

Jonathan L. Tilly, Ph.D.

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Current Professional Appointments

Professor of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School (2009-present)

Director, Vincent Center for Reproductive Biology, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital (1998-present)

Chief, Division of Research, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital (1998-present)

Biologist, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital (1995-present)

Member, Dana-Faber/Harvard Cancer Center (1999-present)

Affiliated Faculty, Harvard Stem Cell Institute (2004-present)

Education, Training and Previous Professional Appointments

B.S., Animal Sciences (Highest Honors); Cook College, Rutgers, the State University of NJ (1984)

M.S., Animal Sciences; Rutgers, the State University of NJ (1987)

Ph.D. in Animal Sciences, Rutgers, the State University of NJ (1990)

Postdoctoral Research Fellow in Reproductive Medicine, University of California-San Diego School of Medicine (1990-91)

Postdoctoral Research Fellow in Obstetrics and Gynecology, Stanford University Medical Center (1991-93)

Assistant Professor of Reproductive Biology and Population Dynamics, Johns Hopkins University School of Hygiene and Public Health (1993-95)

Associate Professor of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School (1995-2008)

Associate Director, Vincent Center for Reproductive Biology, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital (1995-98)

Investigator, Reproductive Endocrine Sciences Center, Massachusetts General Hospital (1995-2000)

Selected Honors, Awards and Professional Memberships

Member: The Endocrine Society (1991-present), American Association for the Advancement of Science (AAAS, 1994-present), American Society for Cell Biology (1996-present), Society for Gynecologic Investigation (1996-present), American Society for Reproductive Medicine (1997-present), European Society of Human Reproduction and Embryology (1998-present), Society for the Study of Reproduction (2002-present)

Organizer/Chair, Serono Symposium on Cell Death in Reproductive Physiology, Chicago, IL (1996)

Organizer/Chair, Symposium on Apoptosis in Reproduction and Infertility, 16th World Congress on Fertility and Sterility, San Francisco, CA (1998)

Principal Investigator (completed grants): American Federation for Aging Research Grant (07/01/94-06/30/95); NIH R55-HD31188 (07/01/94-07/31/95), R01-ES06999 (07/01/94-06/30/97), R01-HD34426 (08/01/95-07/31/99), R01-AG012279 (01/01/95-06/30/06; renewed as an R37 MERIT Award), R01-ES08430 (08/01/97-07/31/06) and R01-AG024999 (09/30/04-01/31/08); U.S. Army CDMRP/Department of Defense Ovarian Cancer Research Program Idea Award DAMD17-00-1-0567 (10/01/00-09/30/04)

Commencement Speaker, Cook College, Rutgers, the State University of NJ, New Brunswick, NJ (2001)

Endocrinology Editorial Board (1996-9); *Journal of Endocrinology* Editorial Board (2000-4); *Endocrine Journal* Editorial Board Special Advisory Committee (2000-present); *Cell Death & Differentiation* Editorial Board (2001-6); Contributing Editor, SAGE-KE (*Science*; 2002-6); *AGING* Editorial Board (2008-present); *Stem Cell Reviews Letters* Editorial Board (2009-present)

National Scientific Advisory Council Member, American Federation for Aging Research (2003-present)

Charter Member, Development-1 (DEV-1) Study Section (2003-7); *Ad-hoc* Reviewer, Reproductive Biology (REB) Study Section (1996, 2001); NIH Site Visit Reviewer, Population Council, New York, NY (1996)

Scientific/Technical Advisor to Federal Court Judge Richard Stearns, Civil Action Number 95-10496-RGS (1996-2000)

Panel Member, International Life Sciences Institute Workshop on the Evaluation and Interpretation of Reproductive Endpoints for Human Health Risk Assessment, Washington, DC (1997)

Lecturer and Apoptosis Laboratory Course Director, NICHD/MBL Training Course on Frontiers in Reproduction; Marine Biological Laboratory, Woods Hole, MA (1998-2001)

Steven and Michele Kirsch Foundation Investigator (named; 2001-3)

Boston Cotillion Award for Distinguished Achievements in Research (2002)

Richard E. Weitzman Memorial Award, The Endocrine Society (2002)

Medical Advisory Board Member, Fertile Hope Foundation (2005-present)
Vincent Award of Distinction for Outstanding Contributions in Women's Healthcare (2008)
American Society for Reproductive Medicine General Program Prize Paper Award (2008)

Selected Peer-reviewed Publications (from 105 manuscripts, 18 book chapters, 19 reviews, and 11 Commentaries/Editorials/News & Views published between 1986-present)

1. Perez GI, Knudson CM, Leykin L, Korsmeyer SJ, **Tilly JL**. Apoptosis-associated signaling pathways are required for chemotherapy-mediated germ cell destruction. *Nature Med* 1997; 3: 1228-32.
2. Kugu K, Ratts VS, Piquette GN, Tilly KI, Tao X-J, Martimbeau S, Aberdeen GW, Krajewski S, Reed JC, Pepe GJ, Albrecht ED, **Tilly JL**. Analysis of apoptosis and expression of *bcl-2* gene family members in the human and baboon ovary. *Cell Death Differ* 1998; 5: 67-76.
3. Bergeron L, Perez GI, McDonald G, Shi L, Sun Y, Jurisicova A, Varmuza S, Latham KE, Flaws JA, Salter J, Hara H, Moskowitz MA, Li E, Greenberg AH, **Tilly JL**, Yuan J. Defects in regulation of apoptosis in caspase-2-deficient mice. *Genes Dev* 1998; 12: 1304-14.
4. Perez GI, Robles R, Knudson CM, Flaws JA, Korsmeyer SJ, **Tilly JL**. Prolongation of ovarian lifespan into advanced chronological age by *Bax*-deficiency. *Nature Genet* 1999; 21: 200-3.
5. Morita Y, Perez GI, Maravei DV, Tilly KI, **Tilly JL**. Targeted expression of Bcl-2 in mouse oocytes inhibits ovarian follicle atresia and prevents spontaneous and chemotherapy-induced oocyte apoptosis *in vitro*. *Mol Endocrinol* 1999; 13: 841-50.
6. Perez GI, Trbovich AM, Gosden R, **Tilly JL**. Mitochondria and death of oocytes. *Nature* 2000; 403: 500-1.
7. Morita Y, Perez GI, Paris F, Miranda S, Ehleiter D, Haimovitz-Friedman A, Fuks Z, Xie Z, Reed JC, Schuchman EH, Kolesnick RN, **Tilly JL**. Oocyte apoptosis is suppressed by *acid sphingomyelinase* gene disruption or by sphingosine-1-phosphate therapy. *Nature Med* 2000; 6: 1109-14.
8. Matikainen T, Perez GI, Zheng TS, Kluzak TR, Rueda BR, Flavell RA, **Tilly JL**. *Caspase-3* gene knockout defines cell lineage specificity for programmed cell death signaling in the ovary. *Endocrinology* 2001; 142: 2468-80.
9. Morita Y, Maravei DV, Bergeron L, Wang S, Perez GI, Tsutsumi O, Taketani Y, Asano M, Horai R, Korsmeyer SJ, Iwakura Y, Yuan J, **Tilly JL**. Caspase-2 deficiency rescues female germ cells from death due to cytokine insufficiency but not meiotic defects caused by *ataxia telangiectasia-mutated (Atm)* gene inactivation. *Cell Death Differ* 2001; 8: 614-20.
10. Matikainen T, Perez GI, Jurisicova A, Schlezinger JJ, Ryu H-Y, Pru JK, Sakai T, Korsmeyer SJ, Casper RF, Sherr DH, **Tilly JL**. Aromatic hydrocarbon receptor-driven *Bax* gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals. *Nature Genet* 2001; 28: 355-60.
11. Ren D, Navarro B, Perez G, Jackson AC, Hsu S, Shi Q, **Tilly JL**, Clapham DE. A sperm ion channel required for sperm motility and male fertility. *Nature* 2001; 413: 603-9.
12. Tilly JL. Commuting the death sentence: how oocytes strive to survive. *Nature Rev Mol Cell Biol* 2001; 2: 838-48.

13. Matikainen TM, Moriyama T, Morita Y, Perez GI, Korsmeyer SJ, Sherr DH, **Tilly JL**. Ligand activation of the aromatic hydrocarbon receptor transcription factor drives Bax-dependent apoptosis in developing fetal ovarian germ cells. *Endocrinology* 2002; 143: 615-20.
14. Paris F, Perez GI, Haimovitz-Friedman A, Nguyen H, Fuks Z, Bose M, Ilagan A, Hunt PA, Morgan WF, **Tilly JL**, Kolesnick R (JLT and RK, co-senior authors). Sphingosine-1-phosphate preserves fertility in irradiated female mice without propagating genomic damage in offspring. *Nature Med* 2002; 8: 901-2.
15. Canning J, Takai Y, **Tilly JL**. Evidence for genetic modifiers of ovarian follicular endowment and development from studies of five inbred mouse strains. *Endocrinology* 2003; 144: 9-12.
16. Johnson J, Canning J, Kaneko T, Pru JK, **Tilly JL**. Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature* 2004; 428: 145-50.
17. Johnson J, Bagley J, Skaznik-Wikiel M, Lee H-J, Adams GB, Niikura Y, Tschudy KS, Tilly JC, Cortes ML, Forkert R, Spitzer T, Iacomini J, Scadden DT, **Tilly JL**. Oocyte generation in adult mammalian ovaries by putative germ cells from bone marrow and peripheral blood. *Cell* 2005; 122: 303-15.
18. Johnson J, Skaznik-Wikiel M, Lee H-J, Niikura Y, Tilly JC, **Tilly JL**. Setting the record straight on data supporting postnatal oogenesis in female mammals. *Cell Cycle* 2005; 4: 1471-7.
19. Perez GI, Jurisicova A, Matikainen TM, Moriyama T, Kim M-R, Takai Y, Pru JK, Kolesnick RN, **Tilly JL**. A central role for ceramide in the age-related acceleration of apoptosis in the female germline. *FASEB J* 2005; 19: 860-2.
20. Perez GI, Acton BM, Jurisicova A, Perkins GA, White A, Brown J, Trbovich AM, Kim M-R, Fissore RA, Xu J, Ahmady A, D'Estaing SG, Li H, Kagawa W, Kurumizaka H, Yokoyama S, Okada H, Mak TW, Ellisman MH, Casper RF, **Tilly JL**. Genetic variance modifies apoptosis susceptibility in mature oocytes via alterations in DNA repair capacity and mitochondrial ultrastructure. *Cell Death Differ* 2007; 14: 524-33.
21. Skaznik-Wikiel M, Tilly JC, Lee H-J, Niikura Y, Kaneko-Tarui T, Johnson J, **Tilly JL**. Serious doubts over "Eggs Forever?". *Differentiation* 2007; 75: 93-9.
22. Perez GI, Jurisicova A, Wise L, Lipina T, Kanisek M, Bechard A, Takai Y, Hunt P, Roder J, Grynepas M, **Tilly JL**. Absence of the pro-apoptotic Bax protein extends fertility and alleviates age-related health complications in female mice. *Proc Natl Acad Sci USA* 2007; 104: 5229-34.
23. **Tilly JL**, Johnson J. Recent arguments against germ cell renewal in the adult human ovary. Is an absence of marker gene expression really acceptable evidence of an absence of oogenesis? *Cell Cycle* 2007; 6: 879-83.
24. Lee H-J, Selesniemi K, Niikura Y, Niikura T, Klein R, Dombkowski DM, **Tilly JL**. Bone marrow transplantation generates immature oocytes and rescues long-term fertility in a preclinical mouse model of chemotherapy-induced premature ovarian failure. *J Clin Oncol* 2007; 25: 3198-204.
25. Lee H-J, Sakamoto H, Luo H, Skaznik-Wikiel ME, Friel A, Niikura T, Tilly JC, Klein R, Styer AK, Zukerberg L, **Tilly JL**, Rueda BR. Loss of CABLES1, a cyclin-dependent kinase-interacting protein that inhibits cell cycle progression, results in germline expansion at the expense of oocyte quality in adult female mice. *Cell Cycle* 2007; 6: 2678-84.

26. **Tilly JL**, Rueda BR. Minireview: Stem cell contribution to ovarian development, function and disease. *Endocrinology* 2008; 149: 4307-11.
27. Selesniemi K, Lee H-J, **Tilly JL**. Moderate caloric restriction initiated in rodents during adulthood sustains function of the female reproductive axis into advanced chronological age. *Aging Cell* 2008; 7: 622-9.
28. **Tilly JL**, Niikura Y, Rueda BR. The current status of evidence for and against postnatal oogenesis in mammals: a case of ovarian optimism versus pessimism? *Biol Reprod* 2009; 80: 2-12 (released online August 27, 2008; doi: 10.1095/biolreprod.108.069088).
29. Pru JK, Kaneko-Tarui T, Jurisicova A, Kashiwagi A, Selesniemi K, **Tilly JL**. Induction of pro-apoptotic gene expression and recruitment of p53 herald ovarian follicle loss caused by polycyclic aromatic hydrocarbons. *Reprod Sci* 2008; doi: 10.1177/1933719108327596 (release online December 15).
30. Selesniemi K, Lee H-J, Niikura T, **Tilly JL**. Young adult donor bone marrow infusions into female mice postpone age-related infertility and improve offspring survival. *AGING* 2009; 1: 49-57.

Books Edited

1. **Tilly JL**, Strauss JF, Tenniswood M, editors. *Cell Death in Reproductive Physiology*. New York: Springer-Verlag; 1997.
2. Lockshin RA, Zakeri Z, **Tilly JL**, editors. *When Cells Die. A Comprehensive Evaluation of Apoptosis and Programmed Cell Death*. New York: Wiley-Liss; 1998.

Current Extramural Funding

1. "Pre-clinical Trials for Female Fertility Preservation"
 Principal Investigator: Jonathan L. Tilly, Ph.D.
 Agency: National Institute of Child Health and Human Development, NIH
 Type: R01 (HD045787, Years 1-5)
 Period: 01/01/04-12/31/08 (no cost extension through 12/21/09)
 Objectives: to test in a pre-clinical trial if sphingosine-1-phosphate (S1P) and its analogs prevent oocyte depletion, sustain ovarian function, and preserve natural fertility in adult female rhesus macaques following radiotherapy.
2. "Origins and Functions of Mammalian Female Germline Stem Cells"
 Principal Investigator: Jonathan L. Tilly, Ph.D.
 Agency: National Institute on Aging, NIH
 Type: R37 Method to Extend Research in Time or MERIT Award (AG021179, Years 11-15)
 Period: 01/01/06-12/31/11 (with 5 additional years of funding through 2016 contingent upon satisfactory institutional/administrative review of progress made during 2006-11)
 Objectives: to identify sources of stem cells in adult female mice that exhibit germline potential, and to test the ability of these cells to alter ovarian function and reproductive potential in aging females, as well as their potential roles in normal physiology.

Patents

1. **Tilly JL**, Kolesnick RN, inventors; Massachusetts General Hospital, assignee. Protection of the female reproductive system from natural and artificial insults. U.S. Patent Number 7,195,775.
2. **Tilly JL**, Kolesnick RN, inventors; Massachusetts General Hospital, assignee. Protection of the female reproductive system from natural and artificial insults (U.S. Patent Application Serial Number 10/217,259; CIP from U.S. Patent Number 7,195,775 above). Under Examination.
3. **Tilly JL**, Johnson J, inventors; Massachusetts General Hospital, assignee. Compositions comprising female germline stem cells and methods of use thereof (U.S. Patent Application Serial Number 11/131,114 and World Intellectual Property Organization International Publication Number WO2005/121321A2). Under Examination.
4. **Tilly JL**, Johnson J, inventors; Massachusetts General Hospital, assignee. Methods and compositions for producing germ cells from bone marrow derived stem cells (U.S. Patent Application Serial Number 11/131,153 and World Intellectual Property Organization International Publication Number WO2006/001938A2). Under Examination.
5. **Tilly JL**, Johnson J, inventors; Massachusetts General Hospital, assignee. Methods and compositions for producing germ cells from peripheral blood derived stem cells (U.S. Patent Application Serial Number 11/131,152 and World Intellectual Property Organization International Publication Number WO2005/113752A2). Under Examination.
6. **Tilly JL**, Selesniemi K, inventors; Massachusetts General Hospital, assignee. Compositions and methods for rescuing fertility (U.S. Patent Application Serial Number 60/995,190). Under Examination.