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# Michigan State University

Information Supporting a Regulatory Status Review of Potato Genetically Modified to Have Resistance to the Potato Pathogen *Phytophthora infestans*, Potato Virus Y and Potato Leaf Roll Virus Resistance

Michigan State University is submitting this information to support a Regulatory Status Review by the USDA Animal and Plant Health Inspection Service under 7 CFR Part 340.4

Submitted on behalf of:
Michigan State University
East Lansing, MI.
United States

Prepared and Submitted by:
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No CBI
Michigan State University does not consider any information contained in this document to be confidential business information or to be a trade secret.

April 3, 2024

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## Abbreviations and Definitions:

ArPORT1: *Agrobacterium rhizogenes* strain that contains the genetic components required for GAANTRY gene stacking within the virulence plasmid. Used directly for plant transformation.

CC-NB-LRR: N-terminal coiled-coil (CC) domain, nucleotide-binding site (NB) and leucine-rich repeats (LRRs)

EHA105: The EHA105 *Agrobacterium tumefaciens* strain is useful for transgenic operations of potato and other plants.

GAANTRY: Gene Assembly in Agrobacterium by Nucleic acid Transfer using Recombinase technology

HS: Hypersensitive Response

JGT105: *Agrobacterium tumefaciens* JGT105 GAANTRY strain, which is a derivative of *Agrobacterium tumefaciens* EHA105, contains the genetic components required for GAANTRY gene stacking within the virulence plasmid. Used directly for plant transformation.

LB: Left Border
MOA: Mechanism of Action
MSU: Michigan State University
NCBI: National Center for Biotechnology Information
NPTII: Neomycin phosphotransferase II
ONT: Oxford Nanopore Technology
ORF: Open Reading Frame
PCR: Polymerase Chain Reaction
PLRV: Potato Leaf Roll Virus
PVY: Potato Virus Y
R genes: Resistance genes
RB: Right Border
RSR: Regulatory Status Review
T-DNA: Transfer DNA

# 1. Confidential Business Information (CBI) Statement

This RSR request does not contain CBI.

# 2. Product Description and Rationale

### 2A. Requester's name and contact information

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### 2B. Description of plant's genus, species

- Order: Solanales
- Family: Solanaceae
- Genus: Solanum
- Species: *Solanum tuberosum* L.

### 2C. Product Description and Rationale

Michigan State University (MSU), as the lead organization for the USAID-funded Global Biotech Potato Partnership, is developing lines of potato (*Solanum tuberosum* L.) with resistance to Potato Virus Y (PVY), Potato Leaf Roll Virus (PLRV) and resistance to *Phytophthora infestans,* the source organism for the devastating fungal disease late blight. The target countries for the marketing of these lines are in Africa and Asia, however, a regulatory status review in the United States will facilitate the development and delivery of these improved lines. For example, a mini-tuber seed grower in the United States will be able to produce certified seed and then ship to our in-country collaborators for large scale grower trials and for the initial distribution to the small shareholder growers. A non-regulated status will save on production costs. Additionally, some potato varieties MSU has in development could also be useful to the United States potato industry. This RSR is similar to a recent submission (24-088-01rsr), with the addition of the Potato Leaf Roll Virus resistance.

Resistance to late blight has been identified in many related *Solanum* species and is due to the presence of specific resistance genes referred to as R genes having a common structure. However, as there are many races of *P. infestans* and their capability of sexual reproduction, single R-genes do not always provide durable resistance. MSU is using a T-DNA construct with three R genes from *Solanum* species and is using this to generate transgenic potato plants. R genes coding for proteins with the structure CC-NB-LRR are ubiquitous in plants forming the major line of resistance to fungal, bacterial and viral pathogens with the specificity commonly provided by CC region of the protein (Paluchowska, et al., 2022). The expression level of the proteins is usually extremely low such that detection of the protein is not possible in the plant.

Potato virus Y (PVY) is a major potato pathogen that causes severe annual crop losses worth billions of dollars worldwide. PVY is transmitted by aphids, and successful control of virus

transmission requires the extensive use of environmentally damaging insecticides to reduce vector populations. The $Ry_{sto}$ gene, from the wild relative *Solanum stoloniferum*, confers extreme resistance (ER) to PVY and related viruses and is a valuable trait that is widely employed in potato resistance breeding programs. $Ry_{sto}$ has been shown to be valuable for creating PVY-resistant cultivars of potato and other Solanaceae crops (Grech-Baran et. al. 2020).

Potato leafroll virus (PLRV) is a widespread and damaging disease of potato. The transmission is through aphids and through seed tubers. Yield loss can be significantly high in developing countries where farmers do not have access to quality seed and pesticides. Velásquez et al. (2007) demonstrated the existence of the gene $Rl_{adg}$ in *S. tuberosum* ssp. Andigena, which controls resistance to the infection and to PLRV accumulation. The $Rl_{adg}$ native promoter, gene and terminator have been identified and it is currently being introgressed into advanced breeding lines (Mihovilovich et al. 2014; Velásquez et al. 2007).

Our T-DNA constructs also incorporate the *nptII* gene as a selectable marker to allow for the efficient selection of transgenic plants during transformation. The NPTII protein has been widely used as a selectable marker in plant transformation and it has been widely studied to identify negative impacts on the environment and human and animal health (Fuchs et al. 1993).

## 3. Description of Host Potato Varieties

The biology of potato (*Solanum tuberosum* subsp. *tuberosum*) is well described and there is a long history of cultivation with very little evidence for weediness as it is unlikely to grow outside of cultivation (OECD 1997). There is a large germplasm base that has been used for breeding purposes, but the low level of self-fertility and other barriers to inter-specific hybridization means that human intervention is required to successfully produce hybrids. Two wild potato species are found in the South-Western United States (Bamberg. et al 2016), but there are no records of outcrossing to these species from cultivated potato.

## 4. Description of Modification

### 4A. Maps of T-DNA and pMSU2DR-02 plasmid

A linear map of the T-DNA of pMSU2DR-02 is represented in Figure 1. The pMSU2DR-02 T-DNA was assembled independently in both *Agrobacterium rhizogenes* strain ArPORT1 and *Agrobacterium tumefasciens* strain JGT105 using the GAANTRY (Gene Assembly in *Agrobacterium* by Nucleic acid Transfer using Recombinase technologY) This is an *in vivo* stacking of multiple genes within an *Agrobacterium* virulence plasmid and it is described further in 4B. A circular map of the pMSU2DR-02 plasmid is represented in Figure 2a. pMSU2DR-02 in *Agrobacterium rhizogenes* strain ArPORT1 and Figure 2b. pMSU2DR-02 in *Agrobacterium tumefasciens* strain JGT105.

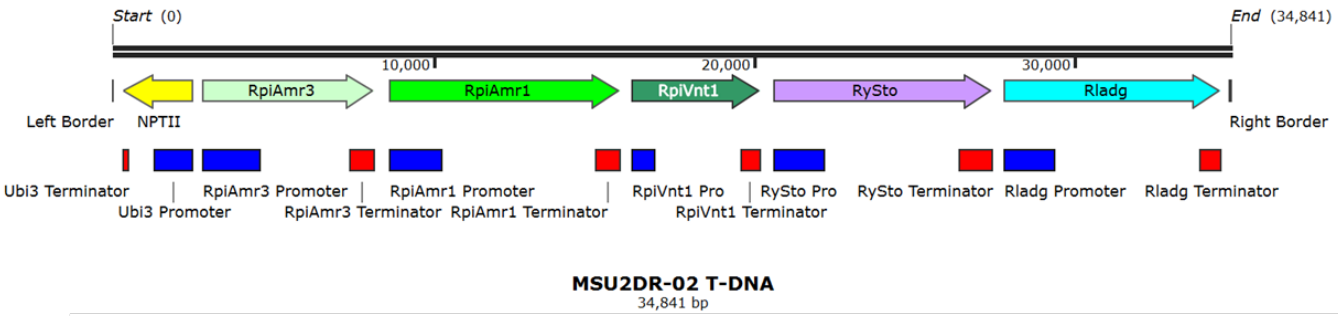
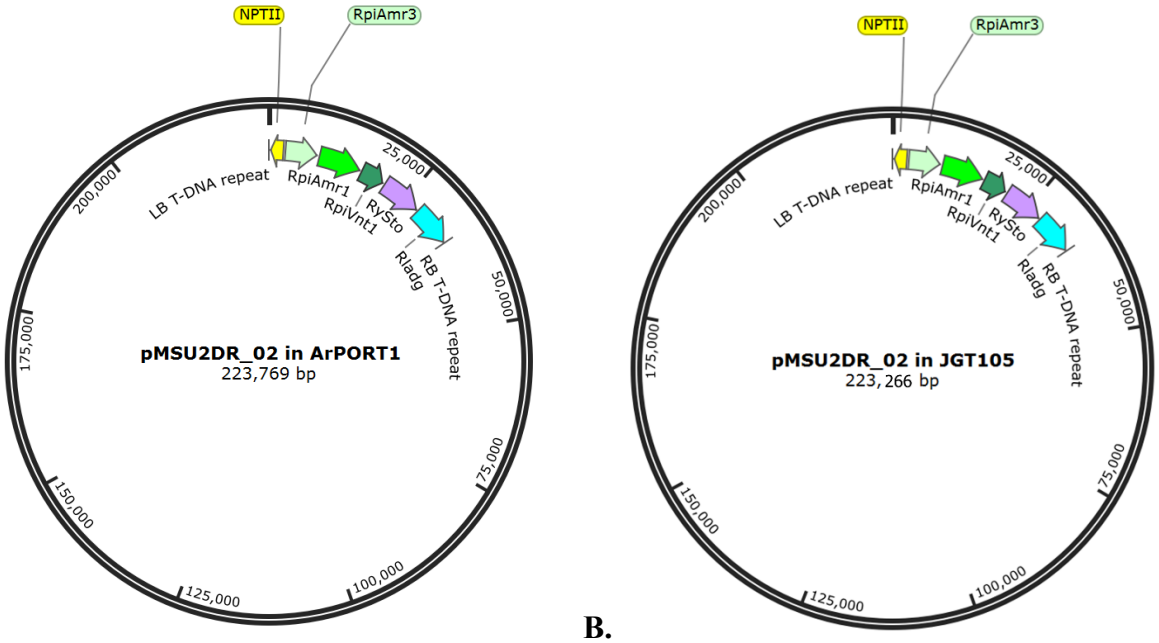



**Figure 1. T-DNA of pMSU2DR-02**




**A.** **B.**

**Figure 2. A. Circular map of pMSU2DR-02 in *Agrobacterium rhizogenes* strain ArPORT1. B. Circular map of pMSU2DR-02 in *Agrobacterium tumefasciens* strain JGT105.**

### 4B. Description of plasmid vector construction

The pMSU2DR-02 plasmid was developed at Michigan State University for the Global Biotech Potato Partnership. The GAANTRY (Gene Assembly in *Agrobacterium* by Nucleic acid Transfer using Recombinase technologY) is an in vivo stacking of multiple genes within an *Agrobacterium* virulence plasmid Transfer-DNA (T-DNA). The pMSU2DR-02 T-DNA was

developed using the GAANTRY technology which is a proven efficient way of developing multi-gene T-DNA (Collier, R., et al., 2018, McCue, K.F. et al., 2019, Hathwaik, et al., 2021). The GAANTRY system utilizes *in vivo* transient expression of unidirectional site-specific recombinases and an alternating selection scheme to sequentially assemble multiple genes into a single transformation construct inside the *Agrobacterium*. The plasmid, inside the *Agrobacterium* host that accepts the T-DNA, is a modified disarmed *Agrobacterium* virulence plasmid and its development is described in detail in Collier, R., et.al, (2018). The *Agrobacterium* produced with the T-DNA, exhibits a much higher rate of incorporation of the entire T-DNA than other methods. Additionally, a much higher rate of single copy insertion without plasmid backbone transfer has been (Collier, R., et al., 2018). pMSU2DR-02 was assembled independently in both *Agrobacterium rhizogenes* strain ArPORT1 and *Agrobacterium tumefasciens* strain JGT105 to allow for a potentially wider range of use for transformation in different varieties of potato. The first transcriptional unit added was the neomycin phosphotransferase II (NPTII) gene which will allow the identification of positive events in potato plants using kanamycin selection. The next four transcriptional units included disease resistance genes *RpiAmr3, RpiAmr1, RpiVnt1,* $Ry_{sto}$ and $Rl_{adg}$. The combination of three R genes confers effective and durable resistance to late blight. The three genes referred to as *Rpi-vnt1* (Foster, S.J., 2009), *Rpi-amr1* (Witek, K, 2021) and *Rpi-amr3* (Lin, X., 2021) come from the wild *Solanum* species *S. venturii, S. americana, and S. americana*, respectively. Late blight protection is achieved in the desired potato variety by the introduction of the R genes with their native promoter and termination sequences. The $Ry_{sto}$ native promoter, gene and terminator confers effective resistance to Potato Virus Y (Grech-Baran et. al. 2020). The $Rl_{adg}$ native promoter, gene and terminator confers effective resistance to Potato Leaf Roll Virus (PLRV) (Mihovilovich et al. 2014; Velásquez et al. 2007).

The 6 gene cassettes (*nptII*, *RpiAmr3, RpiAmr1, RpiVnt1,* $Ry_{sto}$ and $Rl_{adg}$) were subcloned into and sequence confirmed in GAANTRY donor plasmids in preparation for assembly into the final T-DNA. The *Agrobacterium* strains generated from each stacking step were molecularly validated via screening with sequence-specific primers within genes and primers that bridge the junctions between the preexisting and newly inserted sequences. Clones screened following each round of assembly were confirmed to be correct with PCR analysis. Due to the large plasmid size the final clone was sequenced with whole-genome sequencing and assembly of genomic DNA (gDNA) using the long-read sequencing technology from Oxford Nanopore Technologies (ONT). *Solanum tuberosum*, *S. venturii, S. americana,* and *S. stoloniferum* are classified in the series *tuberosa* (Table 2).

**Table 2. Taxonomic classification of gene donor organisms**

| **Taxonomic Rank** | **Classification** | | | | |
|---|---|---|---|---|---|
| | ***Solanum tuberosum*** | ***Solanum venturii*** | ***Solanum americana*** | ***Solanum stoloniferum*** | ***Solanum tuberosum*** |
| **Family** | Solanaceae | Solanaceae | Solanaceae | Solanaceae | Solanaceae |
| **Genus** | *Solanum* | *Solanum* | *Solanum* | *Solanum* | *Solanum* |
| **Section** | Petota | Petota | Petota | Petota | Petota |
| **Subsection** | potato | potato | potato | potato | potato |
| **Series** | *tuberosa* | *tuberosa* | *tuberosa* | *tuberosa* | *tuberosa* |
| **Species** | *tuberosum* | *venturii* | *americana* | *stoloniferum* | *tuberosum* ssp. andigena |

The *nptII* gene is sourced from the Tn5 transposon in *Escherichia coli*. In this construct it has a promoter and terminator sequence from the potato *Solanum tuberosum ubiquitin-3* gene.

We acknowledge that the use of the GAANTRY technology was provided through an agreement between MSU and USDA-ARS. We acknowledge that the use of the genes *RpiAmr3, RpiAmr1, RpiVnt1,* $Ry_{sto}$ and $Rl_{adg}$ was provided through an agreement between MSU, 2Blades and The Sainsbury Laboratory (TSL). We acknowledge that the use of the gene *Rpi-vnt1* was provided through an agreement between MSU and Plant Bioscience Limited.

**4C. Sequence of the T-DNA insert**

The sequence of pMSU2DR-02 T-DNA is provided. Please see Figure 3 on page 18 in the Supplementary 8 section.

**4D. Annotation of the T-DNA Inserted Genetic Material**

An annotation of the T-DNA of pMSU2DR-02 is described in Table 2.
Narrative Description:

The T-DNA cassette contains a copy of the neomycin phosphotransferase II gene (NPTII) from Escherichia coli K12 under the control of the polyubiquitin promoter Ubi3. Transcription termination of the NPTII gene is provided by the potato ubiquitin Ubi3 terminator. There are three late blight resistance genes that include their native potato promoter and native terminator. The *Rpi-vnt1* GenBank accession no. FJ423044, the *Rpi-amr1* GenBank accession no. MW345286 and *Rpi-amr3* GenBank accession no. KT373889. There is a potato $Ry_{sto}$ resistance gene for the virus Potato Virus Y with accession no. MN393235 with a native promoter and native terminator. There is a potato $Rl_{adg}$ resistance gene for the virus Potato Leaf Roll with a native promoter and native terminator.

**Table 2. Genetic elements of the DNA Insert of pMSU2DR-02, from Left Border (LB) site to Right Border (RB)**

| Acronym | Location in pMSU2DR-02 T-DNA seq. | Genetic Element | Origin and description |
|---|---|---|---|
| T Border (L) | 1-26 | T-DNA Left Border | *Agrobacterium tumefaciens* |
| Intervening sequence | 27-326 | Synthetic | GAANTRY B donor Synthetic used for cloning |
| Ubi3 Terminator | 327-507 | Terminator | *Solanum tuberosum* Terminates the transcription of the NPTII gene |
| NPTII | 508-1303 | Kanamycin Resistance gene | *Escherichia coli* K12 Confers kanamycin resistance in plants |
| Ubi3 Promoter | 1304-2458 | Promoter | *Solanum tuberosum* Drives the expression of NPTII gene. |

| | | | |
|---|---|---|---|
| | | | Garbarino, J.E. and Belknap, W.R., 1994. |
| Intervening sequence | 2459-2805 | Synthetic | GAANTRY P donor cloning Synthetic used for cloning |
| *Rpi-amr3* Promoter | 2806-4560 | Native promoter | *Solanum Americanum* Promoter sequence for driving the expression of *Rpi-amr3* gene |
| *Rpi-amr3* | 4561-7416 | Late Blight Resistance gene | *Solanum americanum* Lin, X., Olave-Achury, A., Heal, R., Witek, K., Karki, H. S., Song, T., ... & Jones, J. D. (2021). Rpi-amr3 confers resistance to multiple Phytophthora species by recognizing a conserved RXLR effector. BioRxiv, 2021-06 |
| *Rpi-amr3* Terminator | 7417-8155 | Native terminator | *Solanum americanum* Terminates transcription of *Rpi-amr3* |
| Intervening sequence | 8156-8622 | Synthetic | GAANTRY B donor Synthetic used for cloning |
| *Rpi-amr1* Promoter | 8623-10254 | Native promoter | *Solanum americanum* Drives the expression of the *Rpi-amr1* gene |
| *Rpi-amr1* | 10255-15065 | Late Blight Resistance gene | *Solanum americanum* Witek, K., Lin, X., Karki, H. S., Jupe, F., Witek, A. I., Steuernagel, B., ... & Jones, J. D. (2021). A complex resistance locus in *Solanum americanum* recognizes a conserved Phytophthora effector. Nature Plants, 7(2), 198-208. |
| *Rpi-amr1* Terminator | 15066-15826 | Native Terminator | *Solanum Americanum* Terminates transcription of *Rpi-amr1* |
| Intervening sequence | 15827-16197 | Synthetic | GAANTRY P donor Synthetic used for cloning |
| *Rpi-vnt1* Promoter | 16198-16906 | Native promoter | *Solanum venturi* Drives expression of *Rpi-vnt1* |
| *Rpi-vnt1* | 16907-19583 | Resistance gene | *Solanum venturii* Foster, S. J., Park, T. H., Pel, M., Brigneti, G., Śliwka, J., Jagger, L., ... & Jones, J. D. |

| | | | |
|---|---|---|---|
| | | | (2009). Rpi-vnt1. 1, a Tm-22 homolog from Solanum venturii, confers resistance to potato late blight. Molecular plant-microbe interactions, 22(5), 589-600. GenBank accession no. FJ423044 |
| *Rpi-vnt1* Terminator | 19584-20197 | Native terminator | *Solanum venturi* Terminates transcription of *Rpi-vnt1*gene |
| Intervening sequence | 20198-20644 | Synthetic | GAANTRY B donor Synthetic used for cloning |
| $Ry_{sto}$ Promoter | 20645-22221 | Native promoter | *Solanum stoloniferum* Drives the expression of the *Ry sto gene* |
| $Ry_{sto}$ | 22222-26437 | PVY Resistance gene | *Solanum stoloniferum* Grech-Baran, M., Witek, K., Szajko, K., Witek, A. I., Morgiewicz, K., Wasilewicz-Flis, I., ... & Hennig, J. (2020). Extreme resistance to Potato virus Y in potato carrying the $Ry_{sto}$ gene is mediated by a TIR-NLR immune receptor. Plant Biotechnology Journal, 18(3), 655-667. GeneBank accession no. MN393235 |
| $Ry_{sto}$ Terminator | 26438-27459 | Native terminator | *Solanum stoloniferum* Terminates the expression of the *Ry sto gene* |
| Intervening sequence | 27460-27799 | Synthetic | GAANTRY P donor Synthetic used for cloning |
| $Rl_{adg}$ Promoter | 27800-29389 | Native promoter | *Solanum tuberosum* ssp. andigena. Drives the expression of the $Rl_{adg}$ gene. |
| $Rl_{adg}$ | 29390-33923 | PLRV Resistance gene | *Solanum tuberosum* ssp. andigena. Velásquez, A. C., Mihovilovich, E., & Bonierbale, M. (2007). Genetic characterization and mapping of major gene resistance to potato leafroll virus in *Solanum tuberosum* ssp. andigena. Theoretical 34and Applied Genetics, 114, 1051-1058. |

| | | | |
|---|---|---|---|
| *Rl*$_{adg}$ Terminator | 33924-34578 | Native terminator | *Solanum tuberosum* ssp. andigena. Terminates the expression of the *Rl*$_{adg}$ gene. |
| Intervening sequence | 34579-34816 | Synthetic | GAANTRY B donor Synthetic used for cloning |
| RB | 34817-34841 | T-DNA Right Border | Right border region of T-DNA from *Agrobacterium tumefaciens* nopaline Ti plasmid (GenBank accession no. J01826). Short direct repeat that flanks the T-DNA and is required for the transfer of the T-DNA into the genome of the host plant (Yadav et al., 1982) |

**4E. Description of the Transformation Method**

In 2019, McCue, K.F., et.al., transformed potato plants using the GAANTRY system to generate the T-DNA used in transformations. They used the *Agrobacterium rhizogenes* ArPORT1 strain was used for their transformations. While *Agrobacterium rhizogenes* ArPORT1 strain was initially used to demonstrate the transformation of constructs made with the GAANTRY system, the *Agrobacterium tumefaciens* JGT105 GAANTRY strain, which is a derivative of EHA105, was developed because it was known that the EHA105 transforms potato well. Potato-transformed events are produced using *Agrobacterium* transformation at Michigan State University each containing pMSU2DR-02 T-DNA. Both the *Agrobacterium rhizogenes* ArPORT1 strain and *Agrobacterium tumefaciens* JGT105 strains are used to transform potato internode explants following the method described by Douches et al. (1998). Transformed internode explants are regenerated on medium containing 50 mg/l kanamycin to select for lines containing a T-DNA insert. Polymerase Chain Reaction (PCR) is used to test generated transformed events for the presence of the T-DNA.

**4F. Molecular Characterization**

T-DNA Insert Analysis
A combination of Xdrop™ enrichment technology (Samplix, Denmark) utilizing Nanopore sequencing and followed by PCR with Sanger sequencing will show the presence and intactness of T-DNA. To describe further, the T-DNA sequence data for each advanced event will be generated by first utilizing Xdrop™ enrichment technology. The enriched DNA is then subjected to debranching followed by library generation with the Oxford Nanopore Technology (ONT) Ligation Sequencing Kit. The libraries are then sequenced using GridION (Oxford Nanopore Inc.) sequencing platform to generate long-read sequencing data. Junction-finding scripts using the generated sequences and the DM potato reference genome (Potato Genome Sequencing Consortium, 2011; Sharma et al., 2013), specifically PGSC *S. tuberosum* databases found at Spud Database Potato Genomics Resource http://spuddb.uga.edu/ will indicate the insertion site of the T-DNA for each advanced event. Sanger sequencing will be performed on PCR products across the junctions. At least 1 kb of flanking DNA near the left border and right border of the inserted T-DNA will be identified. The sequence obtained for the T-DNA will compared to the

plasmid T-DNA sequence. An example of this T-DNA characterization can be found in the manuscript Zarka et al. 2024.

An alternative method for obtaining sequence data and T-DNA characterization data is also used in our research program. This method involves a combination of Nanopore LSK114 ligation library construction followed by Nanopore PromethION flow cell sequencing. This is a whole genomic sequencing approach that is capable of achieving greater than 60x coverage across the tetraploid potato genome. In addition to this coverage, an increased coverage across the T-DNA could be reached by adding adaptive sampling technology during Nanopore library construction. Again, PCR and Sanger sequencing would also be used to confirm sequencing data at the junction and flanking regions of the T-DNA inserted into each event.

Integration Site

The Sanger sequencing data from the T-DNA characterization described above is used to locate the insertion site. The location is analyzed with reference to the potato reference genome database (Potato Genome Sequencing Consortium, 2011, SPUD DB Potato Genomics Research) to analyze for potential gene interruption and the creation of new open reading frames. An example of this analysis is described in our manuscript, Zarka et al., 2024.

Absence of Backbone

PCR analysis will be used initially to show the absence of large pMSU2DR-02 plasmid backbone sequences in the transformed potato events.

If the Xdrop™ enrichment technology (Samplix, Denmark) utilizing Nanopore sequencing is used for the T-DNA characterization, then the small backbone analysis will be completed using Southern analysis. A collection of digoxigenin (DIG) PCR or random primed labeled probes that span the entire pMSU2DR-02 backbone region, is used in a series of southern blots to detect any small backbone sequences.

If the Nanopore LSK114 ligation library construction followed by PromethION flow cell sequencing is used for T-DNA characterization, then the whole genomic sequence data obtained can be analyzed using bioinformatic software to identify if any small backbone fragments have been transferred into the potato event.

Inheritance and stability

Commercial potatoes are propagated vegetatively and do not undergo meiotic recombination, therefore potatoes are expected to be genetically stable. To confirm this in our events, PCR analysis is used to determine the presence or absence of the insert in plants that have sustained three generations. An example of this analysis is described in Zarka et al., 2024.

Open reading frame analysis

The ORF Finder algorithm associated with NCBI at https://www.ncbi.nlm.nih.gov/orffinder/ is used to identify all ORFs. Each event is analyzed using the insert flanking sequences (determined as described above). The 1000 bp of the flanking sequence and 500bp of the T-

DNA region for each the left T-DNA border region and the right T-DNA border region is used in the analysis.

The NCBI ORF finder searches for open reading frames (ORFs) in the DNA sequence entered in all six possible reading frames. The program returns the range of each ORF, along with its protein translation. The ORF finder is then used to identify and evaluate any proteins using NCBI's BLASTP. The parameters for the ORF search included using a minimum of length of 25 codons long, standard genetic code and the use of "ATG" as the start codon. This analysis is completed on all potato events after completion of the T-DNA characterization.

# 5 Description of New Trait

## 5A. Intended trait

**Late blight resistance:**
Late blight is a devastating disease of potato caused by the oomycete fungus *Phytophthera infestans*. If uncontrolled it can lead to complete loss of the crop and chemical control is costly and uses large amounts of fungicide. Resistance to late blight has been a goal of potato breeding for many years and germplasm resistant to the disease has been used extensively, leading to the identification of specific resistance genes referred to as R-genes. R-proteins (from the genes *Rpi-vnt1, Rpi-amr1, and Rpi-amr3*) are part of a plant defense mechanism called effector-triggered immunity. These proteins recognize pathogen-secreted effector proteins and activate the plant hypersensitive response (HR). The diverse nature of *P. infestans* strains, with high variability in the pathogen-secreted effector proteins, makes durable resistance through the introduction of single R genes very difficult and a combination, in this case three separate genes, is expected to provide a much more durable resistance.

**Potato Virus Y resistance:**
Potato virus Y (PVY) is a major potato pathogen that causes severe annual crop losses worth billions of dollars worldwide. PVY is transmitted by aphids, and successful control of virus transmission requires the extensive use of environmentally damaging insecticides to reduce vector populations. The $Ry_{sto}$ gene, from the wild relative *Solanum stoloniferum*, confers extreme resistance to PVY and related viruses and is a valuable trait that is widely employed in potato resistance breeding programs. The protein is a different type to the R-proteins utilized for late blight resistance in this construct, although there is similarity in structure. However, $Ry_{sto}$ confers extreme resistance to PVY in potato preventing viral replication without triggering cell death. $Ry_{sto}$ has been shown to be valuable for creating PVY-resistant cultivars of potato and other Solanaceae crops (Grech-Baran et. al. 2020).

**Potato Leaf Roll Virus resistance:**

Potato leafroll virus (PLRV) is a widespread and damaging disease of potato. The transmission is through aphids and through seed tubers. Yield loss can be significantly high in developing countries where farmers do not have access to quality seed and pesticides. Velásquez et al. (2007) demonstrated the existence of the gene $Rl_{adg}$ in *S. tuberosum* ssp. Andigena, which controls resistance to the infection and to PLRV accumulation. The $Rl_{adg}$ native promoter, gene

and terminator have been identified and it is currently being introgressed into advanced breeding lines (Mihovilovich et al. 2014; Velásquez et al. 2007).

**Kanamycin resistance (NPTII):**
The potato contains a protein that confers resistance to the antibiotic neomycin and serves as a selectable marker for plant transformation. This is not a required trait in the final plant and plays no role in the late blight tolerance trait.

**5B. Intended phenotype**

**Late blight resistance:**
Potatoes resistant to infection of *P. infestans* strains prevalent in our USAID Feed the Future Global Biotech Potato Partnership.

**Potato Virus Y resistance:**
Potatoes resistant to infection with Potato Virus Y which is prevalent worldwide and very damaging in our USAID Feed the Future Global Biotech Potato Partnership.

**Potato Leaf Roll Virus resistance:**
Potatoes resistant to infection with Potato Leaf Roll Virus prevalent worldwide and very damaging in our USAID Feed the Future Global Biotech Potato Partnership

**Kanamycin resistance (NPTII):**
Potatoes are resistant to the antibiotic neomycin and the NPTII protein serves as a selectable marker for plant transformation.

**5C. Description of the Mechanism of Action (MOA)**

R-proteins are part of a plant defense mechanism called effector-triggered immunity. They recognize pathogen-secreted effector proteins and activate the plant hypersensitive response (HR). The plant HR is a form of immunity that that destroys infected tissue through programmed cell death (apoptosis), restricting growth of the pathogen and the spread of the disease to the rest of the plant (Jones and Dangl, 2006). R-proteins do not have a pesticidal mechanism of action since they do not act on the invading pathogen (Panstruga et al., 2009). Combining three R-proteins that recognize different effectors proteins reduces the chance that the pathogen can overcome the late blight protection and could improve durability of the late blight protection trait.

R-protein expression and signal transduction are tightly regulated in the cell by maintaining low protein levels, which are kept in an inactive state through intramolecular protein interactions that block signaling until conformational changes due to specific cognate ligand (effector) binding activate signal transduction (Spoel and Dong, 2012). Importantly, unlike Bt proteins, R-proteins do not confer pest resistance by directly targeting the pest or acting as toxins. Instead, they activate a hypersensitive response within the host plant that restricts spread of the pathogen.

**Rpi-vnt1**

The expression of Rpi-vnt1 confers broad-spectrum, late blight resistance in wild and cultivated potato. The VNT1 protein, as part of the plant immune system, recognizes the Avr-vnt1 effector

protein secreted by *P. infestans* and signals a hypersensitive response (Moffett et al., 2002; Morel and Dangl, 1997; Pel, 2010; Rairdan et al., 2008). Previously given non-regulated status (24-046-01rsr and 21-270-01rsr).

**Rpi-amr1**

Like VNT1 and other previously reviewed R-Proteins (AMR3, BLB2 and MCQ-1) R-proteins are part of a plant defense mechanism called effector-triggered immunity. They recognize pathogen-secreted effector proteins and activate the plant hypersensitive response (HR). The expressed AMR1 protein recognizes the Avr-amr1 effector produced by *P. infestans* (Witek, K., et.al. 2021). This recognition initiates the host HR resulting in late blight protection.

**Rpi-amr3**

The expressed AMR3 protein recognizes the Avr-amr3 effector produced by *P. infestans* (Witek et al., 2016). This recognition initiates the host HR resulting in late blight protection. Lin, X., et. al. (2021) showed that *Rpi-amr3* confers resistance to multiple *Phytophthora* species by recognizing a conserved RXLR effector. AMR3 was previously given non-regulated status (21-270-01rsr).

In summary, all three proteins, VNT1, AMR1 and AMR3 have the same mechanism of action except that each of the three proteins recognizes a different pathogen-secreted effector protein. VNT1 and AMR3 have been expressed in previous potato plants reviewed by APHIS and determined to pose no increased plant pest risk. Combining three R-proteins that recognize different effectors proteins reduces the chance that the pathogen can overcome the late blight protection and could improve durability of the late blight protection trait.

**PVY Resistance**

Potato virus Y (PVY) belongs to the genus *Potyvirus*, family *Potyviridae*. The $Ry_{sto}$ gene, from the wild relative *Solanum stoloniferum*, confers extreme resistance (ER) to PVY and related viruses and is a valuable trait that is widely employed in potato resistance breeding programs. PVY resistance with the potato $Ry_{sto}$ gene confers extreme resistance to the virus by preventing viral replication without triggering cell death. Grech-Baran M, et. al., studied $Ry_{sto}$ resistance and found that it is mediated by a TIR-NLR immune receptor. Their results suggest that $Ry_{sto}$-mediated immunity is effective in potato plants not only against different strains of PVY but also against the related virus PVA. Additionally, the PVY viral coat protein (CP) was found to be recognized in $Ry_{sto}$ -mediated immunity against PVY. The CP produced during PVY infection in potato led to ER, indicating that the level of CP determined the type of response. The mechanism of CP recognition by $Ry_{sto}$ was further studied in 2022 by Grech-Baran M, et. al. They found that $Ry_{sto}$ associates directly with PVY CP *in planta* that is conditioned by the presence of a CP central 149 amino acids domain. This region of the CP is conserved, and they found that $Ry_{sto}$ recognizes the CPs of several other crop-damaging viruses. The $Ry_{sto}$ gene is shown to be valuable for creating PVY-resistant cultivars of potato and other Solanaceae crops (Grech-Baran et. al. 2020).

**Potato Leaf Roll Virus Resistance:**

Introgression of the *$Rl_{adg}$* provides resistance to potato leafroll virus as shown by Carneiro, et al., 2017. Heal et al., in 2022, found that *$Rl_{adg}$* is homologous to the *Bs4* gene which contributes to a hypersensitive response (HR) in tomato. This indicates that there is a conservation of the gene and broad function as opposed to acquisition or evolution in potato (Lindqvist-Kreuze, H., et al., 2024). The Rladg protein functions through a TIR-NLR (nucleotide-binding leucine-rich repeat with toll/interleukin-1 receptor domain) recognition of the PLRV polyprotein P1 (Heal et al., 2022).

**NPTII**

The 6th gene transferred encodes neomycin phosphotransferase II (NPTII). Expression of this protein in plant cells confers resistance to the antibiotics neomycin and kanamycin and serves as a selectable marker for plant transformation. The following describes the mechanism of action of NPTII. The antibiotics neomycin and kanamycin, bind to the negatively charged backbone of nucleic acids to disrupt protein synthesis, and therefore inhibits bacterial cell growth. Neomycin phosphotransferase II catalyzes the addition of phosphate from ATP to the 3'-hydroxyl group of the 4,6-disubstituted aminoglycoside neomycin. The NPTII mediated phosphorylation of neomycin/kanamycin introduces a phosphate group on the antibiotic that reduces the binding affinity to nucleic acids due to steric hindrances and unfavorable electrostatic interactions, and thereby disrupts the mechanism of action of the antibiotic (Wright and Thompson, 1999).

In the absence of neomycin or kanamycin the NPTII expressed in the potato transformed event is not expected to exhibit any enzymatic activity. Therefore, NPTII is not expected to have any effect on other potato metabolic pathways. Additionally, the food, feed and environmental safety of NPTII has been well established. Neomycin phosphotransferase II has been used as a selectable marker in many different commercial genetically engineered (GE) crops {e.g. Genuity® DroughtGard™ corn (MON 87460), YieldGard® Rootworm corn (MON 863), Bollgard® cotton (MON 531), Bollgard®II cotton (MON 15985), Roundup Ready® cotton (MON 1445)}, and therefore has a history of safe use in the environment as well as in food and feed uses. Furthermore, the NPTII protein has been fully characterized, and the NPTII protein expressed in GE crops has been shown not to pose any discernable environmental, food or feed safety concerns (Fuchs et al., 1993, Flavell et al., 1992, Nap et al., 1992)

## 5D. Metabolism, Physiology, and Development

None of the modifications with transformation of T-DNA (pMSU2DR-02) have an impact on the metabolism, physiology, or development of the plant.

## 6 Proposed plant-trait-MOA language for the website

Plant: *Solanum tuberosum* (potato)
Trait: Late blight resistance, Potato Virus Y resistance and Potato Leaf Roll virus resistance.
Phenotype: Resistance to *Phytophthora infestans,* resistance to Potato Virus Y (PVY) and resistance to Potato Leaf Roll virus.
MOA: Expression of resistance proteins (R genes) that can recognize *Phytopthora infestans* effector molecules and then activate effector-triggered immunity, 2) PVY resistance with the potato *$Ry_{sto}$* gene confers extreme resistance to the virus by preventing viral replication without

triggering cell death. 3) PLRV resistance with the $Rl_{adg}$ gene confers a hypersensitive response that functions through TIR-NLR) recognition of the PLRV polyprotein P1.

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## 8. Supplementary

**Figure 3. Sequence of the pMSU2DR-02 T-DNA insert:**

**pMSU2DR-02 T-DNA 5' --> 3' direction starting at location 1:**

**TGGCAGGATATATTGTGGTGTAAACAAATTGACGCTTAGACAACTTAATAACAC**
**ATTGCGGACGTTTTTAATGTACTGAATTAAATGTTTAGTTCCTCGTTTTCTCTCG**
**TTGGACGCAAAGAGGGAACTAAACACTTAATTACGCGTTTTATAACGGTCCTAA**
**GGTAGCGAAAAATAGGGATAACAGGGTAATCATCCTCGAGGAAACGCCGGCGA**
**AAGCGGCCGCAAACGTCGACGAAAGCGATCGCAAATTAATTAAAAACGCGCGC**
**GAAACCTCAGCAAAGACGTCAAAACCGGTAAACCTAGGAAAACTAGTAAAAAG**
**CTTGATATCCAAAATAGACGAGAACAATAAGCAAAAACTCTTAGTTTTGAAATA**
**AATCAACAATCCCGAGGGTTGTCACATACATCAAAAACGAAAATCCATATAGCA**
**AAAAAAACTCTAAATTACCGTTCGACAAAAAGAGAAAACTGATAAGACATTTGC**
**TAAACATTAAAATCAGTTTAAACTCAGAAGAACTCGTCAAGAAGGCGATAGAAG**
**GCGATGCGCTGCGAATCGGGAGCGGCGATACCGTAAAGCACGAGGAAGCGGT**
**CAGCCCATTCGCCGCCAAGCTCTTCAGCAATATCACGGGTAGCCAACGCTATG**
**TCCTGATAGCGGTCCGCCACACCCAGCCGGCCACAGTCGATGAATCCAGAAAA**
**GCGGCCATTTTCCACCATGATATTCGGCAAGCAGGCATCGCCATGGGTCACGA**

CGAGATCATCGCCGTCGGGCATGCGCGCCTTGAGCCTGGCGAACAGTTCGGCT
GGCGCGAGCCCCTGATGCTCTTCGTCCAGATCATCCTGATCGACAAGACCGGC
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