BIOGRAPHICAL SKETCH

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NAME: Brand, Martin D.

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

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
University of Manchester (UMIST), UK	B.Sc.	06/1971	Biochemistry
University of Bristol, UK	Ph.D.	09/1974	Biochemistry
Johns Hopkins University, Baltimore, MD		07/1976	Physiological Chemistry
University of Cambridge, UK	M.A.	05/1977	

A. Personal Statement

My laboratory studies mitochondrial and cellular production of reactive oxygen species and regulation of oxidative phosphorylation. To investigate ROS production we have established the specific sites and regulation of superoxide and hydrogen peroxide generation in the electron transport chain using novel endogenous reporters and improved fluorescence methods. Using high-throughput screening we have identified novel suppressors of ROS formation that do not inhibit energy metabolism, and are using them to probe and modulate mitochondrial ROS production *in situ* in cells and in biochemical and behavioral fly and mouse models. To investigate cellular regulation of mitochondrial oxidative phosphorylation, we have established fully quantitative fluorescence microscopy measurements of plasma membrane and mitochondrial membrane potential, and several conventional variables, and are improving the use of extracellular flux analysis on the Seahorse XF for quantitative assay of the rates of ATP production by oxidative phosphorylation and glycolysis. Together, these approaches are aimed at elucidating mitochondrial function *in situ* and the relationships between oxidative phosphorylation and radical production in signaling pathways, aging and pathology.

B. Positions and Honors

Positions and Employment

1974-1976 Postdoctoral Fellow, Johns Hopkins University, Baltimore, MD (with Professor A.L. Lehninger)
1976-1980 University Demonstrator in Biochemistry, University of Cambridge, UK
1977-1999 Official Fellow, College Lecturer, Tutor, Director of Studies, Girton College, Cambridge, UK
1980-1995 University Lecturer in Biochemistry, University of Cambridge, UK
1995-1999 Personal Readership in Cellular Biochemistry, University of Cambridge, UK
1999-2009 Group Leader, MRC Dunn Human Nutrition Unit, Cambridge, UK
2008- Professor and Core Director, Buck Institute for Research on Aging, Novato, CA
2009- Adjunct Professor, Dominican University, San Rafael CA
2014-2016 Adjunct Professor, Touro University College of Pharmacy, Vallejo CA
2014- Adjunct Professor, University of Southern California, Davis School of Gerontology, Los Angeles
2016- Associate Director, Paul F. Glenn Center for Biology of Aging Research at the Buck Institute

Other Experience and Professional Memberships

1973- Member, Biochemical Society
1984- Fellow, Cambridge Philosophical Society
2001- Editorial Board, Physiological and Biochemical Zoology
2004-2018 Editorial Board, Biochimica et Biophysica Acta Bioenergetics
2004- Editorial Board, Cell Metabolism
2008-2014 Scientific Advisory Board, Seahorse Bioscience, Billerica, MA
2008- Editorial Board, Aging Cell

2011-2014 Editorial Board, Longevity and Healthspan
2013- Scientific Advisory Board, Ogenx Therapeutics Corp, Clearwater, FL
2013- Member, American Society for Biochemistry and Molecular Biology
2013- Member, United Mitochondrial Disease Foundation
2014 Scientific Advisory Board, Oklahoma Medical Research Foundation, Oklahoma City, OK
2014- Scientific Advisory Board, Mitochon Pharmaceuticals, Radnor, PA
2017- Member, Society for Redox Biology and Medicine

Honors

1974 Fulbright-Hays Postdoctoral Scholarship
1997 Rudi Lemberg Fellowship of the Australian Academy of Sciences
1999 Life Fellow, Girton College, Cambridge
2003 Elected Fellow of the Academy of Medical Sciences UK
2005 Keilin Memorial Medal, Biochemical Society
2007 Honorary Professor of Cellular Biochemistry, University of Cambridge
2009 Senior Scholar Award, The Ellison Medical Foundation

C. Contribution to Science

343 peer-reviewed papers. Google Scholar (June 2019): total citations 36,827 (12,877 since 2014); h-index 98.

1) **Mechanism of oxidative phosphorylation**. My study of mitochondrial proton pumping started during my postdoc with Albert Lehninger. My paradigm-shifting work showed that the H^+/O stoichiometries of mitochondrial proton pumping are higher by 50-100% than previously thought (1,2). These results had major implications for the mechanisms of proton pumps, and led to significant modifications to the chemiosmotic theory, which underpins all bioenergetics. Subsequently, I helped establish the exact values of these stoichiometries (3,4). This work continues to drive physiological and ecological energetics and work in many labs on the mechanisms of proton pumping by respiratory complexes.
   (1) Brand MD, Reynafarje B, Lehninger AL (1976) Re-evaluation of the H^+/site ratio of mitochondrial electron transport with the oxygen pulse technique. *J Biol Chem* 251, 5670-5679
   (2) Brand MD, Reynafarje B, Lehninger AL (1976) Stoichiometric relationship between energy-dependent proton ejection and electron transport in mitochondria. *Proc Natl Acad Sci USA* 73, 437-441. PMCID: PMC335924
   (3) Brand MD (2005) The efficiency and plasticity of mitochondrial energy transduction. *Biochem Soc Trans* 33, 897-904
   (4) Mookerjee SA, Gerencser AA, Nicholls DG, Brand MD (2017) Quantifying intracellular rates of glycolytic and oxidative ATP production and consumption using extracellular flux measurements. *J Biol Chem* 292, 7189-7207. Corrections: DOI 10.1074/jbc.AAC118.004855. PMCID: PMC5409486
2) **Bioenergetics of physiological systems**. My work on the bioenergetics of intact cells and organs started in the 1980s. I developed techniques and a theoretical framework that allow deep insights into cellular bioenergetics as an integrated system, showing how the rate and efficiency of oxidative phosphorylation are controlled in cells and tissues (5,6), and how they are regulated by hormones, mitogens, substrates, drugs and metabolic depression. This approach clarified cellular bioenergetics and provides powerful tools to analyze its response to any physiological or pharmacological change (6,7). The main theoretical tool that I developed for quantitative analysis of the control of biological systems is metabolic control analysis, devised by Kacser and others. I simplified the analysis to make it straightforward to apply to complex, real systems (the 'top-down', or modular approach) (7,8). We used this approach to produce complete simple descriptions of the regulation of oxidative phosphorylation in mitochondria, cells and intact tissues. We pioneered the use of extracellular flux measurements to characterize cellular bioenergetics (6), which we continue to develop (4,8).
   (5) Buttgereit F, Brand MD (1995) A hierarchy of ATP-consuming processes in mammalian cells. *Biochem J* 312, 163-167. PMCID: PMC1136240
   (6) Brand MD, Nicholls DG (2011) Assessing mitochondrial function in cells. *Biochem J* 435, 297-312. PMCID: PMC3076726
   (7) Hafner RP, Brown GC, Brand MD (1990) Analysis of the control of respiration rate, phosphorylation rate, proton leak rate and protonmotive force in isolated mitochondria using the 'top-down' approach of metabolic control theory. *Eur J Biochem* 188, 313-319

(8) Gerencser AA, Mookerjee SA, Jastroch M, Brand MD (2017) Positive feedback amplifies the response of mitochondrial membrane potential to glucose concentration in clonal pancreatic beta cells. *Biochim Biophys Acta* 1863, 1054-1065. PMCID: PMC5398960

3) **Coupling efficiency of oxidative phosphorylation**. From the 1990s I studied the leak of protons across mitochondrial membranes; its physiological importance, function and molecular mechanism. Proton leak short-circuits oxidative phosphorylation, causing inefficiency. We discovered that it accounts for up to 20% of basal metabolic rate (9). We showed that it correlates with BMR, is stimulated seven-fold by thyroid hormones, and is greater in endotherms than ectotherms and in small mammals and birds than larger ones. Basal conductance is a side-reaction of the adenine nucleotide translocase and my work has shown it to be an attractive target for pharmaceutical thermogenesis for the treatment of obesity and diabetes. My work also led the field in elucidating the function of inducible proton leak catalyzed by novel uncoupling proteins (UCPs). Transgenic mice overexpressing UCP3 are hyperphagic and lean, making them an excellent model for anti-obesity treatments (10). UCPs can be activated by superoxide (11), identifying a pathway of activation and a possible physiological function for this important class of proteins (12).
   (9) Brand MD, Chien L-F, Ainscow EK, Rolfe DFS, Porter RK (1994) The causes and functions of mitochondrial proton leak. *Biochim Biophys Acta* 1187, 132-139
   (10) Clapham JC, Arch JRS, Chapman H, Haynes A, Lister C, Moore GBT, Piercy V, Carter SA, Lehner I, Smith SA, Beeley LJ, Godden RJ, Herrity N, Skehel M, Changani KK, Hockings PD, Reid DG, Squires SM, Hatcher J, Trail B, Latcham J, Rastan S, Harper AJ, Cadenas S, Buckingham JA, Brand MD, Abuin A (2000) Mice overexpressing human uncoupling protein-3 in skeletal muscle are hyperphagic and lean. *Nature* 406, 415-418
   (11) Echtay KS, Roussel D, St-Pierre J, Jekabsons MB, Cadenas S, Stuart, JA, Harper JA, Roebuck SJ, Morrison A, Pickering S, Clapham JC, Brand MD (2002) Superoxide activates mitochondrial uncoupling proteins. *Nature* 415, 96-99
   (12) Brand MD, Esteves TC (2005) Physiological functions of the mitochondrial uncoupling proteins UCP2 and UCP3. *Cell Metab* 2, 85-93

4) **Mitochondrial production of reactive oxygen species (ROS)**. Mitochondrial production of ROS is widely thought to be important in signaling, damage and disease, but the extent to which this is true, and exactly how mitochondria make ROS, are not well understood. Since 2000 my lab has characterized the mechanisms, topologies and kinetics of different sites in the electron transport chain that generate superoxide and hydrogen peroxide (13. We measured the contribution of each site in situ and screened chemical libraries to identify small molecules that suppress ROS production at specific sites without affecting oxidative phosphorylation (14,15). These compounds allow identification of specific sites involved in particular pathways and cells (16), and enable manipulation of mitochondrial ROS production to modify signaling, pathology and disease.
   (13) Brand MD, Affourtit C, Esteves TC, Green K, Lambert AJ, Miwa S, Pakay JL, Parker N (2004) Mitochondrial superoxide: production, biological effects, and activation of uncoupling proteins. *Free Rad Biol Med* 37, 755-767 PMID: 15304252
   (14) Orr AL, Vargas L, Turk CN, Baaten JE, Matzen JT, Dardov VJ, Attle SJ, Li J, Quackenbush, DC, Goncalves RLS, Perevoshchikova IV, Petrassi HM, Meeusen SL, Ainscow EK, Brand MD (2015) Suppressors of superoxide production from mitochondrial complex III. *Nature Chem Biol* 11, 834-836 PMCID: PMC4618194
   (15) Brand MD, Goncalves RLS, Orr AL, Vargas L, Gerencser AA, Borch Jensen M, Wang YT, Melov S, Turk CN, Matzen JT, Dardov VJ, Petrassi HM, Meeusen SL, Perevoshchikova IV, Jasper H, Brookes PS, Ainscow EK (2016) Suppressors of superoxide/H_2O_2 production at site I_Q of mitochondrial complex I protect against stem cell hyperplasia and ischemia/reperfusion injury. *Cell Metab* 24, 1-11 PMCID: PMC5061631
   (16) Wong H-S, Benoit B, Brand MD (2019) Mitochondrial and cytosolic sources of hydrogen peroxide in resting C2C12 myoblasts. *Free Rad Biol Med* 130, 140-150

5) **Mitochondrial function in aging and disease**. Several of the strands discussed above come together in my application of these techniques, insights and ideas to the role of mitochondrial dysfunction in disease and aging. Building on my work on mitochondrial proton leak and ROS production, I have clarified the nature of relationships between metabolic rate and ROS production, and shown how this may be important in aging (17) and diseases such as obesity (10,18), diabetes (8,19) and bone remodeling (20).

(17) Speakman JR, Talbot DA, Selman C, Snart S, McLaren JS, Redman P, Krol E, Jackson DM, Johnson MS, Brand MD (2004) Uncoupled and surviving: individual mice with high metabolism have greater mitochondrial uncoupling and live longer. *Aging Cell* 3, 87-95
(18) Harper JA, Dickinson K, Brand MD (2001) Mitochondrial uncoupling as a target for drug development for the treatment of obesity. *Obesity Rev* 2, 255-265
(19) Green K, Brand MD, Murphy MP (2004) Prevention of mitochondrial oxidative damage as a therapeutic strategy in diabetes. *Diabetes* 53 (Suppl 1), S110-S118
(20) Guntur AR, Gerencser AA, Le PT, DeMambro VE, Bornstein SA, Mookerjee SA, Maridas DE, Clemmons DE, Brand MD, Rosen CJ. (2018) Osteoblast-like MC3T3-E1 cells prefer glycolysis for ATP production but adipocyte-like 3T3-L1 cells prefer oxidative phosphorylation. *J Bone Mineral Res*. 33, 1052-1065. PMID: 29342317

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/martin.brand.1/bibliography/40344782/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01AG051729 (PI: Campisi) 08/01/16 – 04/30/21
NIH/NIA
Cellular senescence as a mediator of mitochondrial dysfunction-induced aging
This proposal will explore the role of mitochondrial dysfunction in driving aging through the induction of cellular senescence and a mitochondrial-specific secretory phenotype.
Role: Co-Investigator

R56AG038688 (PI: Kapahi) - NCE 09/30/17 – 08/31/19
NIH/NIDDKD
Molecular mechanisms of lifespan extension by dietary restriction in Drosophila
In this project, we propose 3 specific aims; 1) Investigate how diet and age-dependent changes in intestinal cell fitness influence intestinal permeability and lifespan. 2) Identify novel genes that regulate intestinal apoptosis in as diet-dependent manner. 3) Investigating the mechanisms of age-related decline in intestinal function
Role: Co-investigator

Calico (PI: Brand) 12/01/15 – 01/19/20
Corporate Agreement
Proprietary

Recently Completed Research Support

Unity Biotechnology (PIs: Brand, Campisi) 09/15/17 – 09/14/18
Corporate Agreement
Proprietary

R41DA043369 (Subc Image Analyst Software, PI: Gerencser) 09/01/16 – 08/31/18
National Institutes of Health - NIDA
Development of a kit for characterization of cellular energetics in single cells in cell and tissue cultures based on the measurement of the absolute magnitude of the mitochondrial membrane potential
Role: Consortium PI

Orphan Partners 2 (PI: Melov) 01/04/16 – 06/30/18
Corporate Agreement
Proprietary
Role: Co-investigator

The Pittsburg Foundation (PI: Melov) 02/09/17 – 02/08/18
Uncovering tissue specific vulnerability to mitochondrial oxidative stress
We will refine and collect data on four tissue specific mouse models of free radical stress, targeting the brain (modeling age-related neurodegenerative disease), the heart (age-related cardiovascular disease), the

pancreas (age-related diabetes), and muscle (age related muscle loss).
Role: Co-investigator

R21AR066120 (Subc Maine Medical Ctr., PI: Rosen) 04/01/15 – 03/31/17
National Institutes of Health
Osteoblastic respiration and IRS Signaling
The long-term goal of this proposal is to delineate how energy utilization in bone cells is regulated and in turn, how substrate availability affects osteoblast differentiation and bone formation
Role: Co-investigator

R56AG048253 (PI: Campisi) 09/30/15 – 08/31/16
National Institutes of Health
Cellular senescence as a mediator of mitochondrial dysfunction-induced aging
This study will determine how the cellular damage response known as cellular senescence links mitochondrial DNA mutations to aging, and will test whether interventions designed to prevent or eliminate senescent cells can prevent the phenotypes associated with aging.
Role: Co-investigator

A-7410 (PI: Brand) 03/01/14 – 02/29/16
CHDI
Mitochondrial ROS production in stem cell-derived neurons expressing mutant huntingtin
We will characterize how mitochondrial production of reactive oxygen species (ROS) is altered by expression of mutant huntingtin to contribute to the molecular pathology of Huntington's disease, and determine if we can normalize mitochondrial ROS production using novel inhibitors to protect against the effects of mutant Htt.

R01DK089202 (SubC UC Berkeley, PI: Stahl) 04/15/11 - 01/31/16
National Institutes of Health
Dependence of thermogenesis and brown adipose tissue function on FATP1 and CD36
We have identified two proteins that are required for heat production and propose to study the mechanisms by which they govern energy expenditure.
Role: Co-PI

R21 AR063919 (PI: Melov) 07/01/13 - 06/30/15
National Institutes of Health
Analysis of gene expression and cell function in single cell cortical osteoblasts
To develop single cell gene expression and mitochondrial physiological measures in a popular mouse model of bone loss, the ovariectomized mouse. We will test the hypothesis that bioenergetic parameters are changed in osteoblasts in this model in conjunction with gene expression measures at the single cell level.
Role: Co-I

R21 CA179452 (PI: Held) 07/01/13 - 06/30/15
National Institutes of Health
The role of p53 redox-modification in cell fate signaling
Oxidation-reduction (redox) reactions mediate pro- and antiapoptotic cellular programs regulating many aspects of carcinogenesis. This proposal will investigate the mechanistic details of p53 redox-regulation in cell fate signaling in response to DNA damage and oxidative stress.
Role: Co-I