

## **Jonathan L. Tilly, Ph.D.**

### **Current Appointments**

Director, Vincent Center for Reproductive Biology, Massachusetts General Hospital (1998-present)  
Chief, Division of Research, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital (1998-present)  
Associate Professor, Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School (1993-present)  
Investigator, Dana-Farber/Harvard Cancer Center (1999-present)  
Affiliated Faculty, Harvard Stem Cell Institute (2004-present)

### **Education, Training and Past Appointments**

B.S. in Animal Sciences, Rutgers, the State University of NJ (1984)  
M.S. in Animal Sciences, Rutgers, the State University of NJ (1987)  
Ph.D. in Animal Sciences, Rutgers, the State University of NJ (1990)  
Postdoctoral Research Fellow, University of California-San Diego (1990-1991)  
Postdoctoral Research Fellow, Stanford University Medical Center (1991-1993)  
Assistant Professor, Division of Reproductive Biology, Department of Population Dynamics, Johns Hopkins University (1993-1995)  
Associate Director, Vincent Center for Reproductive Biology, Massachusetts General Hospital (1993-1998)  
Investigator, Reproductive Endocrine Sciences Center, Massachusetts General Hospital (1995-2000)

### **Selected Honors, Awards and Memberships**

Organizer/Chair, International Sero 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: American Federation for Aging Research Grant (07/01/94-06/30/95); NIH R55-HD31188 (07/01/94-07/31/95); NIH R01-ES06999, (07/01/94-06/30/97); NIH R01-HD34426 (08/01/95-07/31/99); NIH R01-AG012279 (01/01/95-07/31/99, renewed); NIH R01-ES08430 (08/01/97-07/31/01, renewed); U.S. Army CDMRP/Department of Defense Ovarian Cancer Research Program Idea Award DAMD17-00-1-0567 (10/01/00-09/30/04); NIH-R01-ES08430 (08/01/01-07/31/06); NIH-R01-AG012279 (08/01/99-06/30/06; renewed as a MERIT Award); NIH R01-AG024999 (09/30/04-01/31/08)  
Commencement Speaker, Graduation Ceremonies for Cook College, Rutgers, the State University of NJ, New Brunswick, NJ (2001)

*Endocrinology* Editorial Board Member (1996-1999); *Journal of Endocrinology* Editorial Board Member (2000-2004); *Endocrine Journal* Editorial Board Special Advisory Committee Member (2000-present); *Cell Death & Differentiation* Editorial Board Member (2001-2006); Contributing Editor, SAGE-KE (<http://sageke.sciencemag.org>; 2002-2006)

Member of the Massachusetts General Hospital Subcommittee on Review of Research Proposals (1995-2003), the Massachusetts General Hospital Research Council (1995-1998), the Executive Committee of the Massachusetts General Hospital Vincent Obstetrics and Gynecology Service (1997-2003), and the Massachusetts General Hospital Small Animal Users Group Subcommittee (2002-2006)

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

Charter Member, Development-1 (DEV-1) Study Section (2003-2007); *Ad-hoc* Reviewer, Reproductive Biology (REB) Study Section (1996, 2001); NIH Site Visit Reviewer, Population Council, New York, NY (1996)

Scientific Advisor to Federal District Court Judge Richard G. 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; 2001-2003)

Boston Cotillion Award for Distinguished Achievements in Research (2002)

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

Member: Endocrine Society (1991-present), American Association for the Advancement of Science (1994-present), American Society of 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)

Member, Medical Advisory Board, Fertile Hope Foundation (2005-present)

**Selected Publications (from 102 manuscripts, 17 book chapters, 17 reviews, and 11 commentaries/editorials 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: 1228-1232.
2. Perez GI, **Tilly JL**. Cumulus cells are required for the increased apoptotic potential in oocytes of aged mice. *Hum Reprod* 1997; 12: 2781-2783.
3. 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.
4. 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: 1304-1314.

5. 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: 200-203.
6. 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: 841-850.
7. Perez GI, Trbovich AM, Gosden RG, **Tilly JL**. Mitochondria and the death of oocytes. *Nature* 2000; 403: 500-501.
8. 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: 1109-1114.
9. 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: 2468-2480.
10. 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: 614-620.
11. 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: 355-360.
12. 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: 603-609.
13. Tilly JL. Commuting the death sentence: how oocytes strive to survive. *Nature Rev Mol Cell Biol* 2001; 2: 838-848.
14. 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: 615-620.
15. 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: 901-902.
16. Takai Y, Canning J, Perez GI, Pru JK, Schlezinger JJ, Sherr DH, Kolesnick RN, Yuan J, Flavell RA, Korsmeyer SJ, **Tilly JL**. *Bax*, caspase-2 and caspase-3 are required for ovarian follicle loss caused by 4-vinylcyclohexene diepoxide exposure of female mice *in vivo*. *Endocrinology* 2003; 144: 69-74.
17. 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.
18. **Tilly JL**. Pharmacological protection of female fertility. In: Tulandi T, Gosden RG, editors. *Fertility Preservation*. London: Taylor & Francis; 2004. pp 65-75.
19. Johnson J, Canning J, Kaneko T, Pru JK, **Tilly JL**. Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature* 2004; 428: 145-150.

20. 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: 303-315.
21. 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: 1471-1477.
22. 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: 860-862.
23. Jurisicova A, Lee H-J, D'Estaing SG, **Tilly JL**, Perez GI. Molecular requirements for doxorubicin-mediated death in murine oocytes. *Cell Death Differ* 2006; 13: 1466-1474.
24. 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: 524-533.
25. 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.
26. Perez GI, Jurisicova A, Wise L, Lipina T, Kanisek M, Bechard A, Takai Y, Hunt P, Roder J, Grynopas 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: 5229-5234.
27. Takai Y, Matikainen T, Jurisicova A, Kim MR, Trbovich AM, Nakagawa T, Lemmers B, Flavell RA, Hakem R, Yuan J, **Tilly JL**, Perez GI. Caspase-12 compensates for a lack of caspase-2 and caspase-3 in female germ cells. *Apoptosis* 2007; 12: 791-800.
28. **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: 879-883.
29. 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: 3198-3204.
30. Lee H-J, Sakamoto H, Luo H, Skaznik-Wikiel ME, Friel A, Niikura T, Tilly JC, Klein R, Styer A, Zuckerberg 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: 2678-2684.

## 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

Objective: to test in a preclinical trial if sphingosine-1-phosphate (S1P) prevents oocyte depletion and preserves fertility in the adult female rhesus macaque following irradiation.

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 MERIT Award (AG012279, Years 11-15); Period: 02/15/06-01/31/11

Objectives: to identify stem cells with germline potential in bone marrow and peripheral blood of adult female mice, and to determine the contribution of such cells to adult ovarian function and fertility.

## Patents

1. **Tilly JL**, Kolesnick RN, inventors; Massachusetts General Hospital, assignee. Protection of the female reproductive system from natural and artificial insults. Issued, U.S. Patent No. 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 No. 10/217,259; CIP from U.S. Patent No. 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 No. 11/131,114 and World Intellectual Property Organization International Publication No. 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 No. 11/131,153 and World Intellectual Property Organization International Publication No. 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 No. 11/131,152 and World Intellectual Property Organization International Publication No. 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 No. 60/995,190). Under Examination.