

Agency <b>AGRICULTURAL RESEARCH SERVICE</b>	Type of Instrument <b>Reimbursable Cooperative Agreement</b>		Authority <b>7 USC 3318a</b>
Title of Project <b>Genetic Mechanism of Reproductive Heterosis in Dairy Cattle</b>	Agreement Number/FAIN <b>58-8042-0-093</b>	Type of Action <b>New</b>	Correction <b>N</b>
	CFDA No. <b>10.001</b>		
Agency Administrative Point of Contact/ADO <b>KRISTY L WALLACE</b> USDA, ARS, AFM, NEA Administrative Office Financial Management, Travel and Agreements 2775 F and B Road College Station TX 77845-4966 Phone: 979-260-9659 Fax: E-mail: kristy.wallace@usda.gov	Period of Performance Start <b>06/01/2020</b> End <b>05/31/2023</b>		Incoming Award Number <b>H008051403</b>
	Total Amount <b>\$35,200.00</b>	Amount Obligated by This Action <b>\$35,200.00</b>	Indirect Cost Rate <b>0.00%</b>
Agency Principal Investigator <b>PAUL M VAN RADEN</b> AGIL/BARC/NEA BLDG 005, RM 306, BARC-W, 10300 BALTIMORE AVENUE BELTSVILLE MD 20705 Phone: Fax: 301-504-5092 E-mail: Paul.VanRaden@usda.gov	Non-Federal Entity/Federal Agency (Legal Name and Address) <b>REGENTS OF THE UNIVERSITY OF MINNESOTA</b> 1333 GORTNER AVE Saint Paul MN 55108-1098 USA POC: <b>NORRIE ZIER</b> FINANCE PROFESSIONAL 2 Phone: 612-624-8541 Fax: E-mail: <b>NZIER@UMN.EDU</b> DUNS ID: 617361316		
	Non-Federal Entity/Federal Agency Principal Investigator <b>YANG DA</b> PROFESSOR, DEPARTMENT OF ANIMAL SCIENCE 265D HAECKER HALL 1364 ECKLES AVENUE ST. PAUL MN 55108-6118 USA Phone: 612-625-7780 Fax: E-mail: <b>YDA@UMN.EDU</b>		
Agency Finance Office <b>JENNIFER C COURCHAINE</b> USDA, ARS, NEA AO FINANCIAL MANAGEMENT, TRAVEL AND AGREEMENTS 10300 BALTIMORE AVE, BLDG 3 BELTSVILLE MD 20705-2325 Phone: 301-504-5978 Fax: E-mail: jennifer.courchaine@usda.gov	Method of Payment <input type="checkbox"/> HHS/Payment Management System <input type="checkbox"/> Advance Payment Authorized <input type="checkbox"/> EFT/Treasury Check <input type="checkbox"/> Pre-Award Costs Authorized <input checked="" type="checkbox"/> Agency Receives Funds <input type="checkbox"/> UES (for FAS awards only) <input type="checkbox"/> ASAP <input type="checkbox"/> IPAC		

PROVISIONS

This Agreement incorporates the following:

- Statement/Scope of Work
  - Proposal
  - Non-Federal Entity Proposal/Award/Agreement
  - Research & Related Budget (Total Fed + Non-Fed) or REE-454
  - Research & Related Budget or REE-455
  - Prime Award attached (for subrecipients)
  - Comments (REE-451, page 2)
- These are available at <https://www.afm.ars.usda.gov/agreements/partnership/>
- Conflict of Interest Policy
  - USDA Civil Rights Policy Statement  USDA Civil Rights Poster (AD-475-C)
  - REE-157 - Research Support Agreement Management Report Template

Reporting Requirements:

- Submit to:  Agency PI  ADO  Non-Federal Entity/Federal Agency
- |   |   |                                      |
|---|---|--------------------------------------|
| Performance Reports                       | Financial Reports                         | Management Reports                   |
| <input type="checkbox"/> Quarterly        | <input type="checkbox"/> Quarterly        | <input type="checkbox"/> Monthly     |
| <input type="checkbox"/> Semi-Annual      | <input type="checkbox"/> Semi-Annual      | <input type="checkbox"/> Quarterly   |
| <input type="checkbox"/> Annual           | <input type="checkbox"/> Annual           | <input type="checkbox"/> Semi-Annual |
| <input checked="" type="checkbox"/> Final | <input checked="" type="checkbox"/> Final | <input type="checkbox"/> Final       |
- Intellectual Property Reports (www.iEdison.gov)
  - Form SF-428-B Tangible Personal Property Report - Final Report

Applicable Regulations, Terms and Conditions, and Required Certifications (available at <https://www.afm.ars.usda.gov/agreements/partnership/> )

- 2 CFR Part 200 and 2 CFR Part 400
- 7 CFR Part 550 - General Administrative Policy for Non-Assistance Cooperative Agreements, published 10/11/2016
- General Provisions, Research Support Agreement (REE-452R)
- General Provisions, Trust Fund and Reimbursable Cooperative Agreements (REE-22)
- AD-1047 - Certification Regarding Debarment, Suspension and other Responsibility Matters - Primary Covered Transactions
- AD-1048 - Certification Regarding Debarment, Suspension, Ineligibility and Voluntary Exclusion - Lower Tier Covered Transactions
- AD-1049 - Certification Regarding Drug-Free Workplace Requirements (Grants) - Alt I - For Grantees Other Than Individuals
- AD-1050 - Certification Regarding Drug-Free Workplace Requirements (Grants) - Alt II - For Grantees Who Are Individuals
- AD-1052 - Certification Regarding Drug-Free Workplace State and State Agencies
- AD-3031 - Assurance Regarding Felony Conviction or Tax Delinquent Status for Corporate Applicants
- Certification Regarding Lobbying
- REE-26 - Organization Information, Representations, Assurances & Certifications

This agreement, subject to the provisions above, is executed by the United States Department of Agriculture:

Signature	ADO Name <b>KRISTY L WALLACE</b>	Date
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By signing this agreement, the signor certifies that they are vested with the authority to enter into this agreement.

Non-Federal Entity/Federal Agency Signature	Name and Title	Date
Non-Federal Entity/Federal Agency Signature	Name and Title	Date

Agreement Number/FAIN: 58-8042-0-093

Agency Control No.: 53504

Type of Action: New

BOC: 0250

Project Number: 8042-31000-002-013R

Accession No.: 438323

FMMI Customer Code : 6006283

Agency Funds Chargeable - Agency Use Only

Account Code	FY	Amount
171-8042-103	2021	\$35,200.00

Comments:

Annual technical/progress reports will be submitted within 30 days prior to the end of each budget period to the cooperator PI.

A final technical/progress report will be submitted to the cooperator's PI within 60 days of the end of the Project Period or after termination of this award, whichever comes first.

Invoices shall be submitted no less than quarterly for allowable costs and must include current and cumulative costs, breakdown by major cost category, and subaward number (H008051403).

## Statement of Work

Agreement No.: 58-8042-0-093

Type of Action: New

Cooperator: REGENTS OF THE UNIVERSITY OF MINNESOTA

Control No.: 53504

**Objective:**

Declining fertility in dairy cattle is a serious threat to the profitability of dairy cattle. Fertility is one of the traits affected most by crossbreeding. The discovery of genetic variants and their mechanism underlying reproductive heterosis will facilitate developing new strategies to improve dairy fertility. This proposed research is the first attempt to understand reproductive heterosis in dairy cattle and aims at the discovery and utilization of genetic variants and mechanisms underlying dairy reproductive heterosis for genetic improvement of dairy fertility. Specific objectives supporting this overall objective include: 1) Detect chromosome regions and assessing genetic mechanism associated with reproductive heterosis using genome-wide association study (GWAS); 2) Fine-map and identify candidate causal variants underlying reproductive heterosis by an integrated analysis of comparative genomics, and 3) Improve Holstein using heterosis variants and mechanisms. This research will yield a list of genome variants associated reproductive heterosis and their specific effects potentially including additive, dominance and epistasis effects, verification and fine mapping 3 million SNPs from the sequence data of hypothetical Holstein x Jersey crosses, functional relevance from mouse comparative analysis and from comparative analysis of genetic selection in Holstein cattle since 1964. The total contribution of all heterosis variants as well as the total contribution of candidate variants for gene editing will be estimated. The results from this research will be a significant contribution to the scientific understanding of reproductive heterosis in dairy cattle and to the genetic improvement of dairy fertility utilizing heterosis variants and mechanisms.

**Approach:**

**Aim 1:** Detect chromosome regions and assessing genetic mechanism associated with reproductive heterosis using genome-wide association study (GWAS). The GWAS analysis will identify chromosome regions and genetic variants with significant effects on the fertility traits in the crossbreeding population. Assessment of genetic mechanism is achieved by testing the significance of additive and dominance of each SNP, and epistasis effect of each pair of SNPs. For SNPs with significant dominance effects, we will further assess whether the dominance effects were incomplete dominance or overdominance. For epistasis effects, we will determine the exact type of the epistasis effects.

**Aim 2:** Fine map and identify candidate causal variants underlying reproductive heterosis by an integrated analysis of comparative genomics. This analysis will verify heterosis variants from GWAS, find other variants potentially associated with reproductive heterosis using frequency comparison based on sequence data, and investigate functional relevance of heterosis variants to fertility by comparison with mouse knockout genes affecting fertility and chromosome regions affected by genetic selection since 1964. Candidate variants associated with reproductive heterosis will be identified and their contribution to heterosis evaluated.

**Aim 3:** Explorative study of using heterosis variants and mechanisms to improve Holstein fertility, and to predict optimal mating to maximize reproductive heterosis. SNP effects from crossbreds representing fertility heterosis will be added to the mixed model for genomic prediction of fertility traits in Holsteins, and the accuracy change due to crossbred SNP effects will be evaluated using validation studies.

**THE COOPERATOR AGREES TO:**

The Cooperator agrees to conduct genomewide association analyses to identify genomic regions that underlie heterosis effects on fertility, fine-map causal variants that explain reproductive heterosis, conduct a comparative analysis of identified variants with genes known from mouse knockout models to affect fertility, and use the results of those studies to develop mating plans that maximize reproductive heterosis in Holstein cattle.

**AGENCY AGREES TO:**

The Agency agrees to extract genomic DNA of 30 Jersey bulls from semen, construct next-generation sequencing libraries, sequence the resulting libraries to a depth of ~15x coverage, and align the resulting reads against version 1.1 of the ARS-UCD bovine reference genome (or the current version at the time data are generated).

**MUTUAL AGREEMENTS:**

1. Agency receives funds.

U.S. DEPARTMENT OF AGRICULTURE  
RESEARCH, EDUCATION, AND ECONOMICS

Statement of Work

Agreement No.:58-8042-0-093

Type of Action: New

Cooperator: REGENTS OF THE UNIVERSITY OF MINNESOTA

Control No. :53504

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2. Correspondence and documentation submitted by the Cooperator to the Agency PI in reference to this agreement should cite Agreement No. 58-8042-0-093 .
3. Both parties mutually agree to share in the analysis and interpretation of results, and jointly submit manuscripts to peer-reviewed journals.

U.S. DEPARTMENT OF AGRICULTURE  
RESEARCH, EDUCATION, AND ECONOMICS

**GRANT AND COOPERATIVE AGREEMENT BUDGET**

Recipient Name: REGENTS OF THE UNIVERSITY OF MINNESOTA	FUNDS REQUESTED BY PROPOSER	FUNDS APPROVED BY AGENCY (If different)
Agreement No.: 58-8042-0-093 Type of Action: New		
PRINCIPAL INVESTIGATOR YANG DA		
A. Salaries and Wages		
1. Senior/Key Person(s) . . . . .	\$0.00	\$0.00
2. Other Personnel (Post-Doctoral Associates, Graduate Students, Undergraduate Students) . . . . .	\$0.00	\$0.00
3. Support Personnel/Secretarial/Clerical . . . . .	\$0.00	\$0.00
Total Salaries and Wages      —————▶	\$0.00	\$0.00
B. Fringe Benefits (If charged as Direct Costs)	\$0.00	\$0.00
C. Total Salaries, Wages, and Fringe Benefits ( <i>A plus B</i> )      —————▶	\$0.00	\$0.00
D. Equipment (Provide supporting data. List items and dollar amounts for each item exceeding \$5,000.)	\$0.00	\$0.00
E. Materials and Supplies	\$30,000.00	\$0.00
F. Travel (List destination and amount for each trip)		
1. Domestic (Include Canada, Mexico, and U.S. Possessions)	\$2,000.00	\$0.00
2. Foreign	\$0.00	\$0.00
G. Publication Costs	\$0.00	\$0.00
H. ADP/Computer Services	\$0.00	\$0.00
I. Subawards	\$0.00	\$0.00
J. All Other Direct Costs (Provide supporting data. List items and dollar amounts.)		
	\$0.00	\$0.00
K. Total Direct Costs (C through J)      —————▶	\$32,000.00	\$0.00
L. Indirect Costs (Specify rate(s) and base(s) for on/off campus activity.) (Where both are involved, identify itemized costs included in on and off campus bases.)  Rate : 0.00 % Base : \$0.00	\$0.00	\$0.00
M. Total Direct and Indirect Costs (K plus L)      —————▶	\$32,000.00	\$0.00
N. Amount of Deobligation (If applicable)      —————▶	\$0.00	\$0.00
O. TOTAL AMOUNT of this REQUEST (M minus N)      —————▶	\$32,000.00	\$0.00
P. COST SHARING      ▶	\$0.00	

U.S. DEPARTMENT OF AGRICULTURE  
RESEARCH, EDUCATION, AND ECONOMICS

AGREEMENT BUDGET JUSTIFICATION  
FOR 58-8042-0-093

Materials and Supplies

Semen purchase and DNA sequencing	\$30,000.00
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Travel - Domestic

Travel to scientific meetings	\$2,000.00
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