Metabolism* **20**(1):183-90 (2014).

48. Mercken, E.M., Mitchell, S.J., Martin-Montalvo, A., Minor, R.K., Almeida, M., Gomes, A.P., Scheibye-Knudsen, M., Palacios, H.H., Licata, J.J., Zhang, Y., Becker, K.G., Khraiwesh, H., González-Reyes, J.A., Villalba, J.M., **Baur, J.A.**, Elliott, P., Westphal, C., Vlasuk, G.P., Ellis, J.L., Sinclair, D.A., Bernier, M., de Cabo, R. SRT2104 extends survival of male mice on a standard diet and preserves bone and muscle mass. *Aging Cell* **13**(5):787-96 (2014).

49. **Baur, J.A.** and Birnbaum, M.J. Control of gluconeogenesis by metformin: does redox trump energy charge? *Cell Metabolism.* **20**(2):197-9 (2014).

50. Wang, H., Guan, Y., Widlund, A.L., Becker, L.B., **Baur, J.A.**, Reilly, P.M., Sims, C.A. Resveratrol ameliorates mitochondrial dysfunction but increases the risk of hypoglycemia following hemorrhagic shock. *J Trauma Acute Care Surg*. **77**(6):926-33 (2014).

51. Liu, Y., Diaz, V., Fernandez, E., Strong, R., Ye, L., **Baur, J.A.,** Lamming, D.W., Richardson, A., Salmon, A.B. Rapamycin-induced metabolic defects are reversible in both lean and obese mice. *Aging* (Albany NY). **6**(9):742-54 (2014).

52. Frederick, D.W., Davis, J.G., Dávila, A. Jr., Agarwal, B., Michan, S., Puchowicz, M.A., Nakamaru-Ogiso, E., **Baur, J.A.** Increasing NAD Synthesis in Muscle via Nicotinamide Phosphoribosyltransferase is not Sufficient to Promote Oxidative Metabolism. *Journal of Biological Chemistry*. **290**(3):1546-58 (2015).

53. Beier, U.H., Angelin, A., Akimova, T., Wang, L., Liu, Y., Xiao, H., Koike, M.A., Hancock, S.A., Bhatti, T.R., Han, R., Jiao, J., Veasey, S.C., Sims, C.A., **Baur, J.A.**, Wallace, D.C., Hancock, W.W. Essential role of mitochondrial energy metabolism in Foxp3+ T-regulatory cell function and allograft survival. *FASEB J*. **29**(6):2315-26 (2015).

54. Wang, H., Guan, Y., Karamercan, M.A., Ye, L., Bhatti, T., Becker, L.B., **Baur, J.A.,** Sims, C.A. Resveratrol Rescues Kidney Mitochondrial Function Following Hemorrhagic Shock. *Shock* **44**(2):173-80 (2015).

55. Côté, C.D., Rasmussen, B.A., Duca, F.A., Zadeh-Tahmasebi, M., **Baur, J.A.**, Daljeet, M., Breen, D.M., Filippi, B.M., Lam, T.K. Resveratrol activates duodenal Sirt1 to reverse insulin resistance in rats through a neuronal network. *Nature Medicine*. **21**(5):498-505 (2015).

56. Toth, P., Tarantini, S., Davila, A., Valcarcel-Ares, M.N., Tucsek, Z., Varamini, B., Ballabh, P., Sonntag, W.E., **Baur, J.A**., Csiszar, A., Ungvari, Z. Purinergic glio-endothelial coupling during neuronal activity: role of P2Y1 receptors and eNOS in functional hyperemia in the mouse somatosensory cortex. *Am J Physiol Heart Circ Physiol*. **309**(11):H1837-45 (2015).

57. Tran, C.M., Mukherjee. S., Ye, L., Frederick, D.W., Kissig, M., Davis, J.G., Lamming, D.W., Seale, P., **Baur J.A.** Rapamycin blocks induction of the thermogenic program in white adipose tissue. *Diabetes* 65:927-41 (2016). PMCID: PMC4806661

58. Cholsoon, J., Oh, S.F., Wada, S., Rowe, G.C., Liu, L., Chan, M.C., Rhee, J., Hoshino, A., Kim, B., Ibrahim, A., Baca, L.G., Kim, E., Ghosh, C.C., Parikh, S.M., Jiang, A., Chu, Q., Forman, D. E., Lecker, S.H., Krishnaiah, S., Rabinowitz, J.D., Weljie, A.M., **Baur, J.A.**, Kasper, D.L., Arany, Z. A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. *Nature medicine.* **22**(4): 421-6 (2016).

59. Frederick, D.W., Loro, E., Liu, L., Dávila, A. Jr., Chellappa, K., Silverman, I.M., Quinn, 3rd W. J., Gosai, S.J., Tichy, E.D., Davis, J.G., Mourkioti, F., Gregory, B. D., Dellinger, R.W., Redpath, P., Migaud, M.E., Nakamaru-Ogiso, E., Rabinowitz, J.D., Khurana, T.S., **Baur J.A.** Loss of NAD homeostasis leads to progressive and reversible degeneration of skeletal muscle. *Cell Metabolism.* **24**(2):269-82 (2016). PMCID: PMC4985182

60. Mukherjee, S., Chellappa, K., Moffitt, A., Ndungu, J., Dellinger, R.W., Davis, J.G., Agarwal, B and **Baur, J.A.** Nicotinamide adenine dinucleotide biosynthesis promotes liver regeneration. *Hepatology* **65**(2):616-630 (2016). PMCID: PMC5258848

61. Wada S, Neinast M, Jang C, Ibrahim YH, Lee G, Babu A, Li J, Hoshino A, Rowe GC, Rhee J, Martina JA, Puertollano R, Blenis J, Morley M, Baur JA, Seale P, Arany Z. The tumor suppressor FLCN mediates an alternate mTOR pathway to regulate browning of adipose tissue. *Genes Dev*. **30**(22):2551-2564 (2016). PMCID: PMC5159669

62. Krishnaiah SY, Wu G, Altman BJ, Growe J, Rhoades SD, Coldren F, Venkataraman A, Olarerin-George AO, Francey LJ, Mukherjee S, Girish S, Selby CP, Cal S, Er U, Sianati B, Sengupta A, Anafi RC, Kavakli IH, Sancar A, Baur JA, Dang CV, Hogenesch JB, Weljie AM. Clock Regulation of Metabolites Reveals Coupling between Transcription and Metabolism. Cell Metab. **25**(4):961-974 (2017). PMCID: PMC5479132

63. Moon L, Frederick DW, Baur JA, Li LZ. Imaging Redox State in Mouse Muscles of Different Ages. *Adv Exp Med Biol*. **977**:51-57 (2017).

64. Xiong M, Zhu Z, Tian S, Zhu R, Bai S, Fu K, Davis JG, Sun Z, Baur JA, Zheng K, Ye L. Conditional ablation of Raptor in the male germ line causes infertility due to meiotic arrest and impaired inactivation of sex chromosomes. *FASEB J*. (Epub ahead of print, 2017).

65. Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, Wang Z, Quinn WJ 3rd, Kopinski PK, Wang L, Akimova T, Liu Y, Bhatti TR, Han R, Laskin BL, Baur JA, Blair IA, Wallace DC, Hancock WW, Beier UH. Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. *Cell Metab*. **25**(6):1282-1293 (2017). PMCID: PMC5462872

66. Emmett MJ, Lim HW, Jager J, Richter HJ, Adlanmerini M, Peed LC, Briggs ER, Steger DJ, Ma T, Sims CA, Baur JA, Pei L, Won KJ, Seale P, Gerhart-Hines Z, Lazar MA. Histone deacetylase 3 prepares brown adipose tissue for acute thermogenic challenge. *Nature*. **546**(7659):544-548 (2017).

D. Research Support

ONGOING

NIA/NIH R01 AG043483 Baur (PI) 6/1/2013 - 5/31/2018
Molecular Mechanisms of Rapamycin's Effects on Health and Longevity.
The goal of this grant is to test the mechanism of action for rapamycin, the only drug that has been shown to extend maximum lifespan in a mammal, using genetic models. Despite extending life in mice, rapamycin has many detrimental side effects in humans with etiologies that remain poorly understood.
Role: PI

NIDDK/NIH R01 DK098656 Baur (PI) 9/1/2013 – 8/31/2018
Targeting NAD Metabolism to Improve Glucose Homeostasis in Obesity and Aging.
The goals of this award are to test whether restoring NAD levels in tissues where it becomes depleted during aging or obesity will rescue functional deficits, and to determine the roles of NAD metabolites in controlling insulin secretion and the response to caloric restriction.
Role: PI

NCI/NIH R01 CA191207 Li (PI) 7/2/2015 – 6/30/2020
Redox Imaging for Breast Cancer Prognosis.
The goal of this grant is to determine whether the metabolic state of a tumor, as determined by redox imaging, can help predict outcomes in a clinical setting.
Role: Co-Investigator

NIDDK/NIH R01 DK107667 Arany (PI) 7/1/2016 – 6/30/2021
Integrating cellular metabolic pathways into browning of white fat
Browning of white adipose tissue is increasingly recognized as a potential new therapeutic target for the treatment of obesity and diabetes. The mechanisms that govern this process remain incompletely understood,
in particular how the process is linked to intracellular metabolic cues.
Role: Co-Investigator

COMPLETED RESEARCH SUPPORT

NIDDK/NIH P01 Kaestner (PI) 9/1/2014 – 6/30/2017
Regulation of hepatic metabolism by metformin.
This is a subproject within the P01 "Integrative Metabolic Adaptions to Environmental and Nutritional Challenge". The goals of this award are to test whether metformin suppresses hepatic glucose output via effects on complex I of the mitochondrial electron transport chain, AMPK, mitochondrial glycerol-3-phosphate dehydrogenase, or some combination of the three.
Role: project PI

New Scholar Award, Ellison Medical Foundation Baur (PI) 7/15/2010 – 7/14/2014
The Role of NAD Metabolism in Caloric Restriction and Obesity.
The goal of this proposal is to test the hypothesis that changes in NAD metabolism regulate beneficial effects of caloric restriction using a transgenic mouse approach. In addition, the potential role of Nampt, an NAD biosynthetic enzyme, in promoting insulin resistance and inflammation during obesity will be investigated.
Role: PI

GI Center Pilot Award Baur (PI) 8/1/2014 – 7/31/2015
Targeting mTORC1 to treat metabolic diseases: a cell permeable peptide approach.
The goal of this proposal is to test the hypothesis that specific disruption of mTORC1 signaling via cell-penetrating peptides will improve diabetic phenotypes. Available small molecules do not achieve the required degree of specificity, and may worsen diabetic phenotypes through off-target inhibition of mTORC1.
Role: PI

University Research Foundation Award Baur (PI) 8/1/2013 – 7/31/2014
Control of Adipocyte Function and Fate by mTORC2.
The goal of this proposal is to test the hypothesis that mTORC2 is required for the induction of the brown/beige phenotype in adipocytes, and that it's inhibition accounts for some of the detrimental effects of rapamycin on metabolism.
Role: PI

NIA/NIH R00 AG031182-01A1 Baur (PI) 9/1/2009 - 8/31/2012
Does SIRT1 regulate mammalian health and longevity?
The goal of this award is to determine whether SIRT1 is required for some of the beneficial effects that have been shown to result from caloric restriction or resveratrol treatment. Although it has been postulated that SIRT1 is causal in these effects, a direct test has not been possible due to the poor phenotype and viability of the knockout mice. Tissue specific knockouts will be used in order to address these questions in relatively healthy animals.
Role: PI

Research Grant, American Federation for Aging Research Baur (PI) 7/1/09 - 6/30/2010
Does mitochondrial biogenesis regulate longevity?

The major goal of this project is to determine whether mitochondrial proliferation might play a causal role in at least some aspects of the beneficial effects of caloric restriction.
Role: PI

Bingham Trust/Penn IOA Pilot award Trojanowski (PI) 7/1/2009 - 6/30/2010
Mitochondria as mediators of the protective effects of caloric restriction.
The goal of this project is to explore the possibility of targeting mitochondria for therapeutic interventions to slow the onset and development of age-related diseases.
Role: PI (Pilot)

P30 DK019525 (Penn DERC) Pilot award Lazar (PI) 4/1/2009 - 3/31/2011
Characterization of Nampt transgenic mice.
The goal of this project is to test the role of NAD metabolism in regulating beneficial effects of calorie restriction (CR). Nampt is an enzyme that is upregulated during CR and catalyzes the rate-limiting step in NAD generation from nicotinamide. It has been postulated that this increase in NAD drives increased activity of SIRT1 and other enzymes. Transgenic mice overexpressing Nampt should mimic this aspect of caloric restriction and allow a test of the hypothesis that beneficial effects on health result from changes in NAD.
Role: PI (Pilot)