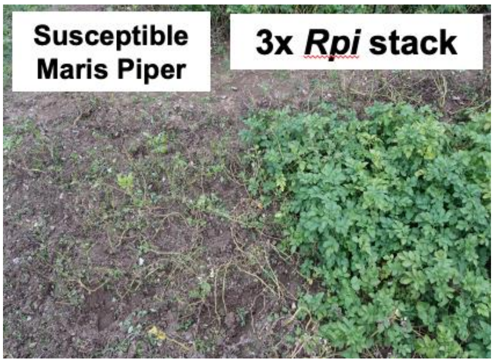
Institution: University of East Anglia		
Unit of Assessment: 5 - Biological Sciences		
Title of case study: Discovery and exploitation of *Resistance* (*R*) genes for crop improvement		
Period when the underpinning research was undertaken: 2001 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Professor Jonathan Jones FRS	Group Leader, The Sainsbury Laboratory, and Professor of Biology	1988 –present
Period when the claimed impact occurred: August 2013 – 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Potato is the third most directly consumed crop worldwide and is important for food security in many low- and middle-income countries. Potato late blight is the most destructive disease of potato. It caused the Irish potato famine of the 1840s and still leads to multibillion dollar annual losses globally. To control it, **Jones** discovered and cloned the first disease *Resistance* (*R*) gene to be deployed in a genetically modified (GM) crop. **Jones** also developed a novel method ("RenSeq") to accelerate *Resistance* gene discovery, and cloned additional blight resistance genes from wild potato relatives. This research has led to impacts on commerce, the economy, production and public policy. Specifically, **Jones**'s initial *Resistance* gene (*Rpi-vnt1*) has been deployed for late blight control in GM commercial potatoes by US company Simplot, and RenSeq kits are now being commercially marketed by another US company, Arbor Biosciences. **Jones's** initial *Resistance* gene and later-discovered ones have also been patented and licensed. In addition, RenSeq has been widely adopted in the public and private sectors for *Resistance* gene cloning in a range of crops and **Jones**'s advice and advocacy have influenced GM policy debates within the UK Parliament and Government.

2. Underpinning research



Potatoes play a key role in food security, in the UK and worldwide. However, potato yield and quality are constrained by susceptibility to diseases and pests, particularly late blight caused by the potato blight microorganism *Phytophthora infestans*, and by fungi, viruses, bacteria and nematodes. According to the Agriculture and Horticulture Development Board, to control late blight, UK potatoes require up to 15-20 sprays of agrichemicals per year, costing UK potato farmers approximately GBP50,000,000 per year. As fungicide-resistant late blight strains have evolved, better blight control is essential.

Resistance (*R*) genes enable plants to detect molecules from pests and pathogens and activate defence mechanisms. But using plant molecular genetics and breeding to exploit *Resistance* genes in crops faces three major challenges. First, if effective *Resistance* genes are absent from the crop gene pool, they must be found in wild relatives. Second, isolating *Resistance* genes from complex genomes such as those of wheat and potato is difficult. Third, *Resistance* genes need to be deployed in crop varieties in a manner that maximises durability. Here, breeders face a problem analogous to that posed by anti-microbial resistance to antibiotics, in that pathogens can rapidly evolve new means of avoiding countermeasures deployed against them. **Jones**'s research [e.g. Grants A-D] has addressed all three of these challenges:

Gene discovery in wild crop relatives: Limited genetic variation for late blight resistance is available to potato breeders in modern potatoes, which is why blight continues to be a problem. To address this challenge, **Jones** and team pioneered the use of a wild relative of potato, American black nightshade (*Solanum americanum*), as a novel source of blight resistance genes [R1].

Identifying genes for resistance in complex genomes: Most *Resistance* (*R*) genes encode "NLR" (nucleotide binding, leucine-rich repeat) immune receptor proteins. Crop genomes such as those of potato and wheat are large and complex and carry many hundreds of NLR-encoding genes. However, identifying which NLR gene among the large numbers present confers a specific and valuable resistance against an important pathogen is challenging. Since 2013, **Jones** and team have invented and refined a novel method termed *Resistance* gene enrichment sequencing ("RenSeq") for this purpose [R2]. RenSeq uses sequence capture of NLR-encoding genes [R2] and then integrates this with long-read genome sequencing such as PacBio circular consensus sequencing [R1]. This advance has created an unprecedented ability to define and distinguish multiple closely-related NLR-encoding genes in potato and wheat, and paved the way for rapid *Resistance* gene discovery in diploid and polyploid plants [R1-R3]. Prior to **Jones**'s work, *Resistance* gene cloning was extremely laborious, involving screening of large insert libraries and "chromosome walking". RenSeq removes the need for this, enabling researchers to "land" on NLR-encoding genes that can then be tested for function. This work has also underpinned novel methods to characterise *Resistance* gene diversity in plants [R3]. **Jones**'s major contributions to the understanding of plant disease resistance were recognised by his election in 2015 as an International Member of the US National Academy of Sciences.

Using RenSeq, **Jones** and team have identified several novel *Resistance to Phytophthora infestans* (*Rpi*) genes, including *Rpi-amr3* [R1] and the recently-discovered *Rpi-amr1* [S1, S2]. The first *Rpi* gene cloned by the **Jones** team (before the development of RenSeq) was *Rpi-vnt1* in 2009 [R4]. In collaboration with Simplot, a US food and agribusiness company, all three of these *Rpi* genes have been transferred into elite US potato cultivars. Commercial release of modified potatoes then began in 2018 in the US. **Jones** and colleagues also used RenSeq to clone Ry_{sto}, which is a *Resistance* gene against potato virus Y (PVY), a major problem for potato growers worldwide [R5]. This gene is being added to the set of *Rpi* genes in the UK's most popular potato variety, Maris Piper.

Gene stacking to slow the evolution of pathogen resistance: Wise and sustainable deployment of *Resistance* genes requires care, because use of single *Resistance* genes applies a strong selective pressure on pathogens, which can evolve to overcome single genes within 3-5 years. To meet this challenge, and to increase the sustainability of modified crops, **Jones** has pioneered the refinement of methods for *Resistance* gene "stacking", in which sets of several *Resistance* genes are added to the genomes of modified crops, requiring pathogens to undergo several mutations to cause disease, thus slowing the evolution of resistance [R6]. The utility of the resulting plants has been verified in multiple GM field trials in the UK. Specifically, trials in 2020 at the National Institute of Agricultural Botany (NIAB) in Cambridge identified lines ("PiperPlus") that are indistinguishable from Maris Piper potatoes, except for full blight resistance (including tuber blight resistance). These lines also showed improved tuber quality (reduced bruising and lowered reducing sugars after cold storage).

Image: Field trial of Maris Piper (left, dead) and GM Maris Piper (right, green, containing *Rpi* gene stack) potato, Norwich, UK, 2018. _Credit_: Jonathan Jones, The Sainsbury Laboratory.

3. References to the research

Underpinning research: The six outputs underpinning the research are all published in competitive, international peer-reviewed journals and have collectively been cited over 740 times (citation numbers are from Google Scholar; UEA author names are in bold):

R1 **Witek K**, Jupe F, **Witek AI**, Baker D, **Clark MD**, **Jones JDG** (**2016**) Accelerated cloning of a potato blight-resistance gene using RenSeq and SMRT sequencing. *Nature Biotechnology* 34: 656-660. DOI: 10.1038/nbt.3540 [135 citations]

R2 Jupe F, **Witek K**, Verweij W, Sliwka J, Pritchard L, **Etherington GJ**, **Maclean D**, Cock PJ, Leggett RM, Bryan GJ, Cardle L, Hein I, **Jones JDG** (**2013**) Resistance gene enrichment sequencing (RenSeq) enables reannotation of the NB-LRR gene family from sequenced plant genomes and rapid mapping of resistance loci in segregating populations. *The Plant Journal* 76: 530-544. DOI: 10.1111/tpj.12307. [246 citations]

R3 Van de Weyer A-L, Monteiro F, **Furzer OJ**, Nishimura MT, **Cevik V**, **Witek K**, **Jones JDG**, Dangl JL, Weigel D, Bemm F (**2019**) A species-wide inventory of NLR Genes and alleles in *Arabidopsis thaliana*. *Cell* 178: 1260-1272. DOI: 10.1016/j.cell.2019.07.038 [57 citations]

R4 Foster SJ, Park T-H, Pel M, Brigneti G, Sliwka J, Jagger L, Vossen E, **Jones JDG** (**2009**) *Rpi-vnt1*, a Tm-2(2) homolog from *Solanum venturii*, confers resistance to potato late blight. *Molecular Plant-Microbe Interactions* 22: 589-600. DOI: 10.1094/MPMI-22-5-0589 [178 citations]

R5 Grech-Baran M, Witek K, Szajko K, **Witek AI**, Morgiewicz K, Wasilewicz-Flis I, Jakuczun H, Marczewski W, **Jones JDG,** 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* 8: 655-667. DOI: 10.1111/pbi.13230 [14 citations]

R6 **Jones JDG**, **Witek K**, Verweij W, Jupe F, Cooke D, Dorling S, **Tomlinson L**, **Smoker M**, **Perkins S**, **Foster S** (**2014**) Elevating crop disease resistance with cloned genes. *Philosophical Transactions of the Royal Society B* 17: 369: 20130087. DOI: 10.1098/rstb.2013.0087. [115 citations]

Funding: Funding of this research since 2001 has come from nine awards of competitive, peer-reviewed funding from BBSRC, the most relevant ones being: Grant A: PI: **JDG Jones**. Title: *Isolation of new potato genes for resistance to* Phytophthora infestans *from wild diploid* Solanum *species*. Funder: BBSRC. Project dates: 5/9/2005 – 4/12/2008. Total value: GBP353,382. Grant B: PI: **JDG Jones**. Title: *New UK potato varieties with late blight and potato cyst nematode resistance, reduced bruising and improved processing quality*. Funder: BBSRC Horticulture and Potato Initiative (HAPI). Project dates: 1/10/2015 – 30/9/2020. Total value: GBP474,002. Grant C: PI: **JDG Jones**. Title: *Defining and deploying Rpi gene diversity in* S. americanum *to control late blight in potato*. Funder: BBSRC Industrial Partnership Award with Simplot. Project dates: 1/10/2017 – 30/09/2021. Total value: GBP777,912. Grant D: PI: **JDG Jones**. Title: *New potato varieties with late blight resistance, reduced bruising and improved processing quality*. Funder: BBSRC Super Follow-on Fund. Project dates: 3/6/2019 – 2/6/2021. Total value: GBP330,310.

4. Details of the impact

The research of **Jones** and team on *Resistance* gene discovery and exploitation has led to impacts on commerce, the economy, production and public policy, benefiting companies, agricultural practitioners, the public and government nationally and internationally:

Impact on commerce, the economy and production via crop improvement: **Jones'**s research enabled isolation of the late blight *Resistance* genes *Rpi-vnt1, Rpi-amr1* and *Rpi-amr3* [R1, R2, R4; S1], and showed that *Rpi-vnt1* functions well in the field in the UK. Patents for all three of these genes have been filed [S1] and licensed by Simplot [S2]. A patent for the potato virus Y *Resistance* gene (*Ry_{sto}*) has also been filed [R5, S1]. **Jones**'s close relationship with Simplot, which arose following an approach by the company, has included two BBSRC Industrial Partnership Awards in which the company has been a 10% contributing partner [e.g. Grant C]. **Jones** collaborated with Simplot and UK biotechnology company BioPotatoes Ltd to bring the three late blight *Rpi* genes to field trials in Maris Piper potatoes. This project is in its fourth year (currently supported by BBSRC Super Follow-on Funding, Grant D), with trials on ten advanced lines having taken place in 2020 at the National Institute of Agricultural Botany, enabling selection of the elite "PiperPlus" line. **Jones** is now advancing this line towards regulatory approval and commercialisation. As the Plant Biology and Molecular Biology R&D Directors at Simplot Plant Sciences stated, *"Prof. Jonathan Jones, in partnership with BioPotatoes Ltd, has enhanced the*

UK potato variety Maris Piper with robust late blight resistance and improved processing qualities. The combination of resources resulted in a Maris Piper potato that has a lower cost of production, higher marketable yield and significant benefits for British producers, processors and consumers. Late blight resistance was accomplished via expression of resistance genes Rpi-vnt1, Rpi-amr3 and Rpi-amr1 cloned and characterized in the Jones lab." [S2].

In addition, Simplot is already selling a genetically modified (GM) blight-resistant potato, Innate® 2.0, carrying **Jones**'s *Rpi-vnt1* in the USA [S2], with this variety having been approved by the United States' Department of Agriculture (USDA), Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) for commercial growing and human consumption [S3]. This represents a breakthrough for the deployment of GM methods as it is the first ever commercial deployment of a cloned *Resistance* gene in a major crop. Simplot will also use *Rpi-amr3* in their next generation of Innate® 3.0 potato lines. Simplot project that use of Innate® potatoes will save growers tens of millions of dollars in money otherwise spent on fungicidal prevention of late blight, and result in a more sustainably grown potato [S2]. Potatoes with *Resistance* genes from **Jones**'s work are also being field-trialled in Africa [S4], Bangladesh and Indonesia [S2], underlining their potential to increase food security in low- and middle-income countries [S2].

Evidencing **Jones**'s overall contribution, Simplot Plant Sciences stated, *"The discoveries of Dr. Jones have enabled Simplot … to achieve its commercial and philanthropic goals."* Moreover, *"[Jones] … played a pivotal role in this potato late blight protection breakthrough and Simplot looks forward to further collaborations in the future. Having accomplished what we consider a genetic solution to late blight for the United States and perhaps most of the world, we anticipate moving on in collaboration with Dr. Jones to solve other potato diseases including potato virus Y."* [S2].

Impact on commerce, the economy and production via new technologies: **Jones**'s work has enabled researchers to investigate immune receptor diversity and accelerate the cloning of useful *Resistance* genes in crops. In particular, **Jones**'s methods are now widely used by publicly-funded laboratories working on other crop species, including wheat [e.g. S5]. In the private plant breeding sector, RenSeq has become standard practice for investigators working on disease resistance. Evidencing this, following **Jones**'s publication of the RenSeq method [R2], the US molecular biology development and manufacturing company Arbor Biosciences has been marketing commercial RenSeq kits (since 2014) and services (as "myReads®" since 2016) [S6]. Arbor Biosciences reported that: *"Our customer base for the RenSeq technology is made up of academics, industry [and] governmental organizations (in the USA, Europe and Oceania) … and has led to a general expansion of disease resistance gene cloning capabilities beyond cereals."* [S6]. Furthermore, *"Jones' RenSeq technology has had a substantial beneficial impact on our company. Arbor's annual NGS* [Next Generation Sequencing] *services income represents roughly 30% of our overall turnover, and RenSeq accounts for roughly 20% of this in the last fiscal year, and roughly 10% of our services income in total since RenSeq was first offered in 2016"* [S6]. The total RENSeq "myReads®" services revenue from launch in 2016 to financial year end 2020 was [redacted] and for financial year 2020 alone was [redacted] [S6].

Jones's work underpinning the intellectual rationale for gene stacking [R6, S4] has been used to develop a wheat variety carrying a stack of five stem rust resistance genes. The 2Blades Foundation, a not-for-profit company partnered with The Sainsbury Laboratory, has collaborated with the International Maize and Wheat Improvement Center (CIMMYT) in Mexico to deploy this wheat rust resistance gene stack in CIMMYT wheat lines [S7].

Impact on public policy via outreach and advocacy: **Jones** is a long-standing advocate of using GM methods for crop improvement and, in this context, is highly active in public education and policy arenas. **Jones** regularly publicly advocates for GM methods in press interviews and articles [S8]. In addition, **Jones** has contributed to the evidence that policy changes on GM regulation would be in the public interest. For example, he was a co-author of a 2014 report cited in the Council for Science and Technology's letter advising the Prime Minister's office on the risks and benefits of GM technologies and has also presented the GM case to UK parliamentarians [S9].

Evidencing the reach of such advice, in his first speech as Prime Minister, Mr Johnson said, *"let's start now to liberate the UK's extraordinary bioscience sector from anti-genetic modification rules, and let's develop the blight-resistant crops that will feed the world"* [S10]. More specifically, a member of the House of Lords with expertise in the field stated, "[Jones's advocacy] *has an enormous impact on the debate within the UK, in Europe and globally. I have attended many meetings in which parliamentarians, civil servants, government ministers, government scientific advisors, media commentators and others have benefited from* [his] *… presentations and discussions, and these have had a real impact on decisions taken. … A good instance of his impact can be found in the current government consultation on changing the regulations to allow gene editing in agriculture, and to consider how to regulate genetic modification after that. This consultation was announced by the government in response to an amendment to the agriculture bill in the Lords. The amendment and many of the speeches in favour of it benefited directly from advice given by Prof Jones, and the shape of the consultation since has also benefited from his wisdom and advice."* [S10]. The Agriculture Bill was passed into law in November 2020 [S10].

5. Sources to corroborate the impact

S1 Patent Filings: Patent for *Rpi-vnt1* (aka *Rpi-oka1*) and *Rpi-mcq1*: US8367893; Patent for *Rpi-amr1: US20190359998*; Patent for *Rpi-amr3*: EP3294892; Patent for Ry_{sto}: WO2019023587.

S2 Letter from the Director of Plant Biology R&D and the Director of Molecular Biology R&D, Simplot Plant Sciences (15.12.20).

S3 US agency approval of Simplot's Innate® 2.0 potato: (a) Article (from nbcnews.com) reporting USDA approval (31.10.16), accessed 14.1.21; (b) Spud Smart article (from spudsmart.com) reporting EPA and FDA approval (28.2.17), accessed 25.2.21.

S4 Ghislain M et al. (2019) Stacking three late blight resistance genes from wild species directly into African highland potato varieties confers complete field resistance to local blight races *Plant Biotechnology Journal* 17: 1119-1129. DOI: 10.1111/pbi.13042

S5 Arora S et al. (2019) Resistance gene cloning from a wild crop relative by sequence capture and association genetics. *Nature Biotechnology* 37:139-143 DOI: 10.1038/s41587-018-0007-9

S6 Arbor Biosciences: (a) Letter from R&D Manager, NGS Division, Arbor Biosciences (18.2.21); (b) company webpage (from arborbiosci.com) advertising RenSeq technology for sale, accessed 14.1.21, citing [R2] in first paragraph; (c) e-mail with RenSeq revenue (10.3.21).

S7 2Blades's announcement (from 2blades.org) (7.12.16), accessed 1.3.21.

S8 Public GM advocacy: (a) BBC News article (from bbc.co.uk), citing [S9a] and **Jones** (14.3.14), accessed 14.1.21; (b) Food Research Collaboration website article (from foodresearch.org) by **Jones** (14.3.17), accessed 14.1.21.

S9 Report/advice to parliamentarians: (a) Baulcombe D … **Jones J** et al. (2014) *GM Science Update: A report to the Council for Science and Technology*; and Council for Science and Technology's letter advising the Prime Minister on the risks and benefits of GM technologies; both available at gov.co.uk, accessed 14.1.21; (b) UK All-party Parliamentary Group on Science and Technology in Agriculture, listing **Jones** as a guest speaker (19.5.20), accessed 1.3.21.

S10 Impact on government: (a) Boris Johnson's first speech (from gov.co.uk) as Prime Minister (24.7.19), accessed 14.1.21; (b) Letter from member of the House of Lords (15.1.21); (c) Announcement of Agriculture Bill becoming law (11.11.20), accessed 10.3.21.