

2014 Research Annual Report

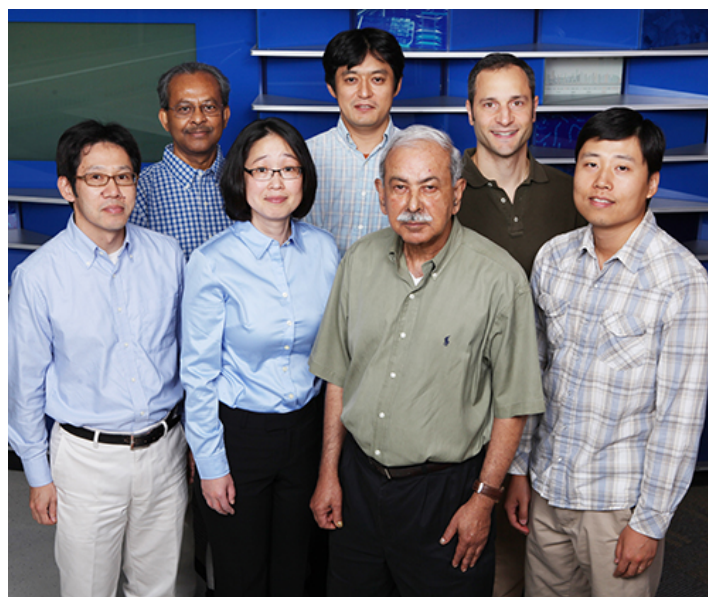
Reproductive Sciences

Division Summary

RESEARCH AND TRAINING DETAILS

Number of Faculty	7
Number of Joint Appointment Faculty	3
Number of Research Fellows	14
Number of Research Students	5
Number of Support Personnel	11
Direct Annual Grant Support	\$1,551,603
Peer Reviewed Publications	21

Division Photo



Row 1: Y Ogawa, T Daikoku, SK Dey, X Sun
Row 2: S Das, S Namekawa, T DeFalco

Significant Accomplishments

PhD/MD Graduate Student Continues to Excel

Jeeyeon Cha, PhD (Dey lab), received a P.E.O. Scholar Award from the Philanthropic Educational Organization in May 2014, a one-time competitive national-level award which celebrates the advancement of women. The award comes with partial monetary support for her study (she is pursuing an MD within the MD/PhD MSTP program at UC) and research.

Jeeyeon is currently supported by an NIH National Institute of Aging F30 Research Fellowship Award titled, "Premature Uterine Ageing and Preterm Delivery." The grant covers her tuition, some research supplies, and offers a stipend. Her individual NRSA grant from NIH/NIA was renewed for the 4th year. Thus far, she has published 4 papers that are related to work on this grant.

Success of Junior Faculty

Tony DeFalco, PhD, has been successful in obtaining funding from a competitive March of Dimes Basil O'Connor Starter Scholar Award (**2014-2016, \$150,000 over 2 years**) titled, "Macrophage regulation of fetal testis vascularization and morphogenesis;" and a CancerFree KIDS Research Grant (**2014-2015, \$22,000 over 1 year**) titled, "The role of macrophages in the testicular cancer microenvironment".

Success of Students

Megan Shroder, a student in the Namekawa Lab (since May 2013), was accepted to the University of Cincinnati College of Medicine **ROSE** program. The program--which stands for **R**esearch, **O**bservation, **S**ervice, and **E**ducation--involves early acceptance, internship, and mentoring. As a member of the Namekawa Lab, Megan worked to elucidate the mechanisms underlying epigenetic regulation of meiotic sex chromosomes.

Kris Alavattam, a student and Research Assistant II in the Namekawa Lab (since May 2012), was accepted into the University of Cincinnati College of Medicine Graduate Program in Cancer and Cell Biology. His work examining the genetic function of the breast cancer susceptibility gene, BRCA1, during meiosis was reported in his co-first author paper published in the **Journal of Cell Biology** in June 2014.

Research Highlights

SK Dey, PhD

In 2013, Dr. Dey became a member of the Advisory Board for the new journal Science Translational Medicine (AAAS).

SK Dey, PhD

Reviewer and Invited Participant, Sero International Foundation, Top Ten in Reproductive Medicine: Debating Breakthrough Basic and Clinical Papers with their Authors, September 20-21, 2013, Florence, Italy. Dr. Dey was invited to talk about his group's 2004 *Nature Medicine* publication titled, **Aberrant cannabinoid signaling impairs oviductal transport of embryos**. This paper was selected as one of the top five in basic science by the conference expert panel.

SK Dey, PhD

Invited Speaker, IFFS/ASRM 2013 Scientific program, October 13-15, 2013, Boston, MA. Title of lecture: **Uterine Function and Dysfunction**.

SK Dey, PhD

Invited Participant, NIH Sponsored 8th Collaborative Team Meeting on Interdisciplinary Research on Blastocyst Implantation, November 15-16, 2013, Rockville, MD.

SK Dey, PhD

Invited Speaker, Seminars in Biomedical Science, University of California San Francisco, May 14, 2014. San Francisco, CA. Title: **Muscle Segment Homeobox genes are critical for implantation and embryonic diapause**.

SK Dey, PhD

Founders' Forum speaker, Milestones in Reproductive Biology, Gordon Research Conference on Mammalian Reproduction, August 10-15, 2014, Colby-Sawyer College, New London, NH. Title: **Orchestration of Embryo-Uterine Interactions in Implantation is Critical to Pregnancy Success**.

Fenghua Bian, PhD

Poster presentation, 16th International Congress of Endocrinology, the Endocrine Society's 96th Annual Meeting Expo,

June 21-24, 2014, Chicago, IL.

Jeeyeon Cha, PhD (MD Student)

Oral presentation, IFFS/ASRM 2013 Scientific program, October 13-15, 2013, Boston, MA. Title of presentation: **Gene-Environment Interactions Underlie Preterm Birth**. Only a few trainees were selected to give an oral presentation at this meeting.

Daesuk Chung, PhD; Fei Gao, PhD

Joint poster presentation, 46th Annual Meeting of the Society for the Study of Reproduction, July 22-26, 2013, Montréal, Québec, Canada.

Tony DeFalco, PhD

Abstract presentation, 46th Annual Meeting of the Society for the Study of Reproduction, July 22-26, 2013, Montreal, Québec, Canada. Citation: DEFALCO, T. and Capel, B. **Macrophage activity regulates vascularization and morphogenesis of the fetal testis**.

Tony DeFalco, PhD

Session Chair: *Sex Differentiation and Development of the Gonads and Tracts*, 46th Annual Meeting of the Society for the Study of Reproduction, July 22-26, 2013, Montreal, Québec, Canada.

Tony DeFalco, PhD

Dr. DeFalco gave a lecture (over the course of two class periods) on Sex Determination as part of the Fall 2013 Introduction to Developmental Biology class (UC MDB program).

Tony DeFalco, PhD

Dr. DeFalco gave a lecture on Introduction to Research and Careers in Biology to UC MDB graduate program students in October 2013.

Tony DeFalco, PhD

Dr. DeFalco gave a lecture on Reproduction as part of the 2014 Developmental Disease course (UC MDB Program, January).

Tony DeFalco, PhD

Featured speaker, Department of Biology PhD recruitment meeting for prospective candidates, Johns Hopkins University, Baltimore, MD, February 2014.

Helen Jones, PhD

Dr. Jones became a member of the Loan Repayment SEP for NIEHS.

Helen Jones, PHD

Dr. Jones organized and chaired the Establishing Connections and Building Collaborations, 1st meeting of the six State Placental Group. This meeting was attended by placental researchers from University of Michigan, Nationwide Children's, Cincinnati Children's, University of Cincinnati, and Metrohealth Medical Center. April 24-25, 2014, Cincinnati, OH.

Yuya Ogawa, PhD

Invited lecture, 37th Annual Meeting of the Molecular Biology Society of Japan, December 3, 2013, Kobe, Japan. Title: **Role of exon 7 of Xist in X-chromosome inactivation**.

Yuya Ogawa, PhD

Invited lecture, Osaka University, December 9, 2013, Toyonaka, Japan. Title: **Transcriptional regulation by long non-coding RNA in X-chromosome inactivation.**

Yuya Ogawa, PhD

Invited lecture, Tokai University School of Medicine, December 11, 2013, Isehara, Japan. Title: **Mechanism of X-chromosome inactivation by long non-coding RNA Xist/Tsix.**

Yuya Ogawa, PhD

Invited lecture, Saitama Medical University, December 13, 2013, Hidaka, Japan. Title: **X-chromosome inactivation as a model system of long non-coding mediated-gene regulation.**

Kathryn Owens (SURF student)

Ms. Owens was awarded a Past Presidents Travel Award of \$2,000 to attend and present in the Hot Topics session at SGI 2014, Florence Italy, March 26-29. Title: **Nanoparticle-Mediated Trophoblast-Specific Gene Therapy Rescues Birthweight in a Murine Model of Placental Insufficiency.**

Satoshi Namekawa, PhD

Invited talk, Gordon Research Conference on Germinal Stem Cells, July 14-19, 2013, Hong Kong, China. Title: **Epigenetic dynamics of the sex chromosomes in the male germline.**

Satoshi Namekawa, PhD

Invited lecture, Mie University Graduate School of Medicine, November 20, 2013, Mie, Japan. Title: **Epigenetic regulation in mammalian reproduction.**

Satoshi Namekawa, PhD

Invited talk, Gordon Research Conference on Meiosis, June 1-6, 2014, Colby-Sawyer College, New London, NH. Title: **Establishment mechanisms of male germline epigenome.**

Significant Publications

Cha J, Bartos A, Egashira M, Haraguchi H, Saito-Fujita T, Leishman E, Bradshaw H, **Dey SK**, Hirota Y. **Combinatory approaches prevent preterm birth profoundly exacerbated by gene-environment interactions.** *J Clin Invest* . 2013 3;123(9):4063-75.

This study found that gene-environment interaction is a significant contributing factor to preterm birth: female mice with a genetic predisposition to spontaneous preterm birth due to premature decidual senescence, increased mTORC1 activity, and COX2 signaling experienced a 100% incidence of preterm birth after exposure to a mild inflammatory insult (LPS). Intriguingly, predisposed mice were protected against preterm birth after combined treatment with rapamycin (mTORC1 inhibitor) and progesterone (P4), with no observable maternal or fetal side effects. The findings in mice were corroborated in women who experienced preterm birth due to a similar signaling pathway interaction. *Biology of Reproduction* highlighted this paper on September 4, 2013 in an article titled, *On Schedule for Labor Day* by Charlotte Schubert.

Broering TJ, Alavattam KG, Sadreyev RI, Ichijima Y, Kato Y, Hasegawa K, Camerini-Otero RD, Lee JT, Andreassen PR, **Namekawa SH**. **BRCA1 establishes DNA damage signaling and pericentric heterochromatin of the X chromosome in male meiosis.** *J Cell Biol*. 2014 9;205(5):663-75.

The genetic functions of the BRCA1 gene that is involved in breast cancer susceptibility was elucidated in this paper. It is demonstrated that the major role of BRCA1 in meiosis is not in meiotic recombination but instead in promotion of the

dramatic chromatin changes required for formation and function of the sex body.

DeFalco T, Bhattacharya I, Williams AV, Sams DM, Capel B. **Yolk-sac-derived macrophages regulate fetal testis vascularization and morphogenesis**. *Proc Natl Acad Sci U S A*. 2014 111(23):E2384-93.

In this publication, a previously unidentified role for macrophages in fetal testis development was uncovered.

Macrophages were shown to be required for the formation of vascular and sex-specific structures in the fetal testis, and this work implicates macrophages as a new cellular player in sexual differentiation.

Haraguchi H, Saito-Fujita T, Hirota Y, Egashira M, Matsumoto L, Matsuo M, Hiraoka T, Koga K, Yamauchi N, Fukayama M, Bartos A, Cha J, **Dey SK**, Fujii T, Osuga Y. **MicroRNA-200a locally attenuates progesterone signaling in the cervix preventing embryo implantation**. *Mol Endocrinol*. 2014 28(7):1108-17.

The authors investigated the molecular reasons why, except in rare cases, the embryo and placenta do not embed in or adjacent to the cervix. They found that the cervix is nonresponsive to implantation due a local molecular mechanism that creates markedly different cell proliferation and differentiation levels from the uterus. Specifically, elevated levels of miR-200a lead to down-regulation of progesterone (P4)-progesterone receptor (PR) signaling and up-regulation of 20 α -hydroxysteroid dehydrogenase (20 α -HSD) which degrades P4 in the cervix. These findings may contribute to a better understanding of what causes cervical pregnancy and placenta previa and how to prevent these life-threatening conditions. *Nature Review Endocrinology* highlighted this paper on June 10, 2014 in an article titled; *A microRNA prevents cervical embryonic implantation* by Joana Osório.

Sun X, Terakawa J, Clevers H, Barker N, Daikoku T, **Dey SK**. **Ovarian LGR5 is critical for successful pregnancy**. *FASEB J*. 2014 28(5):2380-9.

Although Lgr5 is expressed in the female reproductive organs and is considered to be a stem cell marker in many other systems, its physiological function in pregnancy remains unclear. This study found major effects of Lgr5 in the ovaries, specifically in corpora lutea maintenance. Furthermore, the deletion of Lgr5 was shown to cause a drop in progesterone levels, which in turn led to pregnancy termination. P4 supplementation was successful in rescuing decidualization and allowing pregnancy to continue to term in Lgr5 deleted females.

Division Publications

1. Broering TJ, Alavattam KG, Sadreyev RI, Ichijima Y, Kato Y, Hasegawa K, Camerini-Otero RD, Lee JT, Andreassen PR, Namekawa SH. **BRCA1 establishes DNA damage signaling and pericentric heterochromatin of the X chromosome in male meiosis**. *J Cell Biol*. 2014; 205:663-75.
2. Cha J, Vilella F, Dey SK, C. S. (2013) **Molecular Interplay in Successful Implantation in Ten Critical Topics in Reproductive Medicine**. Top Ten Project in Reproductive Medicine: Debating breakthrough basic and clinical papers with their authors. Florence, Italy, Science/AAAS. 44-48.
3. Cha J, Bartos A, Egashira M, Haraguchi H, Saito-Fujita T, Leishman E, Bradshaw H, Dey SK, Hirota Y. **Combinatory approaches prevent preterm birth profoundly exacerbated by gene-environment interactions**. *J Clin Invest*. 2013; 123:4063-75.
4. Daikoku T, Yoshie M, Xie H, Sun X, Cha J, Ellenson LH, Dey SK. **Conditional deletion of Tsc1 in the female reproductive tract impedes normal oviductal and uterine function by enhancing mTORC1 signaling in mice**. *Mol Hum Reprod*. 2013; 19:463-72.

5. DeFalco T, Bhattacharya I, Williams AV, Sams DM, Capel B. **Yolk-sac-derived macrophages regulate fetal testis vascularization and morphogenesis**. *Proc Natl Acad Sci U S A*. 2014; 111:E2384-93.
 6. Gao F, Das SK. **Epigenetic regulations through DNA methylation and hydroxymethylation: clues for early pregnancy in decidualization**. *Biomolecular Concepts*. 2014; 5:95-107.
 7. Habli M, Jones H, Aronow B, Omar K, Crombleholme TM. **Recapitulation of characteristics of human placental vascular insufficiency in a novel mouse model**. *Placenta*. 2013; 34:1150-8.
 8. Haraguchi H, Saito-Fujita T, Hirota Y, Egashira M, Matsumoto L, Matsuo M, Hiraoka T, Koga K, Yamauchi N, Fukayama M, Bartos A, Cha J, Dey SK, Fujii T, Osuga Y. **MicroRNA-200a Locally Attenuates Progesterone Signaling in the Cervix, Preventing Embryo Implantation**. *Mol Endocrinol*. 2014; 28:1108-17.
 9. Hasegawa K, Namekawa SH, Saga Y. **MEK/ERK signaling directly and indirectly contributes to the cyclical self-renewal of spermatogonial stem cells**. *Stem Cells*. 2013; 31:2517-27.
 10. Jones H, Crombleholme T, Habli M. **Regulation of amino acid transporters by adenoviral-mediated human insulin-like growth factor-1 in a mouse model of placental insufficiency in vivo and the human trophoblast line BeWo in vitro**. *Placenta*. 2014; 35:132-8.
 11. Jones HN, Crombleholme T, Habli M. **Adenoviral-mediated placental gene transfer of IGF-1 corrects placental insufficiency via enhanced placental glucose transport mechanisms**. *PLoS One*. 2013; 8:e74632.
 12. Katoh H, Wang D, Daikoku T, Sun H, Dey SK, Dubois RN. **CXCR2-expressing myeloid-derived suppressor cells are essential to promote colitis-associated tumorigenesis**. *Cancer Cell*. 2013; 24:631-44.
 13. Kusama K, Yoshie M, Tamura K, Daikoku T, Takarada T, Tachikawa E. **Possible roles of the cAMP-mediators EPAC and RAP1 in decidualization of rat uterus**. *Reproduction*. 2014; 147:897-906.
 14. Lanekoff I, Burnum-Johnson K, Thomas M, Short J, Carson JP, Cha J, Dey SK, Yang P, Prieto Conaway MC, Laskin J. **High-speed tandem mass spectrometric in situ imaging by nanospray desorption electrospray ionization mass spectrometry**. *Anal Chem*. 2013; 85:9596-603.
 15. Namekawa SH. **Slide preparation method to preserve three-dimensional chromatin architecture of testicular germ cells**. *J Vis Exp*. 2014; :e50819.
 16. Raines AM, Adam M, Magella B, Meyer SE, Grimes HL, Dey SK, Potter SS. **Recombineering-based dissection of flanking and paralogous Hox gene functions in mouse reproductive tracts**. *Development*. 2013; 140:2942-52.
 17. Sin HS, Namekawa SH. **The great escape: Active genes on inactive sex chromosomes and their evolutionary implications**. *Epigenetics*. 2013; 8:887-92.
 18. Sun X, Bartos A, Whitsett JA, Dey SK. **Uterine deletion of Gp130 or Stat3 shows implantation failure with increased estrogenic responses**. *Mol Endocrinol*. 2013; 27:1492-501.
 19. Sun X, Dey SK. **Synthetic cannabinoids and potential reproductive consequences**. *Life Sci*. 2014; 97:72-7.
 20. Sun X, Terakawa J, Clevers H, Barker N, Daikoku T, Dey SK. **Ovarian LGR5 is critical for successful pregnancy**. *FASEB J*. 2014; 28:2380-9.
 21. Troja W, Kil K, Klanke C, Jones HN. **Interaction between human placental microvascular endothelial cells and a model of human trophoblasts: effects on growth cycle and angiogenic profile**. *Physiol Rep*. 2014; 2:e00244.
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Faculty, Staff, and Trainees

Faculty Members

Sudhansu K. Dey, PhD, Professor

Leadership Division Director; Lova Rieker Chair

Research Interests Pregnancy and implantation; reproductive cancers; endocannabinoids

Takiko Daikoku, PhD, Associate Professor

Research Interests Reproductive cancers; blastocyst implantation

Sanjoy Das, PhD, Professor

Research Interests Uterine decidualization; environmental estrogens

Tony DeFalco, PhD, Assistant Professor

Research Interests Genetic and molecular mechanisms of sexual development disorders

Yasushi Hirota, MD, PhD, Adjunct

Research Interests Human reproduction; endometrial biology; implantation (Home Institution: National Institute of Genetics of Japan)

Hyunjung "Jade" Lim, PhD, Adjunct

Research Interests Embryo Implantation (Home Institution: Konkuk University, Korea)

Satoshi Namekawa, PhD, Assistant Professor

Research Interests Epigenetics of germ cells; X chromosome inactivation

Yuya Ogawa, PhD, Assistant Professor

Research Interests Molecular mechanisms of X chromosome inactivation

Joint Appointment Faculty Members

Helen Jones, PhD, Assistant Professor (Pediatric Surgery)

Research Interests Regulation of placental growth and function; fetal growth restriction

Trainees

- **Fenghua Bian, PhD**, State Key Laboratory of Reproductive Biology, Institute of Zoology/Chinese Academy of Sciences, China
- **Indrashis Bhattacharya, PhD**, National Institute of Immunology, Jawaharlal Nehru University, India
- **Jeeyeon Cha, BS**, University of Cincinnati Medical School
- **Daesuk Chung, PhD**, University of Colorado
- **Fei Gao, PhD**, Vanderbilt University
- **Kazuteru Hasegawa, PhD**, The Graduate University for Advanced Studies, Japan
- **Yosuke Ichijima, PhD**, Harvard University
- **Yasuko Kato, PhD**, Kyoto Institute of Technology, Japan
- **Yingju Li, MD**, Nanhua University, China
- **Craig Park, PhD**, McGill University, Canada

- **Ho-Su Sin, PhD**, Kanazawa University, Japan
 - **Xiaofei Sun, PhD**, Vanderbilt University
 - **Jumpei Terakawa, PhD**, Yamaguchi University, Japan
 - **Macarena Vargas Vargas, PhD**, Pontificia Universidad Católica de Chile
 - **Norishige Yamada, PhD**, Kagoshima University, Japan
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Division Collaboration

Joint collaboration between the Dey and Whitsett labs: Dey lab managed the animal models with mice received from Dr. Whitsett and handled the reagents, while several immuno detection studies with antibody were conducted in Whitsett's lab.

Resulting paper: Sun X, Bartos A, Whitsett JA, Dey SK. Uterine deletion of gp130 or Stat3 shows implantation failure with increased estrogenic responses. Mole Endo 27 (9): 1492-501. Sept 2013. PMID:PMC3753427

(SK Dey, PhD)

Neonatology and Pulmonary Biology » Jeff Whitsett, MD

Reproductive aspects (experiments, data interpretation, manuscript writing and managing animal models) of this project were handled by the Dey Lab.

Resulting paper: Raines AM, Adam M, Magella B, Meyer SE, Grimes HL, Dey SK, Potter SS. Recombineering-based dissection of flanking and paralogous Hox gene functions in mouse reproductive tracts. Development 140 (14): 2942-52, July 2013. PMID:PMC3699281

(SK Dey, PhD)

Developmental Biology » Steve Potter, PhD

DNA damage response pathways in germ cells

To elucidate the roles of DNA damage response pathways in germ cells, specifically focusing on the events on the sex chromosomes in meiosis. (Satoshi Namekawa, PhD)

Experimental Hematology and Cancer Biology » Paul R. Andreassen, PhD

Establishment of germline epigenome

To elucidate the landscape of germline epigenome and its underlying mechanism.

Division of Allergy and Immunology, Division of Human Genetics. (Satoshi Namekawa, PhD)

Allergy and Immunology, Division of Human Genetics » Artem Barski, PhD

Functional role of FoxM1 in estrogen signaling and during the early pregnancy. (Das Lab)

Pulmonary Biology » Vladimir Kalinichenko, PhD

i) Epigenetic regulation of uterine receptivity for embryo implantation and ii) Analysis of molecular signaling axis for Hoxa-10 and H19 during uterine decidualization in human. (Sanjoy K. Das, PhD)

Endocrinology » Stuart Handwerger, MD

Molecular analysis of uterine epithelia-stromal. (Sanjoy K. Das, PhD)

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct

Cha, J

Premature Uterine Aging and Preterm Delivery

National Institutes of Health

F30 AG 040858	09/16/11-09/15/15	\$47,232
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De Falco, T

Macrophage Regulation of Fetal Testis Vascularization and Morphogenesis

March of Dimes

#5-FY14-32	02/01/14-01/31/16	\$68,182
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Dey, S

Endocannabinoid Signaling via CB2 Protects Against Preterm Birth by Modulating Immune Responses

March of Dimes

#21-FY12-127	03/01/12-02/28/15	\$164,000
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Molecular Signaling in Uterine Receptivity to Implantation

National Institutes of Health

R01 HD 068524	09/26/11-06/30/16	\$201,663
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The Role of Bioactive Lipids in Inflammation and Cancer

National Institutes of Health(Mayo Clinic)

P01 CA 077839	06/01/13-05/31/17	\$159,030
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March of Dimes Prematurity Research Center (Project 3)

March of Dimes

22-FY-13-543	07/01/13-12/31/13	\$130,486
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March of Dimes Prematurity Research Center Ohio Collaborative (Project 3)

March of Dimes

22-FY14-470	01/01/14-12/31/14	\$263,636
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Namekawa, S

DNA Damage Response Pathways in Meiotic Sex Chromosome Inactivation

National Institutes of Health

R01 GM 098605	08/01/11-07/31/16	\$182,385
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Regulatory Mechanism of Active Epigenetic Modifications and its Transgenerational Effects

March of Dimes

#1-FY13-510	06/01/13-05/31/16	\$90,909
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Ogawa, Y

Organization of the Inactive X-Chromosome

National Institutes of Health

R01 GM 102184	09/01/12-08/31/17	\$169,840
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Regulation of Escape Genes on the Inactive X-Chromosome

March of Dimes

#6-FY12-337	06/01/12-05/31/15	\$74,240
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Current Year Direct	\$1,551,603
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Total	\$1,551,603
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