**W3112: Reproductive Performance in Domestic Ruminants**

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Administrative

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**Statement of Issue(s) and Justification:**

The W-112 Regional Research Project was established in 1970 to create a cooperative research group combining both basic and applied expertise to determine factors, and develop methods to improve fertility of domestic ruminants in the Western states. The philosophy and mission for the W-3112 project, established more than forty years ago, continues to be the guiding tenet of our group; that is, cooperative multi-state research, providing product and technique development and outreach for the benefit of animal producers in the Western region and beyond.

The project serves as a forum for the development and conduct of collaborative studies aimed at solving problems that limit the reproductive performance of domestic livestock. Scientists associated with the project collectively possess expertise required to discover basic physiological mechanisms and translate such new knowledge to the management of domestic ruminants. Some stations are best equipped to evaluate the applicability of their results in production situations. In contrast, other stations have the animal resources to test new treatment paradigms arising from the basic studies, but do not have the laboratory facilities (or modern equipment) necessary to perform the basic research studies. These circumstances create an ideal situation for our regional collaborative project. Renewal of the W-2112 Regional Research Project is crucial because interactions among scientists with a broad range of expertise are necessary for the discovery, translation, and transfer of new knowledge to the livestock industry.

Poor reproductive efficiency in domestic ruminants limits profitability and sustainability of animal production systems in the West and throughout the nation. Therefore, we seek to continue our work in this critical area. Participation in the project since its inception has greatly increased in scope and is now comprised of scientists located in the states of Alaska, Arkansas, Arizona, California, Colorado, Connecticut, Idaho, Illinois, Kansas, Louisiana, Maine, Mississippi, Missouri, Michigan, Minnesota, Montana, Nebraska, Nevada, New Mexico, North Dakota, Ohio, Pennsylvania, Texas, Utah, Vermont, Washington, and Wyoming. We believe the reproductive challenges important in the Western states and shared by other states are best addressed by combining the expertise and resources from all regions. The addition of leading reproductive biologists from states outside the West has increased the breadth and greatly strengthened the scientific expertise of the W-2112 (W-3112) project. Renewal of this multi-state project is essential to continue to provide a forum that stimulates the development of new hypotheses, conduct of new collaborative research projects, sharing of resources, and identification and testing of new methods to manage reproduction in domestic ruminants.

The livestock industry is a critical component of the agricultural industry in the states represented by scientists involved with the project. The dairy, beef, and sheep industries together contribute approximately $81.5 billion in farm receipts and an estimated overall production value of $192 billion. In addition, direct and indirect employment related to the production and processing of these animals or their products supports over 2.3 million jobs (Otto and Lawrence, 2002; Cryan, 2004; Shiflett, J.S. 2008). Over 64 percent of the nation’s breeding cows (beef and dairy) and 76 percent of the US sheep inventory exist in states represented by participating W-3112 scientists (USDA-NASS, 2012).

W-3112’s goals are consistent with the USDA 2010-2015 Strategic Plan’s Goals 1, 3 and 4. Specific objectives addressed by the project include **Objective 1.1** (Enhance rural prosperity), **Objective 1.3** (Support a sustainable and competitive agricultural system), **Objective 3.1** (Ensure U.S. Agricultural resources contribute to enhanced global food security), **Objective 3.2** (Enhance America’s ability to develop and trade agricultural products derived from new technologies), **Objective 4.1** (Increase access to nutritious food), and **Objective 4.4** (Protect agricultural health by minimizing major diseases and pests to ensure access to safe, plentiful, and nutritious food). Our primary stakeholders are farmers and ranchers in states represented by scientists participating in the project, but there is broad applicability of our work nation-wide. Our secondary stakeholders are the consumers of animal products that benefit from the reduced prices associated with efficient animal production systems. Our tertiary stakeholders are the citizens of communities whose economies are improved by their proximity to profitable and sustainable animal industries and that benefit from the multiplier effects these industries have on community economies.

Reproductive efficiency is widely regarded as the most limiting factor to profitability in animal production systems. Nowhere is this more evident than in the modern dairy industry. Beef producers also suffer as a result of delayed onset of puberty and extended postpartum anestrus, low fertility, and lighter calves at weaning. In the beef industry alone, the cost of infertility to U.S. producers was estimated to be over $1.06 billion annually (Lamb, et al., 2008). Sheep producers also miss out on the potential for added revenue by not realizing the genetic potential for lambing rates in their flocks. Finally, new challenges are faced by farms and ranches managing domesticated exotic ruminants whose reproductive physiology is relatively unknown.

Sub-optimal reproductive efficiency of domestic ruminants and feed costs associated with producing those animals are major obstacles to maintaining the profitability and sustainability of livestock production enterprises. Up to 70 percent of costs associated with producing viable offspring can be attributed to feed required to maintain their dams during gestation. Likewise, decreased fertility resulting from delayed onset of puberty, prolonged postpartum anestrous intervals, early embryonic mortality, and seasonality of breeding continues to limit production. One of the objectives of our work in W-3112 is to provide the scientific and technical expertise that will encourage development and application of science-based management tools to improve the productivity, efficiency, and profitability of livestock producers. In the current project plan we expect to increase our efforts to bring knowledge to producers helping them make decisions based on sound science while at the same time, expanding our understanding of factors that affect reproductive efficiency.

For the current project, research will be focused in four main areas: mechanisms of ovulation and potential causes of anovulation, establishment of pregnancy, fetal development/prenatal programing that affects fetal development, and male reproduction.

**Related, Current and Previous Work**

Many of the stations that are members of this collaborative agreement are located in the arid western states. Due to the relative paucity of vegetation in these states compared to those in other regions of the U.S., different management techniques are necessary. Therefore, most of the approaches to improve reproductive efficiencies of cattle and sheep in these regions will, of necessity, be different than approaches where these species are maintained in smaller pastures or in confinement as is the case with projects focusing on reproduction in North Central and North East regions.

Related, current and previous research by members of W-2112 (W-1112) is based on the premise that applied research experiments stem from a foundation of previous basic research studies. Studies reported herein, therefore, describe the discovery of mechanisms that regulate reproduction and the translation of those results into methods to improve reproductive performance in domestic ruminants. The list of research achievements, publications, and student theses that are the product of the collaborative work of members of the Project is extensive. During the last 5 year period, 333 refereed publications and technical bulletins and 6 book chapters were generated. In addition, a symposium of research findings was presented to a regional audience of extension educators at the 2015 Western Section American Society of Animal Science Beef Symposium in Ruidoso, New Mexico. Although it is not possible to detail each significant accomplishment, a summary of the major advances is provided below.

**Major Advances:**

***Biology of the Hypothalamic-Pituitary-Gonadal Axis.*** Estradiol induces the pre-ovulatory LH surge through genomic actions but the onset, duration and magnitude of the surge are controlled by non-genomic effects of estradiol on numbers of GnRH receptors. KiSS-1 peptide modulates LH secretion by regulating the secretion of GnRH without effects on the anterior pituitary gland and independent of the actions of estradiol and progesterone. Microarray analysis identified genes that are differentially expressed in the pituitary gland of cows during the transition from postpartum anestrus to estrous cycling. The higher frequency of GnRH pulses is associated with a higher content of kisspeptin in the hypothalamus during the breeding season, reflecting an increase in kisspeptin input to the preoptic area and mediobasal hypothalamus. Studies will be undertaken to stimulate onset of breeding activity during the nonbreeding season in sheep using anti-estrogens to block the hypersensitivity to estradiol that suppresses the rapid pulses of GnRH needed to promote ovarian activity.

A radioimmunoassay was developed allowing for the quantification of kisspeptin in the brain. The quantification of kisspeptin lead to the determination that kisspeptin (rather than GnRH) changes throughout the year in sheep brain and is likely responsible for seasonal differences in reproductive activity.

***Ovarian Biology and Follicle Development Research.*** Studies focused on vascular endothelial growth factors (VEGF) in ovarian development and follicle number demonstrated the importance of angiogenic VEGF isoforms on granulosa cell survival and follicle development. Three variants of the FSH receptor are produced at different stages of follicular development. Stable granulosa cell lines expressing specific FSH receptors were used to characterize precise roles for each receptor variant. It was determined differences in gene expression for the regulation of folliculogenesis are partially attributed to breed.

Cows with androgen excess have theca cells phenotypically similar to women with polycystic ovarian syndrome (PCOS). Gene expression of CYP17 and CYP11 are increased along with GATA6, a transcription factor which can upregulate both CYP17 and CYP11, causing excess androgen to be produced. Furthermore, granulosa cells from these androgen excess cows appear to be arrested in the cell cycle and do not proliferate appropriately since FSH stimulated cows with androgen excess have 50% reduction in number of granulosa cells in similar stage follicles. Thus, compromised granulosa cell function may retard appropriate oocyte development.

***Estrous Cycle, Physiology, & CL Function.*** Corpora lutea (CL) function is primarily dependent on number of theca and granulosa cells within the ovulatory follicle that luteinize following ovulation to form luteal cells. CL function is also dependent on the luteal microenvironment which is affected by immune cells that also secrete cytokines. Studies using microarray analysis of CL collected 4, 2, and 1 hour after Prostaglandin F2-alpha (PGF) administration demonstrated that PGF induces expression of immune regulatory genes in vivo. Of particular interest was the prediction of IL-17 signaling and NFκB activation. It was determined that IL-17, but not PGF, directly activated NFκB signaling in luteal cells and IL-17, in combination with TNF and PGF, reduced LH-stimulated progesterone secretion. Thus, PGF induced IL-17 and cytokine activation of NFκB signaling contributes to the dampening of progesterone synthesis by inhibiting LH-stimulated progesterone secretion which appears to be critical during CL regression in beef cows. Additional studies evaluated the expression of interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), IL12, IL10, chemokine ligand twelve (CXCL12), and chemokine receptor four (CXCR4) in CL tissue from non-pregnant (NP) compared to pregnant ewes. An increase in Th1 cytokines and CXCL12 in CL from pregnant ewes was observed. The CXCL12/CXCR4 signaling may play a role in regulating the cytokine milieu in the CL thereby influencing CL integrity and function. This is especially important because CL function is obligatory to pregnancy establishment and CL destruction is obligatory during the estrous cycle to allow a subsequent cycle and another opportunity to establish pregnancy.

Cows with androgen excess also have sporadic anovulation (do not ovulate two consecutive estrous cycles) and appear to have lower sex hormone binding globulin which may be due to altered metabolic function related perhaps to decreased estrogen carrying capacity in the blood. These cows also have 17% reduction in calving rate and appear to develop persistent follicles. Furthermore, calves from androgen-excess cows wean approximately 26 lbs heavier which may be due to excess androgens during gestation. Alternatively, this compensatory growth could have developed due to feeding high protein supplements either during gestation or early life and be a result of prenatal/neonatal programming. Current efforts include characterization of liver steroid metabolism and CL response to PGF of androgen excess and normal cows. The incidence of androgen excess cows within herds has been as high estimated to be as high as 10%.

***Oocyte-Embryo-Uterine Physiology.*** An oocyte/embryo specific gene (JY-1) was identified. This gene regulates cumulus expansion, is dependent on the presence of additional oocyte-secreted factors, and is potentially mediated in part by PGE2 and genes related to stabilization of the hyaluronan-rich extracellular matrix. Cumulus expansion and progression to metaphase II, fertilization, and cleavage rates following IVF are reduced following siRNA mediated ablation of JY-1 in oocytes. Such effects can be rescued by addition of recombinant JY-1 to culture medium suggesting an obligatory role for JY-1 in pregnancy establishment. Additional studies using siRNA demonstrated an obligatory role for follistatin in regulation of early embryogenesis. A negative association of cumulus cell cathepsin expression with oocyte competence and development to the blastocyst stage was established. Treatment with a cathepsin inhibitor during meiotic maturation enhanced blastocyst development.

Reciprocal embryo transfer and duration of proestrus studies demonstrated that effects of ovulatory follicle size on fertility may be manifested through effects of estradiol on the oocyte and uterus. Preovulatory concentrations of estradiol did not influence expression of ISG-15, MX-2, embryonic CSH-1 or IFNt on d 17.5 of gestation or the estrous cycle in cattle. However, estradiol tended to increase the expression of endometrial nuclear progesterone receptors, and is essential in the peri-ovulatory period for subsequent successful embryo implantation in the cow. It was demonstrated the embryo induces endometrial expression of an uncharacterized gene referred to as decidual restricted gene 1 (*Drg1*). *Drg1* may be required for the establishment and maintenance of pregnancy. Endocrine effects of IFNt on the CL between Days 13 and 14 of pregnancy in the ewe may protect the CL through mechanisms complementary, yet independent to IFNt’s paracrine effects on the endometrial oxytocin receptor pathway. Infusion of IFNt into the uterine vein in non-pregnant sheep induced IFN-stimulated genes in the CL.

Conceptus elongation coincides with the expression of peri-attachment factor (PF). The use of lentiviral-mediated RNA interference demonstrated that PF is required for normal conceptus elongation and survival.

The roles of fibroblast growth factors (FGFs) on oocyte competency and pregnancy establishment were elucidated. Embryo development in vitro is improved by supplementing FGF2 or FGF10. At least four FGF receptors (FGF-R) reside in pre- and peri-attachment bovine conceptuses. Conceptuses express at least three candidate FGFs during elongation. FGF2 may signal through a downstream PRKCD to regulate IFNt expression in bovine trophectoderm and promote embryonic endoderm development. Blocking FGF receptor activity with specific kinase-domain inhibitors did not affect blastocyst formation in vitro but compromised subsequent development and function. Treatment with FGF receptor inhibitors during maturation limited subsequent embryo development.

A highly specific radioimmunoassay was developed for ovine IFNT, which has different levels of detection in uterine flushing compared to serum. Unfortunately, this ovine assay may not recognize all forms of bovine IFNT and for this reason a new radioimmunoassay and ELISA for IFNT in bovine tissues and fluids will be developed.

The roles of chemokine ligand twelve (CXCL12) and its receptor, chemokine receptor four (CXCR4) exert during early gestation was investigated by delivering a CXCR4 antagonist directly into the uterine lumen during embryo attachment and initial placentation in ewes. A decrease in VEGF was noted in caruncle tissue from treated ewes and alterations in expression of various cytokines were observed. Impaired CXCL12/CXCR4 signaling may lead to poor pregnancy outcomes, such as impaired trophoblast attachment and compromised embryonic growth. A better understanding of CXCL12/CXCR4 signaling during early gestation, may lead to novel applied techniques to improve embryo survival during early gestation in livestock.

***Testicular Physiology.*** Studies were conducted to evaluate bovine testis and spermatogonial stem cell (SSC) xenografts. Effects of VEGF on testis development and spermatogenesis were evaluated to elucidate factors critical for SSC differentiation and maintenance. Using magnetic activated cell sorting technology, Thy 1 was identified as a conserved marker of SSC. Peritubular myoid cells and testosterone are important components of the SSC renewal in the adult testis. Three angiogenic and three tissue growth factors that may improve efficiency of ectopic testis tissue grafting were identified. In conditional KO mice models, it was determined VEGFA angiogenic isoforms appear to enhance SSC renewal while antiangiogenic isoforms cause either apoptosis or allow for SSC differentiation into later stage germ cells. This information will be applied to bovine or ovine systems to determine effects on stem cell populations in domestic livestock.

Active immunization of ram lambs against inhibin increased sperm production 26%. The magnitude of increase in sperm production was directly proportional to the inhibin antibody titer. Inhibin appears to be involved in regulation of the number of primary spermatocytes in males. Based on DNA parent verification, variation in offspring proportion that is not correlated with scrotal size exists in serving capacity or unknown fertility measures of bulls in multiple sire breeding herds. Novel biomarkers on sperm associated with fertility have been characterized and removal of abnormal sperm from the ejaculate of bulls prior to extending and freezing of semen for artificial insemination (AI) increased pregnancy rates in cattle.

***Uterine-Placental-Fetal Nutritional Interactions****.* Intrauterine growth restriction (IUGR) is associated with metabolic complications that limit performance in offspring. These studies indicate that developmental adaptions to conditions resulting in IUGR permanently impair insulin-producing pancreatic β-cells. Growth-restricted fetuses have decreased β-cell mass and reduced insulin secretion capacity. A sheep model of placental insufficiency-induced IUGR has similar deficiencies in β-cells. The aim of these studies was to elucidate mechanisms responsible for β-cell dysfunction first by determining gene expression of the islet exome from IUGR fetuses. Near term placental insufficiency-induced IUGR (established by environmental hyperthermia) islets were isolated. Isolated RNA was sequenced with Illumina hiseq2500 and analyzed using the Tuxedo Suite. Reference annotation based assembly using both bovine and ovine genomes identified differentially expressed transcripts. RNA transcripts were queried for enrichment and modeled to functional pathways previously defined. In IUGR islets, 197 transcripts were upregulated and 493 were downregulated using the ovine genome reference. For the bovine genome reference, 425 transcripts were upregulated and 652 downregulated. The two lists were combined for pathway analysis. For downregulated genes, pathways over-represented were cytokine-cytokine receptor interactions (4.8%) and chemokine signaling pathway (2.3%). IUGR islets had reduced expression of CCL2, CCL3, CCL4, CCL5, CCL21, CXCR4, and a portion of the interleukin family of cytokines including IL-1β, IL-8, and IL-6. IUGR islets expressed greater concentration of CXCL12, IL-6R and GPR75. Placental insufficiency-induced IUGR fetuses have decreased pro-inflammatory chemokines and cytokines that regulate homeostatic processes in the islets. Previous findings indicate IUGR suppresses the inflammatory response in postnatal animals and transiently alters neonatal islet T-helper cells. However, findings also indicate a role for cytokines in β-cell dysfunction because the CXCL12/CXCR4 axis promotes pancreatic β-cell growth and genesis in human and rodent systems.

Fetuses from ewes obese at conception and continuously fed above NRC requirements throughout gestation exhibit marked increases in glucose and fatty acid uptake and adiposity by mid-gestation. At birth, lambs from obese dams had greater body fat and reduced pancreatic function, and were prone to overeating and obesity. These effects remain evident in the second generation in absence of maternal obesity. Second generation males and females remain insulin resistant. However, females, but not males, are insulin resistant in absence of obesity or a feeding challenge. Changes in liver production of IGFBP-3 in the offspring may be partially responsible for growth and adiposity differences noted in offspring from obese mothers.

Impaired placental function was a primary cause of fetal growth restriction. Undoubtedly the placenta plays a major role in determining fetal growth rate. This is obvious from its role as the interface between the maternal and fetal systems, providing for nutrient transport to the fetus and waste removal from the fetus. Additionally, the placenta is a rich source of hormones and growth factors that likely impact the fetus, mother or both. The existence of the placental lactogens (PLs) has been known for over 50 years, and it has been hypothesized that human and sheep PL modulate maternal and fetal metabolism. Lentiviral-mediated transgenesis within the sheep placenta was used to assess the importance of PL in fetal growth regulation at mid (50 d) or late (135 d) gestation. A 50% reduction in oPL mRNA and a 38% reduction in placental oPL protein was achieved using the “knockdown” model. This reduction in oPL was associated with reduced fetal liver (41%) and body (32%) weight. Fetal liver insulin like growth factor (IGF)-1 and -2 mRNA concentrations were reduced 82% and 71%, respectively, with a 62% reduction in umbilical artery IGF-1 concentration. There was a similar reduction in IGFBP-2 (74%) and IGFBP-3 (81%) mRNA. Thus, *in utero* nutrition has epigenetic effects on the offspring that influence metabolic and production efficiency of livestock.

***Statistical Methodology.*** Statistical methodology and software tools were developed for the appropriate and meaningful analysis of gene expression data, primarily to advance discovery of genomic mechanisms influencing embryo development. A statistical measure JED (Jackknife Expression Difference) was developed to assess the level of numerical dependence induced by various preprocessing methods for gene expression data. Based on this measure, researchers using the Affymetrix platform were given greater confidence in the statistical properties of common preprocessing methods such as RMA. A statistical framework and software package (mvGST, for multivariate gene set testing) was developed to identify differentially active (up or down) Gene Ontology terms based on gene-level significance tests from any experimental design and any transcriptomic platform, used for non-model organisms, including across multiple stages of embryonic development. This mvGST package includes a SFL (Short Focus Level) statistical approach developed to limit the probability of any false positives in testing Gene Ontology terms. This approach is more powerful than other approaches while also being computationally 15,000 times faster. Taken together, these statistical approaches applied to an RNA-Seq study have allowed greater statistical power and computational efficiency in confirmatory identification of biological processes that are differentially active between embryos derived from different assisted reproductive technologies at specific stages of development, while making fewer Type I errors.

The statistical issues originally motivated by this RNA-Seq study were found to have extensions (with multiple hypothesis testing) for quantitative trait mapping in natural populations. This limitation lead to the development of a two-stage LD-based QTL mapping approach that is more powerful and computationally much faster than current methods. While these QTL methods have yet to be applied to reproductive genetics data, they deserve mention here due to their origins in this project.

***Behavior and Stress.*** Objective identification of temperament, and the coupling of stress-responsiveness with immune function, provided impetus to develop methods to select for calm, stress-tolerant, immune-competent, disease-resistant cattle. Exit velocity from a standard squeeze chute was indicative of stress perception in cattle and can be measured reliably as early as 21 d after birth. Calf exit velocity was associated with serum cortisol concentrations but not with temperament of its dam.

Prenatal stress may program bull calves to function more normally when presented with stressors later in life. When stressed at maturity, the prenatally stressed bulls had more frequent LH pulses than control bulls. This research resulted in the development of an EPD for docility for Brahman cattle used by the American Brahman Breeders Association.

Dopamine synthesis and release in the ventral tegmental area (VTA) of the brainstem is credited for pleasurable aspects of mating activity and is central to the reinforcement and repeated expression of that behavior. Following exposure to a putative sexual stimulus, inactive rams had fewer dopamine-synthesizing neurons in the VTA than sexually active rams. Lack of sexual interest in low sexually performing rams may be partially a result of decreased dopamine synthesis in the VTA leading to a less pleasurable experience and attenuated reinforcement of sexual behavior.

***Fertility,*** ***estrous synchronization and AI.*** The optimal timing, dose, and route of administration of progesterone, PGF, and GnRH to induce ovulation or estrous cycles was investigated and a protocol developed that increased success to AI by more than 10% in both heifers and cows.

 A genome-wide association study was conducted using the EMMAX mixed-model association test to compare genomic differences related to cow fertility. These studies indicate that conceptus growth is not compromised in sub-fertile heifers up to d 14 after estrus. Observed differences in capacity for pregnancy success is manifested between days 14 and 28 when pregnancy recognition signaling and conceptus implantation must succeed for the establishment of pregnancy. Genetic markers identified in this study may be useful to select animals for fertility and enhance our understanding of the physiological pathways governing pregnancy success and loss in mammals.

A number of circulating exosomal-derived miRNAs were identified that differ in abundance in non-pregnant and pregnant cows. Future studies are essential to confirm their suitability as biomarkers for assessment of embryonic presence and viability in cattle and facilitate characterization of mechanisms associated with pregnancy failure.

Late embryonic mortality (> d 28 of gestation) has been reported in both beef and dairy cattle and may vary from 3.2 to 42.7%. The majority of these losses occur around the time that placentomes are beginning to form (~d 35-40 of gestation). Pregnancy associated glycoproteins at day 31 of gestation may be a potential biomarker of late embryonic mortality and a possible model to help understand this period of pregnancy loss in cattle.

 *Disease, immune function.* Epizootic bovine abortion (EBA) is the cause of late-term abortions in beef cattle grazing within regions endemic for the pajahuello tick vector and can result in abortion rates reaching 60%. The pathogen causing EBA as an intracellular bacterium in the class *Myxococalesk* transmitted through the tick vector. In affected cattle, immunity to subsequent EBA induced abortions occurs but the duration of this protective effect is undetermined. Ongoing efforts indicate that cows are unlikely to abort if exposed to the pathogen in the year subsequent to abortion and that some protection is evident on a herd-wide basis in the second year. A SCID mouse model was developed to serve as a method to raise the etiologic agent of EBA. This allowed for the consistent transmission of the disease with quantifiable amounts of agent. Ongoing research using the mouse grown agent as a source of antigen to vaccinate cattle herds has shown to be a safe method of protection against EBA when administered to non-pregnant cows and heifers. Further research is ongoing but preliminary studies have shown the vaccine provides nearly 100% protection in cows and heifers tested.

Bovine viral diarrhea (BVDV) is a widespread problem that can result in abortions, stillbirths, and birth of weak and chronically sick calves that are carriers of the disease. Cows exposed to the virus during early gestation give birth to persistently infected calves. Persistent infection with ncpBVDV induces a chronic type I interferon response. Because type I interferon acts as a growth suppressive cytokine, this long-term upregulation may contribute to the IUGR observed in persistent BVDV calves and in other viral infections during pregnancy. Through clarifying how BVDV persists, better biocontainment (detection) and treatment (antivirals) strategies can be implemented. Identification and selection of breeding animals resistant to viral infection will also be imperative to control this insidious disease.

**Objectives:**

Discover mechanisms within five years that have potential to translate into applicable biotechnologies to improve reproductive efficiency in domestic ruminants. While we have independent objectives, it is the work of the whole and the culmination of each objective working together that allows for a greater understanding of reproductive physiology in domestic ruminants. The W2112 (W3112) project has a long history of interdisciplinary and long-standing collaborations that underpin our success. In short, each objective, albeit independent, supports and enhances the other objectives. Our Specific Objectives include:

1. Further understand mechanisms of gonadotropin synthesis and release to improve management of reproductive behavior, the reproductive cycle, gamete development and the ovulatory event.
2. Determine the interaction of growth factors and steroid production on gonadal function, and utilize this knowledge to improve gamete quality and develop technologies to mediate infertility.
3. Improve management of reproductive cycles through increased understanding of follicle recruitment, ovulation and corpus luteum development.
4. Increase knowledge of mechanisms that allow for the establishment of pregnancy. Further understanding the interface of the reproductive and immune systems will allow for the development of technologies that target the immune system decreasing the incidence of early embryonic/fetal loss.
5. Increase the understanding of communication and nutrient flow between the embryo/fetus and the dam. This understanding would improve fetal health outcomes and adult wellbeing, and would be important for the optimization of livestock production goals.

**Methods:**

W-2112 (W3112) collaborators share a common interest in developing methods to optimize reproduction in domestic ruminants but differ in regards to expertise, laboratory facilities, availability of research animals, and basic or applied approaches to research. This combination of abilities provides unique opportunities to discover and translate scientific information crucial for the development of methods to optimize reproduction in domestic ruminants. Examples of such collaborative efforts follow in a later section.

Presented below are studies that will be conducted in the areas of: mechanisms of ovulation, establishment of pregnancy and placental development, and fetal development and male reproduction. The collaborations among states are stated with each project.

***Mechanisms of ovulation (Objectives a, b, c)*.**  A population of cattle with excess androgen (A4) in follicular fluid of dominant follicles, with reduced sex hormone binding globulin (SHBG), that are either chronic or sporadic anovulatory will be utilized to determine how inflammation, metabolism, and steroidogenesis disruption results in anovulation. These cows have elevated markers for inflammation, liver damage and androgen excess in theca cells with less response to FSH in granulosa cells and also have a 17% reduced calving rate. In this project, *scientists from Nebraska, New Mexico, Mississippi, Colorado, and Connecticut* will identify alterations in liver enzymes and liver function, gonadotropin secretion and function, metabolic function (muscle and fat), to determine if these are similar phenotypes to women with metabolic syndrome, polycystic ovary syndrome (PCOS), and type II diabetes as well as address how

A4 cows might be identified in producer herds to either select against and/or develop unique strategies to enable reproductive success (capitalizing on the 26 lbs. increased weaning weight).

To mitigate pregnancy loss in cattle, mechanisms by which ovulatory follicle size (indicative of estradiol production and follicle maturity) influence oocyte maturity and uterine receptivity for pregnancy will be investigated. Intra-follicular mechanisms may include differential expression of transcripts from follicular cells and oocytes of cows induced to ovulate mature and immature follicles compared to follicles allowed to progress toward final stages of spontaneous ovulation.  Preliminary evidence has shown that peri-ovulatory estradiol is critical to implantation of the bovine conceptus. Differences in the transcriptome of cumulus cells and oocytes, and follicle wall collected from dominant bovine follicles that differ in physiological maturity following a spontaneous or GnRH-induced gonadotropin surge will be determined.  Finally, microRNAs derived from exosomes of maternal serum will be utilized to identify potential markers of pregnancy and early embryonic mortality in cattle. *Scientists from Missouri, Montana, and Kentucky* will collaborate on this project with comparisons to the androgen excess model from the previous project to determine how less estrogen may contribute to the ovulatory process with *scientists from Nebraska, New Mexico, Mississippi, Colorado, and Connecticut.*

Environmental toxins including phthalates are ubiquitous chemicals that can contaminate many products including animal feed. In women, phthalate exposure is associated with early menopause, decreased hormone levels, and early pregnancy loss. Because ingestion of polluted feed is a source of phthalate exposure for production animals, understanding the mechanisms by which phthalates interact with the female reproductive system will be beneficial to women as well as production animals. As such, the impact of environmental toxins in reproductive biology addresses all objectives. *Scientists from Nebraska and Arizona* will collaborate on this project.

Application of reproductive technologies is central to adoption of practices and improved reproductive performance. The relationship between additives and nutrients fed during the transition period and early postpartum follicular development and uterine health in dairy cattle will be determined. Specifically the effects of rumen-protected methionine and choline supplementation on follicular development and vaginal discharge in the Holstein cow will be determined. *Scientists at Miles City Montana, New Mexico State, Mississippi State, North Dakota State, Louisiana* will collaborate on this effort*.*

***Male reproduction (Objective a, b).*** Studies will be conducted to understand how the angiogenic and antiangiogenic isoforms of VEGFA may be critical for spermatogonial stem cell (SSC) renewal. These studies are important to translate studies in conditional knockout mice to beef calves to further develop tools that enhance spermatogenesis. Experiments to isolate SSCs from the bovine testes will be essential to identify factors that may aid stem cell renewal. PRAMEY identified as a biomarker for sperm quality will be used to analyze semen collected from musk ox, reindeer and beef bull semen. Managerial factors associated with fertility in peripubertal beef bulls and reindeer will be evaluated by assays using fecal testosterone. The neuroendocrine control of the expression of sexual behavior will be continued. These studies are important to identify high libido males, but also determine the neural pathways that may limit the expression of sexual behavior. *Scientists from Nebraska, Washington State, Montana, Missouri, Penn State, Kansas State, Wyoming and Alaska* will participate and collaborate on these projects*.*

***Behavior and Stress (Objectives a, b)***. Research efforts in effects of temperament and stress responsiveness on reproduction and performance of cattle will be continued. How stress during gestation influences the epigenome will be determined. The evaluation of calves sired by prenatally stressed bulls and calves from prenatally stressed cows will determine if these DNA methylation changes are present in the second generation.

Studies will determine physiological mechanism(s) by which the biostimulatory effect of the male influences metabolic profiles of hormones to accelerate the reproductive neuroendocrine-endocrine cascade culminating in the resumption of ovulatory cycles in anovulatory females. A nuclear magnetic resonance (NMR) library will be established for ewes and will be useful to determine metabolic and hormonal profiles in different reproductive states. The neuro-endocrine control of ram reproductive behavior will be continued. Differences in neuropathways which cascade from sexual interest to mating will be identified. *Scientists from Montana, Texas and Wyoming* will collaborate on these projects*.*

***Establishment of Pregnancy (Objective d).***Pregnancy failures are common in cattle, and miscues between the uterus and embryo underlie many of these failed pregnancies. The overall goal of this work is to better understand the physiologic, endocrine, immune, cellular and molecular mechanisms that control establishment and maintenance of pregnancy so that strategies to minimize pregnancy losses can be conceived and tested. An assay to quantify interferon-tau (IFNT) in bovine fluids and tissues will be developed and used to detect release of INFT from the conceptus and presence in bovine fluids such as uterine luminal flushings and serum. This assay will be used to help provide insight into the timing and cause of early embryonic loss. The role of IFNT on sustainability of the ovine corpus luteum during maternal recognition of pregnancy will also be examined and may help identify high and low fertility cows. Likewise, use of pregnancy specific microRNAs mentioned in a previous effort will aid in characterization of early pregnancy loss. The influence of other chemokines, their receptors and subsequent signaling will also be conducted in pregnant sheep to investigate their functions during implantation and placental development. The use of specific inhibitors of CXCR4 to elucidate the role of CXCL12/CXCR4 in embryo attachment and subsequent placentation will be continued. Additionally factors affecting blood flow, microRNA and development of the placenta will be conducted with implications on early pregnancy and embryonic mortality.

While increasing knowledge of mechanisms establishing pregnancy and enhancing understanding of the interface of reproductive and immune systems, it is important to note the intimate association of CL function and maintaining pregnancy. Function of CL is dependent on a closely regulated relationship between cells comprising the CL, which regulate luteinization, steroidogenesis, and angiogenesis and these cells are often regulated by immune cells and their products (i.e. cytokines). Research during estrous cycles has yielded valuable information on cytokine functions in the CL, but the role of immune cells in CL during early pregnancy is lacking. Investigation of cytokines in CL function is underway and similar to roles of CXCL12-CXCR4 signaling at the fetal maternal interface, this chemokine axis is involved in CL function also. As noted for IFNT influencing CL sustainability, it appears other cytokines at the fetal maternal interface are active in the CL as well. These studies underscore the importance of understanding the interface of the reproductive and immune systems to decrease early embryonic loss in the uterus and CL. *Scientists from Colorado State, Missouri, Montana, Kentucky, North Dakota State, Mississippi State, New Mexico and Nebraska* will lead this effort.

***Fetal Development (Objective e).*** The uterine environment influences adult health and wellbeing of the offspring. Nutrient availability during gestation is central to the production of healthy offspring and is delivered by the placental vasculature. Thus, studies to determine how neuroendocrine mechanisms influence placental blood flow in late pregnancy are planned. It is well known that stress has adverse effects on fetal outcomes and these effects may have transgenerational influence through the epigenome.

Studies to determine the mechanisms by which poor maternal nutrition during gestation affects offspring growth and health will be continued.  Experiments will primarily focus on changes in muscle, fat, bone, and organs involved in metabolism (pancreas, liver, heart). Altering specific gene expression within the placenta, using lentiviral-mediated transgenesis will help determine the impact of diminished placental lactogen expression throughout gestation elucidating its role in fetal growth.

The fetus can experience stress from many different mechanism including nutrient lack or overabundance, heat, as well as maternal temperament. These stresses influence fetal growth and often result in growth restriction. Insulin regulation and placental function appear to be a common theme to regulate growth. It is important to identify mechanisms of fetal growth to test the efficacy of treatment to correct developmental changes in chronically nutrient deprived fetuses. Again, highlighting the interdependent nature of our objectives, results gleaned from “*Objective d*” are closely associated with “*Objective e*.” *Scientists from Arizona, New Mexico, Connecticut, Colorado State, North Dakota State, Montana, Mississippi State, Nebraska, Texas and Wyoming* are involved in leading these investigations*.*

***Collaboration between Stations.*** Project members meet annually to present results of completed studies, review the progress of on-going work, discuss industry issues and plan and coordinate the initiation and collaboration of new studies for the upcoming year(s). We have created a network of collaborating scientists focused on improving the fertility of domestic ruminants in the West and throughout the nation. The founding members of the W-112 Regional Research Project established a tradition of cooperation that the current members strive to continue. Indeed, in this era of instant and direct communication, cooperation and collaboration has never been greater or more significant. The extent of collaboration between stations is extensive and may best be described by providing examples of collaborative projects.

Perhaps more important is the unrestrained exchange of advice and information that occurs at the annual meeting and in countless telephone and email conversations that occur during the interval between meetings. Jointly, the members of this project constitute a vast reservoir of experience, knowledge and technical expertise that is an invaluable resource for all members of the project. Established members of the group work together to help mentor and guide junior faculty members (eg., invite them to present seminars at their institution, act as reviewers for manuscripts, act as external reviewers on promotion and tenure files, and enhance collaborative research efforts). Sharing of course notes for Endocrinology, Physiology and Anatomy, and Reproduction courses has been a major teaching aide for new members along with ways to develop assessment of learning in courses. Finally, members work together to enhance graduate education by identifying superior students and help to place them in member labs that best fit the student’s career goals and by hosting students from collaborating labs.

Specific collaborations are discussed within each project; however, a compiled list of stations that have plans to work on specified objectives is presented below:

Discover mechanisms within five years that have potential to translate into applicable biotechnologies to improve reproductive efficiency in domestic ruminants. Specific objectives include:

1. Further understand mechanisms of gonadotropin synthesis and release to improve management of reproductive behavior, the reproductive cycle, gamete development and the ovulatory event.

*Nebraska, New Mexico, Mississippi, Colorado, and Connecticut, Missouri, Montana, and Kentucky, Arizona, Miles City Montana, North Dakota State, Louisianna, Washington State, Penn State, Kansas State, Wyoming, Texas and Alaska.*

1. Determine the interaction of growth factors and steroid production on gonadal function, and utilize this knowledge to improve sperm and oocyte quality and develop technologies to mediate infertility caused by gamete production and ovulation.

*Nebraska, New Mexico, Mississippi, Colorado, and Connecticut, Missouri, Montana, and Kentucky, Arizona, Miles City Montana, North Dakota State, Louisianna, , North Dakota State, Louisianna, Washington State, Penn State, Kansas State, Texas, Wyoming and Alaska.*

1. Improve management of reproductive cycles through increased understanding of follicle recruitment, ovulation and corpus luteum development.

*Nebraska, New Mexico, Mississippi, Colorado, and Connecticut, Missouri, Montana, and Kentucky, Arizona, Miles City Montana, North Dakota State, Louisianna.*

1. Increase knowledge of mechanisms that allow for the establishment of pregnancy. Further understanding the interface of the reproductive and immune systems will allow for the development of technologies that target the immune system decreasing the incidence of early embryonic loss.

*Colorado State, Missouri, Montana, Kentucky, North Dakota State, Mississippi State, New Mexico and Nebraska*

1. Increase the understanding of communication and nutrient flow between the fetus and the dam. This understanding would improve fetal health outcomes and adult wellbeing, and would be important for the optimization of livestock production goals.

*Arizona, New Mexico, Connecticut, Colorado State, North Dakota State, Montana, Mississippi State, Nebraska and Wyoming*

**Measurement of Progress and Results**

**Outputs:**

* The primary output from the project members is peer-reviewed, scientific works including abstracts, publications, and presentations that represent unique contributions of new knowledge to the fields of reproductive biology. These results fill critical gaps in our knowledge regarding the reproductive physiology of ruminant animals and facilitate the development and implementation of management strategies designed to optimize reproduction.
* Data generated through the W2112 project has yielded necessary and essential data used in many grant proposals to different agencies. Collaborative research activity carried out through the W2112 regional project has been leveraged and has resulted in > $18.4 million dollars in grant funding to participating AES.
* During the W2112 project more than 100 undergraduate students received research training with approximately 50 MS and 20 PhD students being granted degrees through projects partially initiated with the W2112 project.
* Research findings of W2112 were presented to a regional audience of livestock producers at the 2015 Beef Symposium at the Western Section of American Society of Animal Science (WSASAS) in Ruidoso, NM. A similar presentation is planned for the sheep symposium at the combined WSASAS at Fargo, ND in 2017.
* Application of new knowledge to improve reproductive performance which sustain rural populations and increase food security is always the ultimate goal. However, how the application of basic knowledge gained today will be applied is not always clear. It is, however, important to understand basic mechanisms in hopes that adoption of practices will improve production efficiency. Many of these practical implications are presented in state publications, university extension guides, and Western Section Animal Science Proceedings. State publications (eg. Nebraska Beef Report is available at extension meetings, on Nebraska Beef Website (Beef.unl.edu)) are utilized by producers as well as consultants. Extension educators also have informative podcasts available for producers and consultants. Furthermore, states may also have a monthly newsletter (eg. Nebraska has BeefWatch also available on University Beef Website- <http://beef.unl.edu/> and information available on the Livestock Range Research Laboratory, Miles City, MT website <http://www.ars.usda.gov/main/Docs.htm?docid=16665>) .

**Outcomes or projected Impacts:**

It is difficult to project with certainty the outcomes and impacts of the project because of the long-term nature of many of the basic studies. Regardless, fulfillment of the objective should lead to the development and application of methodologies to improve animal health, well-being, and reproductive efficiency of domestic ruminants in the short-term. The impact those methods have on the sustainability of livestock production systems will depend on their impacts on quantitative measures of reproductive performance including: days open, services per conception, pregnancy rates, birth of healthy offspring, age at puberty, and lifetime productivity. Examples of monetary impacts of selected outcomes include:

The identification of beef and dairy females that are less fertile due to either genetic or prenatal development (nutrition interacting with genetics) may allow for sorting these females off the breeding herd or selection against these females for herd replacements. It may also allow for different treatments during gestation to ensure that less of these females are developed in the herd. Currently, it is estimated that sub-fertile females comprise 10% of the national cow population. The economic impact of even reducing infertile females by 5% overall in the US would allow for a reduction in losses of approximately 12 million dollars annually. This moderate estimate would be even more dramatic in dairy animals.

* The development of a vaccine for Epizootic bovine abortion (EPA) is projected to save beef producers in California alone an estimated $10 to $15 million annually.
* Decreasing embryonic mortality in beef and dairy cows of just 5% would result in an estimated savings of $25 million annually to beef and dairy producers.
* The economic impact of BVDV was projected to range from $15.33 to $20.16 per cow calving. Hence, the development of methods to control this disease would result in an annual savings of $481 to $632.5 million for U.S. cow-calf producers.
* Identification of rams with high libido would increase producer profitability by decreasing the number of rams needed during the breeding season and increasing the rate desirable genes are incorporated into a flock while decreasing the risk of non-pregnant ewes.
* Timing and intensity of environmental stresses is crucial to subsequent production traits in livestock. Although nutrient stress experienced during gestation leads to glucose dysregulation in adult offspring, transportation stress experienced in utero is protective against stress experienced later in life.

It is important to recall that the net calf crop for the U.S., based on number of breeding cows that calve annually, was estimated to be 72.7% (Bellows and Lammoglia, 1996). In terms of calves alone, this equates to an annual loss that exceeds $5.5 billion. Categories identified with these losses were; animals that failed to become pregnant by the end of the breeding season (14.6%), losses during gestation (1.6%), losses at or near parturition (5.9%), and losses from birth to weaning (5.2%). Although we are unaware of comparable data for other species, it is reasonable to speculate similar losses occur in sheep, dairy and other ruminants. Because of the magnitude of these losses, we expect research conducted by members W-2112 (W-3112) will continue to lead to new innovations increasing the profitability and sustainability of livestock production enterprises.

**Milestones.**

* A producer symposium on sheep reproduction will be presented prior to the termination of the project (2021) to facilitate the transfer of new knowledge and reproductive management protocols that have been elucidated from research conducted by W-3112 scientists while providing a venue for producers to influence research priorities for W-3112 researchers.
* Members of W3112 project will be involved with organizing the combined society ASAS-SSR Reproductive Symposia to commemorate the 50th anniversary of SSR at their annual meetings in 2017.  It is expected that select members of the W3112 project will present at that symposia. This is an opportunity to provide outreach to other reproductive biologist in two important yet distinct societies.
* Beef Website at the University of Nebraska, Lincoln will be used as a platform to post project results including reports, podcasts, and monthly newsletters. A similar website targeted to sheep producers will be developed and placed on the University of Wyoming, Agricultural Experiment Station website. Links to the beef and sheep websites will be provided on other participating states AES websites.

**Projected Participation:**

Appendix E forms will be submitted by participating scientists.

**Outreach Plan:**

We will disseminate information obtained from the proposed research studies to academic and industry leaders by publication in peer-reviewed journals, industry journals, popular press, and other, more widely read technical bulletins. In addition, the information obtained from these collaborative studies will be presented at national and international conferences, industry meetings, and producer field days. Further, the W3112 will take the lead in developing symposia for the Western Section of the American Society of Animal Science meetings in coming years. The Western Section meetings are attended by many beef and sheep extension and research personnel. By providing symposia on reproduction of ruminant animals at these meetings, the effective audience is greatly enhance as information from the W3112 is provided to Extension Specialists who then provide information to producers and industry personnel in their region and state. Currently, project personnel have requested to organize the symposium for the 2017 Western Section meeting of the ASAS. W3112 member will also be active participants in the combined society ASAS-SSR Reproductive Symposia for the 2017 annual meeting of SSR.

**Organization and Governance:**

The members of the W3112 Regional Research Project receive direction from the Executive Committee composed of a Chairman, Secretary and Member-at-Large. Each year a Member-at-Large is elected. In year two, that individual serves as Secretary and then serves as Chairman during year three. The Administrative Advisor, appointed by the Western Directors, also sits on the Executive Committee. Tenure of individuals elected to the Executive Committee is three years.

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**Attachements:**

**Internal Linkages:**

**External Linkages:**

**Signatures:**