BIOGRAPHICAL SKETCH

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NAME: Bertha K. Madras, PhD

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

POSITION TITLE: Professor of Psychobiology, Department of Psychiatry, Harvard Medical School, Mclean Hospital

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
McGill University, Montreal, Canada	B.Sc.	1963	Biochemistry
McGill University, Montreal, Canada	Ph.D.	1967	Biochemistry
Postdoctoral Fellow, Tufts University, Boston, MA		1966-1967	Biochemistry
Postdoctoral Fellow, MIT, Cambridge, MA		1967-1969	Biochemistry
Research Associate, MIT, Cambridge, MA		1972-1974	Neuroscience

A. Personal Statement

My research has focused on clarifying the immediate and downstream targets of psychoactive drugs, with the long-term objective of developing novel diagnostic and therapeutic agents to alleviate the burden of addiction and other neuropsychiatric disorders (e.g. Parkinson's disease, ADHD). My Division of Neurochemistry at the New England Primate Research Center campus of Harvard Medical School campus was a translational research program comprised of a collaborative team with expertise in medicinal chemistry, molecular and cell biology, receptor/transporter pharmacology, primate behavioral biology and brain imaging. My lab was the first to: (1) discover the intriguing properties of phenyltropane analogs of cocaine, as exceptionally selective probes for the dopamine transporter and dopamine neurons in post-mortem and living brain. The dopamine transporter is a key target of psychostimulant therapeutics and drugs of abuse. We developed the most widely used probe, for monitoring these sites in vitro and in living brain with PET or SPECT imaging. Using these probes with brain imaging, we showed that: (1) imaging the DAT detects Parkinson's disease in living brain; (2) the pharmacokinetic properties of extended release methylphenidate differed from immediate release methylphenidate formulation that correlated with abuse potential; (3) that, in contrast to previous views, the anti-narcolepsy drug modafinil targeted the dopamine transporter in living brain; (4) that the 3'-UTR noncoding region of the dopamine transporter gene is correlated with dopamine transporter expression in living brain; (5) that potent transport inhibitors we co-invented containing no amine nitrogen were potent transport inhibitors that do not enter the brain, implying potential actions at peripheral sites. My lab also (6) characterized, mapped and cloned dopamine receptor subtypes/transporter from primate brain and collaboratively showed dopamine transporter and receptor subtype contributors to the behavioral effects of stimulants; (7) showed synergistic behavioral effects of cannabinoid agonists and dopamine D2 (not D1) dopamine receptor agonists in primates; (8) showed that THC alters mRNA expression and dopamine receptor heteromer formation in various brain regions, a response attenuated by co-administration with cannabidiol. During service as Deputy Director for Demand Reduction in the White House Office of National Drug Control Policy, the Division reverted to laboratory status. Upon my return, the research program focused on comparing adolescent and adult brain responses to psychoactive drugs of abuse (cannabinoids, methamphetamine, MDMA). After the Primate Center closed, the research program relocated to McLean Hospital, in a newly created Laboratory of Addiction Neurobiology. In public policy research, I collaborated with government agencies to report: (1) the effectiveness of the federal SBIRT program in reducing substance use; (2) that marijuana use, cigarette smoking, or alcohol consumption

by youth is associated with other substance use; (3) President's Commission on Combating Drug Addiction and the Opioid Crisis. (4) Update on Cannabis and its Medical Uses, World Health Organization

B. **Positions and Honors**

Positions and Employment

2018- Director, Laboratory of Addiction Neurobiology, Mclean Hospital
2017 President's Commission on Combating Drug Addiction and the Opioid Crisis
2014- Professor of Psychobiology, Dept Psychiatry, Harvard Medical School, at McLean Hospital
2006-2008 Deputy Director for Demand Reduction, White House Office of National Drug Control Policy, Executive Office of the President (leave of absence)
1999-2014 Professor of Psychobiology, Harvard Medical School at New England Primate Research Center
2013- Chair, Radiation Safety Committee, Harvard University
2004- Research scientist, Massachusetts General Hospital
1998-1999 Acting Director, New England Primate Research Center, Harvard Medical School
1996-2008 Chair, Division of Neurochemistry, New England Primate Research Center
1990-1999 Associate Professor of Psychobiology, Dept. Psychiatry, Harvard Medical School
1986-1990 Assistant Professor of Psychobiology, Dept. Psychiatry, Harvard Medical School

Other Professional Activities (partial list)

2018- National Academy of Medicine, Opioid Collaborative
2018 NIH External IC Director review for NIH Director Collins
2018 NIH Advisory Committee to NIH Director Collins: Ethical Considerations for Industry Partnership on Research to End the Opioid Crisis
2016 Vatican Pontifical Academy of Sciences, Advisory panel on global drug policy
1989- 45+ NIDA, NIMH, NINDS, NIAAA review committees
2015-2016 World Health Organization, Advisor, Expert Committee on Drug Dependence
2014-2015 U.S. Department of Justice, expert witness on marijuana; designer drugs
2013-2015 Drug Advisory Panel, National Football League (NFL)
2009-2012 Subcommittee of Professors, Harvard Medical School: promotion to rank of Professor
2012 Member, CDC Panel: Insights from the Demand Side, Atlanta, GA
2012 Member, FDA panel: "Role of Naloxone in Opioid Overdose Fatality Prevention"
2011-2012 Member, NIDA Council Work Group: Transfer of treatment research to Community Centers
2011 Ad hoc member, Board of Scientific Counselors, NIAAA
2006-'08 Deputy Director, Demand Reduction, White House Office of National Drug Control Policy
2006-'08 Member, Office of Juvenile Justice, Delinquency Prevention Committee, US Dept. of Justice
2005-'06 Member, Medications Development Scientific Advisory Board, NIDA-NIH
2004-2006 Subcommittee of Professors, Harvard Medical School: promotions to rank of Professor
2004 Member, Medications Development Subcommittee, NIDA Advisory Council on Drug Abuse
2004 Advisor and story-board writer, NIDA-DEA Exhibit, 1 Times Square, New York, NY
2003-2004 Chair, Faculty Partners Committee, Harvard Medical School
2001-2005 Course creator, Director, "Cell Biology of Addiction"; Cold Spring Harbor Laboratory, NY
2003-2005 Member, Molecular Neuropharmacology Signaling Study Section (MNPS)
2004-2006 Member, Medications Development Subcommittee and Scientific Advisory Board, NIDA.
1999-2005 Member, Science and Technology Advisory Committee, Brookhaven National Laboratory
1984-1990 Chair ('88-'90), Ontario Mental Health Fdn, Ontario Ministry of Health, Fellowships, Awards Cte
1998-2003 Member, Molecular, Developmental, Cellular, Neuroscience-5 Study Section (MDCN)
1998-2004 Associate Director, Public Education, Division on Addictions, Harvard Medical School
1998 Chair, NIDA/B Study Section
1992-1996 NIDA Medications Development Expert panel; Dopamine transporter, receptor review committee,
1993-1998 Member, NIDA/B, Molecular, Cellular, Chemical Neurobiology Res Cte; Chair, 1998

Awards and Recognition (partial list)

2019 Innovators Award, College on Problems Drug Dependence
2019 Jack Mendelson Memorial Research Award
2018 Distinguished Service Award, College on Problems Drug Dependence
2018 National Leadership Award, CADCA
2018 Nils Bejerot Award for Global Drug Policy Leadership
2014 Louisiana State University School of Medicine, Speaker's Award
2011 Marian W. Fischman Award; for outstanding woman scientist in drug abuse research, CPDD

2008 Recognition Award, 7th Bi-National United States-Mexico Demand Reduction, Monterrey, Mexico
2006 U.S. Senate unanimously confirms Presidential appointment as ONDCP Deputy Director
2005 NIDA Public Service Award
1998-2006 MERIT Award, NIDA; Research Scientist Career Award (K02, K05)
2006 Founder's Award, American Association of Addiction Psychiatry
2006 The Better World Report 2006; Invention of PET and SPECT imaging agent altropane selected as one of 25 technology transfer innovations that changed the world.

Invited Lectures, Keynotes; selected from over 450 invited presentations (recent)

2017- National Academy of Medicine, Brookings Institution, Council Foreign Relations, CSIS, Accreditation Council for Continuing medical Education, Federation State medical Boards, American Bar Association, Organization of American States, others
2016 Government of Mexico National Debate on Marijuana, Cancun, Mexico (Jan); Mexico City (Apr)
2015 Marijuana as Medicine; Expert Committee on Drug Dependence, World Health Organization, Geneva
2015 Marijuana, Opioids; US Dept of State and DEA, Queretaro, Mexico and El Paso, TX
2015 Children and the Sustainable Development Goals Symposium; United Nations, New York, NY
2013 Stimulant Designer Drugs and Transporters: NIDA symposium, Rockville, MD
2010 SBIRT: A Public Health Approach: Organization of American States, Panama City, Panama
2010 Chair of NIDA Brain Development Web Symposium: Neurodevelopment and Drugs of Abuse
2006 Congressional testimonies: methamphetamine, prescription drugs, steroids, Capitol Hill, Washington

Patents. 19 U.S. patents issued; **27 international patents** issued

C. Contributions to Science

1. Psychopharmacology of stimulants and cannabinoids.

Cocaine's acute behavioral effects are triggered by the dopamine transporter which activates D1 and D2 dopamine receptors. Repeated cocaine alters neural circuitry. Dopamine receptors regulate *DCC,* an axonal guidance gene implicated in dopamine circuitry development. The stimulant and reinforcing properties of cocaine are mediated via the dopamine transporter (Madras et al, Spealman et al, Bergman et al (1989). Monkeys repeatedly exposed to cocaine manifest altered motor responses that correlated with induction of regionally and compartmentally specific striatal activation patterns. Postulating that axonal guidance molecules conceivably contribute to cocaine-induced neuroadaptation, we showed that dopamine receptor agonists in vitro modulated expression of a gene, *DCC*, implicated in mesocortical dopamine circuitry development during adolescence. *(1) Saka E, Goodrich C, Harlan P, Madras BK, Graybiel AM. Repetitive behaviors in monkeys are linked to specific striatal activation patterns. J Neurosci. 2004;24(34):7557. (2) Jassen AK, Yang H, Miller GM, Calder E, Madras BK. Receptor regulation of gene expression of axon guidance molecules: implications for adaptation. Mol Pharmacol. 2006 ;70(1):71-7.*

Axonal guidance molecule distribution in squirrel monkey brain. We were the first to map immunohistochemically, the distribution of axonal guidance molecules in monkey brain, to determine the feasibility of quantifying their drug-induced changes that may affect adolescent brain development. *Xiao D, Miller GM, Jassen A, Westmoreland SV, Pauley D, Madras BK. Ephrin/Eph receptor expression in brain of adult nonhuman primates: implications for neuroadaptation. Brain Res. 2006, 1067(1):67-77.*

THC alters expression of DCC, a guide for adolescent dopamine circuitry development. Postulating that THC may alter dopamine circuitry in the adolescent brain, we showed that adolescent rats administered THC repeatedly during adolescence, showed persistent changes in *DCC* expression levels in their adult brain. This finding, presented as a "Hot Topic" at the ACNP meeting 2017, is in preparation. It conceivably uncovers a mechanism by which THC can alter dopamine circuitry and blunted dopamine signaling in early initiators of marijuana (Volkow et al 2014). *(1) Madras BK et al., Adolescent Mice Exposed to THC Manifest Persistent Neuroadaptive Changes in Adult Brain Cerebellum, CPDD and ACNP Abstracts 2014; (2) Madras BK. Dopamine challenge reveals neuroadaptive changes in marijuana abusers. Proc Natl Acad Sci U S A. 2014, 111(33):11915-6. (commentary).* **D2 dopamine and cannabinoid receptor agonists sedate monkeys synergistically.** Monkeys treated at low subthreshold doses of D2 dopamine receptor agonists (not D1 agonists) and a cannabinoid agonist, precipitated profound sedation. We postulate that D2-CB1 receptors (but not D1-CB1 receptors) uniquely synergize in primate brain. *Meschler JP, Clarkson FA, Mathews PJ, Howlett AC, Madras BK. D(2), but not D(1) dopamine receptor agonists potentiate cannabinoid-induced sedation in nonhuman primates. J Pharmacol Exp Ther. 2000 Mar;292(3):952-9. PMID: 10688609.* We recently reported on the risks of adolescent use of tobacco, alcohol and marijuana on using other drugs. *Dupont RL, Han B, Shea CL, **Madras BK.** Drug Use Among Youth: National Survey Data Support a Common Liability of all Drug Use. Preventive Medicine, 113: 68-73, 2018.*

2. Translational research

A novel marker for dopamine transporter/neurons and diagnostic markers for Parkinson's disease. My laboratory discovered a chemical class of the most effective, objective diagnostic imaging agents for Parkinson's disease. We initially identified a phenyltropane analog of cocaine, [^{3}H]CFT (WIN 35,428) that detected, with high specificity, the dopamine transporter, a protein localized exclusively on dopamine neurons. It is the most widely used probe for the dopamine transporter. After we mapped the transporter in primate brain with [^{3}H]CFT,and showed its marked selectivity for dopamine neurons and ability to detect Parkinson's disease in post-mortem brains, our discovery led to the development of analogs to detect Parkinson's disease in living brain of patients. CFT and analogs have been used to assess transporter levels and dopamine neuron status in more than 20 neuropsychiatric disorders. *(1) Madras BK, Spealman RD, Fahey MA, Neumeyer JL, Saha JK, Milius RA. Cocaine receptors labeled by [3H]2 beta-carbomethoxy-3 beta-(4-fluorophenyl)tropane. Mol Pharmacol. 1989 36(4):518-24. (2) Kaufman MJ, Madras BK. Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's-diseased striatum. Synapse. 1991 Sep;9(1):43-9. (3) Fischman AJ, Bonab AA, Babich JW, Palmer EP, Alpert NM, Elmaleh DR, Callahan RJ, Barrow SA, Graham W, Meltzer PC, Hanson RN, Madras BK. Rapid detection of Parkinson's disease by SPECT with altropane: a selective ligand for dopamine transporters. Synapse. 1998 Jun;29(2):128-41.*

A genotype/phenotype association: the dopamine transporter and Attention Deficit Hyperactivity Disorder (ADHD). Initially in primates, and in the human genome, molecular genetic probing revealed that the 9-repeat sequence of the 3'-untranslated region of the human dopamine transporter gene expressed higher levels of a transfected reporter gene than the gene with the 10-repeat sequence. This genotype/phenotype association was confirmed in human subjects, as the 9-repeat genotype correlated with elevated levels of the dopamine transporter in living human brain. [^{11}C]Altropane also detected higher levels of the transporter in caudate nucleus of subjects with ADHD, as corroborated by some, but not all groups. Higher transport levels may reflect pathophysiological processes involving the transporter or the caudate nucleus. *(1) Miller GM, Madras BK. Polymorphisms in the 3'-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. Mol Psychiatry. 2002;7(1):44-55. (2) Spencer TJ, Biederman J, Faraone SV, Madras BK, Bonab AA, Dougherty DD, Batchelder H, Clarke A, Fischman AJ. Functional genomics of attention-deficit/hyperactivity disorder (ADHD) risk alleles on dopamine transporter binding in ADHD and healthy control subjects. Biol Psychiatry. 2013 Jul 15;74(2):84-9. (3) Faraone SV, Spencer TJ, Madras BK, Zhang-James Y, Biederman J. Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter: a meta-analysis. Mol Psychiatry. 2014 (19):880-9.*

A genotype associated with opioid response in primates parallels human opioid response. We discovered a functional SNP in the coding region of the primate mu opioid receptor that corresponded to the functional SNP in the human mu opioid receptor, associated with human heroin addiction in some studies. In primates, this SNP correlated with altered beta-endorphin affinity, endocrine function and behaviors, analogous to humans. The finding supports the development of naturalistic primate models of human genetic neuropsychiatric disorders. *Miller GM, Bendor J, Tiefenbacher S, Yang H, Novak MA, Madras BK. A mu-opioid receptor single nucleotide polymorphism in rhesus monkey: association with stress response and aggression. Mol Psychiatry. 2004 Jan;9(1):99-108. PMID: 14699447*.

A plausible target of modafinil in brain. Modafinil, a widely used anti-narcoleptic drug, was designated atypical because of conflicting theories underlying its pharmacological mechanisms. With PET imaging, we were the first to show that modafinil occupied the dopamine and norepinephrine transporters in living primate brain, a discovery corroborated in human subjects by our group and others. This plausible molecular target for modafinil catalyzed renewed interest in its therapeutic potential and triggered synthesis of a cascade of chemical variants. *(1)Madras BK, Xie Z, Lin Z, Jassen A, Panas H, Lynch L, Johnson R, Livni E, Spencer TJ, Bonab AA, Miller GM, Fischman AJ. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. J Pharmacol Exp Ther. 2006 319:561-9. (2) Spencer TJ, Madras BK, Bonab AA, Dougherty DD, Clarke A, Mirto T, Martin J, Fischman AJ. A positron emission tomography study examining the dopaminergic activity of armodafinil in adults using [¹¹C]altropane and [¹¹C]raclopride. Biol Psychiatry. 2010 68(10):964-70.*

A novel target to block MDMA-induced psychoactive effects. In seeking novel medications for MDMA overdose, we showed that MDMA is a potent norepinephrine transporter (NET) blocker *in vitro* and that a norepinephrine transport inhibitor attenuated MDMA-induced cognitive impairment and stimulant effects in primates. Our proof of concept in primates was corroborated by others in two MDMA clinical studies with NET inhibitors. (*1) Verrico CD, Miller GM, Madras BK. MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment. Psychopharmacology (Berl). 2007 189(4):489-503. (2) Verrico CD, Lynch L, Fahey MA, Fryer AK, Miller GM, Madras BK. MDMA-induced impairment in primates: antagonism by a selective norepinephrine or serotonin, but not by a dopamine/norepinephrine transport inhibitor. J Psychopharmacol. 2008 Mar;22(2):187-202.*

3. Drug Discovery. Cocaine and psychostimulant addiction: medications development. In seeking novel candidate medications for cocaine addiction, a collaboration was formed with a medicinal chemist Dr. Peter Meltzer that resulted in the design of over 600 novel compounds as candidate cocaine medications and 19 US and 27 international patents. Among the seminal and counterintuitive discoveries was that novel monoamine transport blockers that contained no amine nitrogen in their structures retained high potency at transproters. The finding radically revised conventional dogma of how drugs dock to, and block transporters.
Novel psychostimulant targets: trace amine receptor1. Decades ago, trace amines were implicated in neuropsychiatric disorders and addiction. In seeking immediate and downstream novel targets for medications development, we cloned the rhesus monkey trace amine receptor1. Phenethylamine (PEA) and amphetamines directly activated the receptor, with dopamine transporter or presynaptic D2 receptors enhancing its activity. Intriguingly, we showed an excellent correlation between drug blockade of PEA transport by the dopamine transporter and the behavioral effects of the drugs, implicating them in therapeutic drug response. The role of trace amine receptor1 and trace amines is under investigation, as contributors or medications for addictions.

4. Public Service and Education: (1) President's Commission on Combating Drug Addiction and the Opioid Crisis; (2) Office of National Drug Control Policy; Museum Exhibit; Cold Spring Harbor Course.
During service on the President's Commission, I was tasked with shepherding and composing the final report and set of recommendations for the President.
https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-15-2017.pdf
As Deputy Director, Demand Reduction in the White House Office of National Drug Control Policy, I wrote the first manuscript summarizing federal SBIRT data and succeeded in obtaining billing codes (CPT, "H", "G") for these services, catalyzing SBIRT nationally and internationally and ACA. *Madras BK, Compton WM, Avula D, Stegbauer T, Stein JB, Clark HW. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: comparison at intake and 6 months later. Drug Alcohol Depend. 2009 Jan 1;99(1-3):280-95.* PI, project director and storyboard creator for a NIDA SEDAPA grant that produced a museum exhibit, a play and a CD, on exhibit at the Museum of Science, Boston (11 years), and a national tour. In 2001, I created and organized a Cold Spring Harbor Course on the "Cell Biology of Addiction". It is an ongoing course.

D. Additional Information: Research Support and/or Scholastic Performance

Current

NIH/NIDA R01 DA042178: Madras (PI)
Project title: Long term THC Elicits Distinct Changes in Adolescent Brain Dopamine Signaling
Project start date: 9/15/2017 **Project end date:** 7/31/2022

NIH/NIDA D004100 PI: Rigotti, Nancy; Mentor BK Madras, as needed
Title: Career Development Program in Substance Use and Addiction Medicine
Project Start Date: 04/01/2018 **Project End Date:** 03/31/2023

HMS Research Support 400993 and 401022: Madras (PI)
Project title: Psychoactive Drug Effects in Adolescent and Adult Brain
Dates: 5/01/2014 - 5/31/2019

Completed

NIH/NIDA R21 DA029790-01: Madras (PI)
Project title: Methamphetamine and neurodevelopment in adolescent and adult mice;
Dates: 9/30/2010 - 08/31/2012
Objectives: To compare METH effects in adolescent and adult mice on conditioned place preference, expression of axonal guidance molecules and response to agonists and antagonists.

NIH/AG 1R01AG035361-01A1: Rowlett, J. PI, Madras BK Co-I
Project title: Novel GABA-A Modulators as Cognitive Enhancers
Dates: 08/15/2010 – 06/30/2014
Objectives: To develop new GABA-A drugs for cognitive improvement