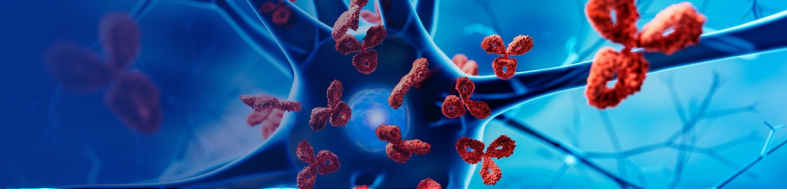


Xist-ing Data: Why Might Autoimmune Diseases Be More Common in Women?

OADR-ORWH ScienceTALKS

April 23, 2024, 12 – 2 p.m. EDT

Event Webpage
Event Recording

Welcome and Opening Remarks

Victoria Shanmugam, MBBS, MRCP, FACR, CCD, Director, NIH Office of Autoimmune Disease Research in the Office of Research on Women's Health (OADR-ORWH)

Dr. Victoria Shanmugam welcomed the audience to the inaugural OADR-ORWH ScienceTALKS webinar, reviewed housekeeping items, and introduced the moderators and speakers of the symposium.

Moderators:

- Stacy Ferguson, Ph.D., is the chief of the Autoimmune and Primary Immunodeficiency Diseases Section, National Institute of Allergy and Infectious Diseases.
- Marie Mancini, Ph.D., is the program director of the Systemic Autoimmune Disease Biology Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Speakers:

- Montserrat Anguera, Ph.D., is an associate professor of epigenetics in the Department of Biomedical Sciences at the University of Pennsylvania School of Veterinary Medicine.
- Diana Dou, Ph.D., is a basic life research scientist and postdoctoral scholar at the Center for Personal Dynamic Regulomes, Program in Epithelial Biology in the Department of Dermatology at the Stanford University School of Medicine.
- Brendan Antiochos, M.D., is an assistant professor of rheumatology at the Johns Hopkins School of Medicine.

X-Chromosome Inactivation Mechanisms in Immune Cells

Montserrat Anguera, Ph.D., Associate Professor of Epigenetics, Department of Biomedical Sciences, University of Pennsylvania, School of Veterinary Medicine

Dr. Anguera began her presentation with a brief overview of systemic lupus erythematosus (SLE). SLE is a systemic rheumatic autoimmune disease that can affect multiple organ systems and has numerous presentations. Autoantibodies, specifically anti-double stranded DNA (anti-dsDNA) and anti-Smith ribonucleoprotein (anti-Smith RNP) complex antibodies, are elevated in the serum of patients with SLE. Patients also display increased numbers of activated B cells, age-associated B cells, and plasma cells. B cells are important initiators and effectors of the immune response—they secrete autoantibodies and cytokines, and they play a key role in antigen presentation. Autoantibody production and detection in patients with SLE are critical, as elevated levels of autoantibodies can often be detected before clinical disease onset.

The X chromosome is also a crucial player in autoimmunity. X chromosomes contain a high density of immune-related genes, and X chromosome genetics and epigenetics contribute to the sex bias seen in autoimmune diseases. Increased risk of certain autoimmune diseases corresponds to the number of X chromosomes an individual has; for example, individuals with two or more X chromosomes have an increased risk for SLE, systemic sclerosis, scleroderma, polymyositis, and dermatomyositis.

Dr. Anguera reviewed the process of typical X chromosome inactivation. Eutherian mammals have XY chromosomal sex determination, with females typically possessing two X chromosomes and males possessing an X and a Y chromosome. During embryonic development in females, one X chromosome is randomly silenced so that only one X chromosome is active per cell. In this process, future inactive X chromosomes produce a long noncoding RNA (lncRNA) called X-linked X-inactive-specific transcript (XIST). XIST RNA remains tethered to the chromosome that expresses it, which results in transcriptional silencing. The inactivated X chromosome also receives several epigenetic modifications, or heterochromatic marks, that aid in silencing the chromosome. Some genes can escape silencing, including XIST RNA, which is critical to maintain dosage compensation.

Dr. Anguera noted that, while it was once thought that all cells experience the same X chromosome inactivation process, her lab discovered that immune cells achieve inactivation very differently from other cell types, and they "dynamically" maintain X chromosome inactivation. There are no observed epigenetic modifications in naïve B cells, including the production of XIST RNA. However, when the B cells are stimulated, XIST RNA colocalization and other epigenetic modifications occur. The inactivation process and the localization of XIST are independent of XIST RNA transcription.

X Chromosome Inactivation Maintenance

The Anguera Lab examined the epigenetic mechanisms of X chromosome inactivation in various immune cells in healthy individuals and individuals with SLE. They also studied the epigenetic features of the inactivated X chromosome in pediatric and adult populations. Their studies found that XIST RNA is mis-localized in activated B cells from individuals with SLE. Circulating naïve B cells and in vivo activated B cells have a barren expression of X-linked genes, which indicates that mis-localized XIST RNA is potentially impacting gene silencing and expression from the inactive X chromosome. Additional work showed that mice with lupus-like disease displayed mis-localized XIST RNA from the inactive X chromosome in late-stage disease.

Dr. Anguera summarized the correlative findings by explaining that, when a healthy B cell is activated, XIST RNA and heterochromatic marks return to the inactivated X chromosome to maintain transcriptional silencing. In B cells impacted by sex-biased autoimmune diseases, the tethering of the XIST RNA to the chromosome is compromised and the enrichment of epigenetic modifiers on the X chromosome is reduced. Both corruptions lead to permissive chromatin, which allows the activation of some genes from the inactivated X chromosome. These observations led to the hypothesis that impaired "dynamic" X chromosome inactivation maintenance in B cells contributes to the susceptibility for individuals with two X chromosomes to develop autoimmune diseases.

Impaired Chromosome Inactivation Maintenance in B Cells

To test this hypothesis, Dr. Anguera's team generated a knockout mouse model, cKO/cKO, in which the *Xist* gene was deleted from both X chromosomes in B cells. The team observed normal total B cell counts in the spleen, but the counts of certain B cell subsets were higher in the knockout mice than in wildtype (WT) mice. No differences in anti-dsDNA autoantibodies were observed between Xist knockout mice and WT mice between the ages of 6 weeks and 12 months; however, after 12 months of age, some

knockout mice were found to have very high levels of anti-dsDNA autoantibodies in their serum. The team examined the following groups:

(1) WT mice
(2) Xist knockout mice with high levels of anti-dsDNA (cKO High)
(3) Xist knockout mice with low levels of anti-dsDNA (cKO Low).

Investigators found that, compared to cKO Low mice and WT mice, cKO High mice had increased numbers of anti-dsDNA secreting cells and significantly elevated levels of 16 different autoantigens. cKO High mice had elevated anti-dsDNA and anti-Smith RNP complex compared to the other two groups, which is relevant because these autoantibodies are elevated in patients with SLE. Additional elevated autoantibodies seen in patients with SLE were likewise found to be elevated in the cKO High mice, and the cKO High mice experienced a higher glomerular pathology that is similar to the damaging kidney pathology often observed in patients with SLE. Compared to WT and cKO Low mice, the cKO High mice also had more splenic CD11c+ age-associated B cells, GL7+ activated B cells, short-lived plasma cells, long-lived plasma cells, and class-switched B cells.

Investigators looked at how gene expression was altered among the three groups of mice. Ten X chromosome-linked genes were upregulated in the cKO High mice, notably *Tasl. Tasl* codes for an adaptor protein that helps activate a pathway involved in the downstream production of type 1 interferons, and persistent stimulation of this pathway contributes to the pathogenesis of SLE. Investigators also found that the expression of several autosomal genes were altered in the cKO High mice. Overall, this study demonstrated that B cell-specific *Xist* deletion in some animals can result in spontaneous lupus-like disease and elevated autoantibody production, increased glomerular pathology, and increased activated B cells.

Xist Deletion in Mouse Models

Next, Dr. Anguera described subsequent studies investigating the impact of *Xist* deletion in mouse models with lupus-like disease. The team used pristane to induce lupus-like disease and compared the following groups:

(1) WT mice
(2) WT/pristane-treated mice
(3) Xist knockout/pristane-treated mice

Compared to both WT groups, Xist knockout/pristane-treated mice had higher serum levels of anti-dsDNA, developed more age-associated B cells and short-lived plasma cells, and had higher total numbers of GL7+ activated B cells and class-switched B cells. Thus, this study demonstrated that Xist increases activated B cells that are responsible for producing antibodies. Furthermore, investigators detected 10 upregulated X chromosome-linked genes in the Xist knockout/pristane-treated mice, including *Tasl*.

Findings

Dr. Anguera concluded her presentation with a summary of the team's findings, emphasizing that *Xist* deletion can lead to the upregulation of X-linked immune genes and contribute to SLE phenotypes. *Xist* deletion in B cells resulted in a loss of Xist RNA and epigenetic modifications, which in turn resulted in the upregulation of certain genes, such as *Tasl*. The *Xist* deletion in B cells also increased the number of

activated B cells, memory B cells, autoantibodies, and several glomerular pathologies, which are also phenotypes seen in patients with SLE.

Xist Ribonucleoproteins Promote Increased Prevalence for Autoimmunity in Females

Diana R. Dou, Ph.D., Basic Life Research Scientist and Postdoctoral Scholar, Center for Personal Dynamic Regulomes, Program in Epithelial Biology, Department of Dermatology, Stanford University School of Medicine

Dr. Dou began her talk with an overview of the complexities of the immune system, noting that a balance is needed between self-tolerance and protection in the system. Too much self-tolerance can result in cancer, while too much protection can result in autoimmunity. Autoimmunity is challenging to diagnose and there are limited therapeutic options, which primarily target symptomatology. A strong genetic component and an environmental component are both involved in autoimmunity; however, Dr. Dou stated that being biologically female is the greatest risk factor for autoimmune diseases. As noted by Dr. Anguera, this is because biological females have two X chromosomes, and the X chromosome has a large number of immune genes. To function properly, gene expression needs to be tightly controlled through XIST, which operates by randomly silencing one of the X chromosomes in biological females. Incorrect Xist patterning affects gene expression, which results in a high risk of autoimmunity.

Howard Chang's, M.D., Ph.D., laboratory, where Dr. Dou works, has focused on XIST, the complex it forms, and its impact on autoimmune risk. Dr. Dou explained that many ribonucleoproteins (RNPs) are known autoantigens, and nucleic acid protein complexes, like RNPs, can engage toll-like receptors (TLRs) and activate immune cells.

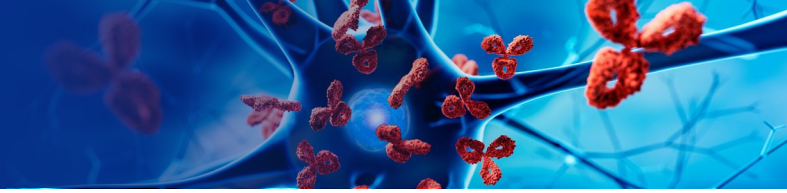
The Chang Lab developed an RNA-directed proteomics technique called ChIRP-MS that "pulls down" the Xist complex and uses mass spectrometry to identify proteins bound to the complex. The investigators found 81 unique binding proteins, a third of which are known autoantigens with associations to autoimmune diseases. The investigators hypothesized that the Xist RNP complex is a trigger for autoimmunity by stimulating prolonged activation of the immune system, which leads to chronic inflammation and disease.

Does Expression of Xist RNPs Elevate Risk of Autoimmune Diseases?

Investigators at the Chang Lab used pristane-induced lupus mice to develop a mouse model (tgXist) that allowed for the controlled activation of Xist with doxycycline. Pristane-induced lupus mice display many similarities to patients with lupus, including a female sex bias, multi-organ impact, and development of multiple autoantibodies.

In the first experiment were autoimmune-resistant and female mice displayed lupus-like symptoms. Fifty-two weeks after treatment with pristane, investigators looked at spleen T cells in the following groups:

(1) female tgXist mice treated with pristane (positive control)
(2) male tgXist mice treated with doxycycline and pristane (test subject)
(3) male tgXist mice treated with pristane (tgXist control)
(4) male WT mice treated with pristane (treatment control)
(5) male WT mice (negative control)



Investigators found that the epigenetics of test subjects (male tgXist mice treated with doxycycline and pristane) most resembled the pattern observed in the pristane-treated tgXist female mice, the positive controls. This included many TLRs and cascades important in lupus pathogenesis.

In the second experiment, the male mice were autoimmune-permissive and displayed less severe lupus-like symptoms while the female mice displayed more severe lupus-like symptoms. Sixteen weeks after treatment with pristane, investigators looked at T cells in the following groups:

(1) female WT mice treated with pristane (positive control)
(2) male WT mice (negative control)
(3) male tgXist mice treated with doxycycline (Dox/tgXist control)
(4) male WT mice treated with pristane and doxycycline (treatment control)
(5) male tgXist mice treated with doxycycline and pristane (test subject)

Investigators found elevated autoantibodies and greater pathological organ damage in the test subjects (male tgXist mice treated with doxycycline and pristane) compared to the negative control, treatment control, and Dox/tgXist control, which were also found in female WT mice treated with pristane, the positive control. The single cell multiome gene expression showed close clustering of test subjects and positive controls. Furthermore, the test subjects had indicators of atypical B cells, which are similarly observed in the pathogenesis of lupus in patients.

Dr. Dou summarized that both tgXist model experiments demonstrated that Xist RNPs promote female-biased autoimmunity. At the physiological level, the test subjects had increased autoantibody production and more severe organ disease penetrance. At the cellular level, the test subjects had increased autoimmunity and decreased immune modulation.

What is the Clinical Impact of the Xist RNP?

Autoantibodies, a type of antibody produced by B cells against self-antigens, are considered a clinical biomarker for autoimmune diseases. Because of the heterogeneity and overlapping symptoms early in autoimmune diseases, the identification of specific biomarkers is important for improving diagnostics.

In the next Chang Lab study, investigators collaborated with the Human Protein Atlas project to look at the seroreactivity of XIST antigens in control patients and patients with scleroderma, dermatomyositis, and lupus. Dozens of autoantibodies were detected in patients grouped by disease, while nine autoantibodies were found to be common in patients regardless of the specific autoimmune disease. Additionally, 28 novel autoantigens were identified. Further study in this area could lead to the creation of seroreactivity profiles for improved diagnosis and therapy.

Findings

Dr. Dou summarized the studies' findings by stating that XIST lncRNA is a polymeric antigen scaffold in female-biased autoimmunity. In mouse models, Xist expression promoted increased autoimmunity (epigenetically and at the gene expression level) while increasing autoantibody production and causing more severe organ disease penetrance. In the Human Protein Atlas study, samples from patients with autoimmune diseases were seroreactive to many RNP components, and this critical finding could lead to progress in the development of new diagnostics and therapeutics.

XIST lncRNA as a Sex-Specific Reservoir of TLR7 Ligands in Lupus

Brendan Antiochos, M.D., Assistant Professor of Rheumatology, Johns Hopkins School of Medicine

Dr. Antiochos stated that his presentation would review toll-like receptor 7 (TLR7) signaling in SLE pathogenesis and report a novel role for lncRNA XIST as a damage-associated molecular pattern (DAMP). To date, XIST is the only example of a female-specific DAMP identified. Studies have found upregulated XIST expression in cells from female patients with lupus compared to healthy female controls.

TLR7 as a Key Contributor to SLE Pathology

As previously described, being female is a well-known risk factor for developing SLE, with females 9 to 10 times more likely to develop lupus than males. There is an interesting dose-response related to the X chromosome that is spotlighted in individuals with Klinefelter syndrome (XXY) and Turner syndrome (XO)—individuals with Klinefelter have an increased risk for SLE while those with Turner syndrome have a decreased risk.

There are also sex differences for host immune responses in humans and multiple other species; females have enhanced type 1 interferon signaling and enhanced antibody responses. This raises the question of whether there are specific immune pathways that could give females an advantage in host defense but, when dysregulated, could also contribute to autoimmunity and sex-biased rheumatic diseases.

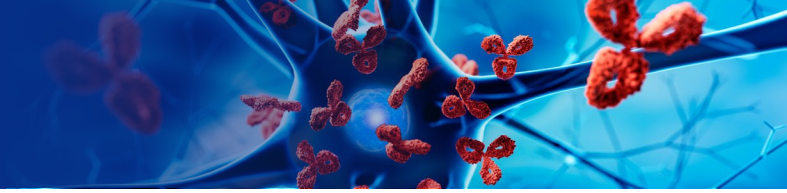
Dr. Antiochos described TLR7 as an innate pattern recognition receptor found in immune cells that serves as a sensor of single stranded RNA and RNA degradation products detected in the endosome. TLR7 ligation in B cells activates proliferation in antibody responses, while TLR7 ligation in dendritic cells triggers type 1 interferon production—both of these features are dysregulated in patients with SLE and have been shown in mouse models with polymorphisms described in humans. Dr. Antiochos further described various studies that supported the importance of TLR7 in autoimmunity, specifically lupus.

Female-Specific TLR7 RNA Ligands

TLR7 has two binding sites that promote activation. One of the sites binds RNA fragments, with UU dinucleotide repeats identified as a potent ligand. A specific nine-base motif surrounding UU repeats also plays an important role for binding to the site.

Dr. Antiochos' research group utilized the Genotype-Tissue Expression (GTEx) database to identify RNA molecules rich in UU dinucleotide repeats. By plotting the enrichment of UU dinucleotide repeats against female and male expression, researchers observed XIST as an outlier for being both specific to females and containing a high degree of UU richness. The group then probed for the nine-base motif, which was contained in about 300 RNAs in the dataset, but XIST was the only female-specific RNA with this motif. Considering female expression bias, total number of UU dinucleotide repeats, maximum UU richness, and expression levels in samples from the blood and tissues present in the GTEx database, Dr. Antiochos' group concluded that XIST is a top ligand for TLR7 expression.

The research group identified two sections of the XIST molecule to study further: XIST 1.1 and the A-repeat. XIST 1.1 contains the nine-base motif previously identified as a TLR7 agonist. Researchers demonstrated that the insertion of XIST 1.1 into healthy donor plasmacytoid dendritic cells (PDC) activated interferon expression; similar results were seen in a HEK-293 reporter cell line. A fluorescence anisotropy-based ligand binding assay demonstrated that XIST and a positive control interacted directly



with the TLR7 site in a similar fashion and with similar affinities. Thus, XIST 1.1 appears capable of binding to and activating TLR7 in primary cells and a reporter cell system.

Next, the research group examined the A-repeat. The A-repeat fragment of the XIST molecule is densely enriched with UU dinucleotide repeats, and, like the XIST 1.1 studies, researchers demonstrated that the A-repeat fragment appears capable of activating TLR7 in the reporter cell system and primary cells.

A subsequent study compared the potency of XIST 1.1 and the A-repeat fragment as TLR7 ligands and found the A-repeat to be the more potent agonist capable of generating an interferon response at a lower concentration. This finding provides evidence that the UU richness is likely a more important factor than the presence of the nine-base motif.

Loss of XIST Reduces Activation of TLR7

In the next study, the research group created cell lines with varying degrees of XIST knockout that culminated in a cell line with complete XIST knockout. RNA was isolated from the cells, and assays were used to test their ability to activate TLR7. The group found a dose effect of TLR7 activation based on the degree to which XIST had been removed from the transcriptome of the cells. The complete XIST knockout cell line activated TLR7 50% less compared to WT. RNA-Seq confirmed that XIST was the most important source of endogenous TLR7 ligands lost in XIST knockout mice.

XIST Expression in Patients with SLE

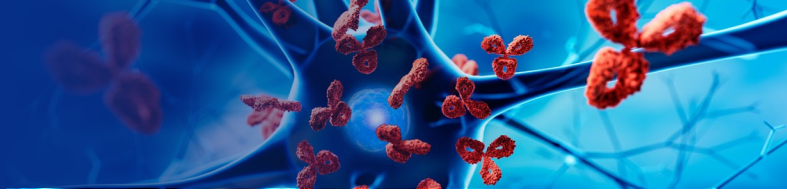
Dr. Antiochos' research group then used the RNA PrimeFlow assay to compare XIST expression in blood from healthy female controls and females with lupus. Peripheral blood mononuclear cells (PBMCs) from the lupus cohort had higher expression levels of XIST compared to the healthy controls. This expression level difference was most exaggerated in the B cell compartment, but T cells and monocytes from the lupus cohort also displayed a trend toward higher expression.

Next, the research group queried whether there was a relationship between XIST expression and lupus disease activity. They observed a trend toward higher XIST expression in PBMCs among patients with active lupus compared to patients with clinically quiet lupus. Additionally, the research group identified a positive correlation between XIST expression and the Systemic Lupus Erythematosus Disease Activity Index, a common measure of disease activity. Dr. Antiochos summarized that XIST appeared to be upregulated in the peripheral blood of patients with lupus compared to controls, and he noted a positive correlation between XIST expression and disease activity.

XIST Levels and Interferon Expression

By using a dataset with renal biopsies from patients with lupus nephritis, Dr. Antiochos' research group found a strong positive correlation between XIST and interferon expression in immune cells in the kidney. A possible explanation for this finding might be that XIST itself is an interferon-induced gene. However, cell lines that expressed XIST had no change in XIST levels after they were treated with interferons in vitro. Therefore, XIST is not induced by interferon and Dr. Antiochos surmised that XIST is more likely a driver of interferon expression.

Dr. Antiochos concluded by highlighting XIST as a TLR7 ligand and its role in X chromosome inactivation and autoantigen RNP interactions.



Panel Question and Answer

Moderators:

Stacy Ferguson, Ph.D., Chief of Autoimmune and Primary Immunodeficiency Diseases Section, National Institute of Allergy and Infectious Diseases

Marie Mancini, Ph.D., Program Director, Systemic Autoimmune Disease Biology Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Question 1: How will XIST research evolve over the next 3–5 years?

Speakers noted that this is an exciting time for XIST research and that there will likely be immense growth in its basic and clinical research. There will be opportunities to observe XIST functioning across different autoimmune diseases, to examine functions of other lncRNAs, and to examine existing datasets with new perspectives. Identifying subsets of patients based on various XIST phenomena and new therapies will be possible, as will opportunities for greater interdisciplinary collaboration.

Question 2: What research gaps need to be filled to accelerate progress?

Speakers noted that collaboration and communication is crucial to accelerating progress, and that engaging clinicians and creating hubs to promote interdisciplinary approaches will be key. There must be a balance between both fundamental and translational research. Funding dedicated to autoimmune diseases will also be critical.

Question 3: In lupus, is it thought that there is a defect in how XIST inactivates the X chromosome, or is there another trigger? What is happening in other cells of the body, outside of B cells? Since autoimmune diseases frequently co-occur, do the mice get any other diseases beyond lupus?

Dr. Anguera addressed the first part of Question 3, stating that both T cells and B cells have problems with X chromosome inactivation maintenance. XIST RNA does not go back to the inactive X chromosome as it should in peripheral blood cells with activated T cells and B cells. There is also a diversity of unique localization in cells. For example, neutrophils in females express XIST RNA, but XIST is not on the inactive X chromosome.

With regard to mice with lupus getting additional autoimmune diseases, Dr. Dou noted that her team assessed only for signs of lupus, so they cannot rule out that there may have been signs of other diseases.

Dr. Antiochos added that it will be important to study XIST expression and phenotypes in large cohorts over time, both in the preclinical and disease phases.

Question 4: While there are some male patients with extra X chromosomes who get lupus, there are males (XY) who also get lupus. How can this be studied?

The speakers emphasized the importance of recruitment in clinical trials and the challenge of recruiting male participants, particularly because the sex bias in autoimmune diseases is prominent. Because rheumatic diseases are so heterogenous, assembling a cohort can also be difficult. Lupus is impacted by multiple factors, not just XIST; for example, there is a strong genetic component in lupus.

Closing Remarks

Dr. Shanmugam thanked the speakers and moderators for their time and presentations. She highlighted the forthcoming "Updates on OADR-ORWH" sessions and the 8th Annual Vivian W. Pinn Symposium, and noted that Audience members can stay connected with OADR-ORWH via email subscription.

Speaker Biographies

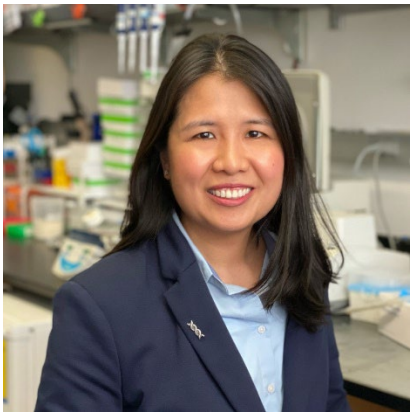
Montserrat Anguera, Ph.D.

Montserrat Anguera, Ph.D., is an associate professor of epigenetics in the department of Biomedical Sciences at the University of Pennsylvania (Penn), School of Veterinary Medicine. She is a member of the Epigenetics Institute, the Institute for Immunology, and the Institute for Regenerative Medicine at Penn. She also serves on the executive committees for various graduate groups and training grant programs across Penn.

Professor Anguera received her B.A. from University of California, San Diego, in chemistry and her Ph.D. from Cornell University in biochemistry and molecular and cellular biology. She completed her postgraduate studies at Massachusetts General Hospital/Harvard University where she developed an interest in X-chromosome inactivation. Her laboratory studies epigenetic gene regulation that underlies sex differences in development and disease. Her current research investigates how gene expression from the X chromosome is regulated in the immune system and how these mechanisms become altered in diseases exhibiting a sex bias, such as autoimmunity. Her lab discovered a novel and dynamic mechanism of X-chromosome inactivation maintenance specific to female lymphocyte activation and how perturbations in these pathways contribute to the autoimmune disorder, lupus.

She is currently a member of the Council for the Midwinter's Conference on Immunology and the NIH study section on Hypersensitivity, Autoimmune, and Immune-mediated Diseases.

Diana R. Dou, Ph.D.



Diana R. Dou, Ph.D., is currently a National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) K99 fellow in Dr. Howard Chang's laboratory at Stanford University. Prior to Stanford, she earned her B.S. with honors from the California Institute of Technology (Caltech) with double majors in biology and business, economics, and management. Dr. Dou received her Ph.D. in molecular biology at the University of California, Los Angeles, while working with Hanna Mikkola, M.D., Ph.D. Dr. Dou was introduced early to RNA biology as an undergraduate researcher studying synthetic modifications and nonviral, nanoparticle-based delivery methods of RNA in the laboratories of Mark E. Davis, Ph.D. and Scott E. Fraser, Ph.D., at Caltech. Dr. Dou developed a lasting interest in immune diseases while investigating immune defenses in viral infections as an Intramural Research Training Award (IRTA) postbaccalaureate researcher in Anthony S. Fauci, M.D.'s lab at NIAMS. In her graduate work with Dr. Mikkola, Dr. Dou sought to understand the developmental patterning of the hematopoietic stem cell (HSC), which is the multipotent progenitor for the immune system, and she showed that medial HOXA cluster gene expression demarcates definitive

human HSCs. Dr. Dou is currently investigating the involvement of lncRNAs and chromatin accessibility in autoimmune disease, and she recently discovered a novel role for the Xist ribonucleoprotein as a driver for autoimmunity underlying the sex-biased female preponderance for developing autoimmune diseases.

In addition to the NIAMS K99/R00 Pathway to Independence Award, Dr. Dou has been the recipient of the National Science Foundation Graduate Research Fellowship Program, International Society for Experimental Hematology New Investigator Dirk van Bekkum Award, and numerous departmental and institutional trainee awards throughout her career. In her future lab, she plans to continue her research with lncRNA complexes to understand how immune tolerance deteriorates into autoreactivity and disease from the perspective of lncRNA and epigenetic gene regulation.

Brendan Antiochos, M.D.

Brendan Antiochos, M.D., is a physician scientist in the Division of Rheumatology at Johns Hopkins School of Medicine. His primary research interest is the role of the innate immune system in the pathogenesis of rhematic disease. It has been known for decades that interferon is upregulated in many of these diseases, including systemic lupus erythematosus (SLE) and Sjogren's syndrome. Dr. Antiochos is interested in understanding the identity of specific endogenous nucleic acids and sensor-ligand interactions that are responsible for eliciting this response.

Dr. Antiochos also has a clinical interest in vasculitis, and he serves as the director of the Johns Hopkins Vasculitis Center. He received his bachelor's degree from Dartmouth College and his medical degree from Dartmouth Medical School. He completed his residency in internal medicine at Oregon Health & Science University and his rheumatology fellowship at Johns Hopkins University School of Medicine.