**Institution:** University of East Anglia

**Unit of Assessment:** 5 – Biological Sciences

**Title of case study:** Transforming the landscape of drug development with life-changing RNAi-based drugs

**Period when the underpinning research was undertaken:** 2000-2008

**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: |
|---|---|---|
| Sir David Baulcombe FRS | Group Leader, The Sainsbury Laboratory | 1988 – 2007, and then various contracts to the present. |

**Period when the claimed impact occurred:** August 2013-December 2020

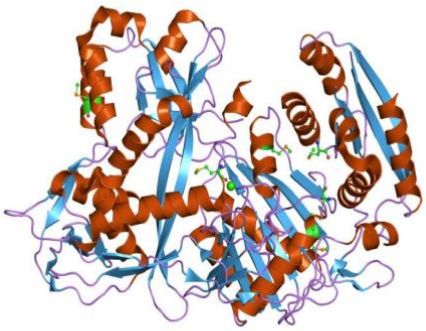
**Is this case study continued from a case study submitted in 2014?** Yes

## 1. Summary of the impact

**Baulcombe** and colleagues' ground-breaking discovery of small interfering RNA (siRNA) has proved transformative in drug design by permitting the development of drugs that treat previously "undruggable" diseases in humans. Specifically, this work has led to the development of four therapeutic drugs based on RNAi (RNA interference), ONPATTRO®, GIVLAARI®, OXLUMO™ and LEQVIO®. These have been designed to treat serious genetic disorders affecting many thousands of patients worldwide. The drugs realise the ability of RNAi to target disease-causing genes and represent the first RNAi-based therapeutics developed anywhere in the world. Over 1,300 patients have received ONPATTRO® and GIVLAARI®, with life-changing benefits. Many more will benefit from the recent approval of LEQVIO in the UK/EU. A patent issued to **Baulcombe** and colleagues for RNAi technology has generated GBP10,000,000 in licensing income, while the current impact of the global RNAi therapeutics sector is reflected in its growth in value to approximately USD1,090,000,000 (12-2018).

## 2. Underpinning research

In 1990, plant molecular geneticists observed a strange phenomenon: when they inserted a gene controlling flower colour into the Petunia genome, it resulted in white flowers instead of the expected coloured ones. Work over the following years established that the inserted DNA caused gene "silencing", so launching the field of RNA interference (RNAi). RNAi is a cellular mechanism by which small RNA molecules can prevent the expression of individual genes by interfering with those genes' messenger RNA, i.e. silencing them. Various aspects of the molecular mechanisms underlying RNAi were discovered by different groups, with **Baulcombe**'s laboratory making a number of seminal contributions.



For example, **Baulcombe**, Hamilton and colleagues demonstrated that gene silencing effects could spread within individual plants, between different cells and parts of the plant, and discovered the role of small antisense RNAs (25 nucleotides in size) in mediating RNAi in plants. Since 2000, they have also identified the key genes involved in the production of small antisense RNAs, specifically RNA-dependent RNA polymerase [R1], RNA helicase [R2], RNA polymerase IV [R3] and genes that bind small RNAs and slice target RNAs to mediate RNAi (ARGONAUTE [R4]). Moreover, they have characterised the role of the RNA polymerase PolIVb in siRNA biogenesis and RNA-directed DNA methylation [R5]. This body of research, supported by Grants A-D,

underpinned the fundamental understanding of RNAi, a process that is shared across eukaryotic organisms (animals, plants, fungi and protists).

In REF2014, the unit submitted an impact case study based on **Baulcombe**'s RNAi research that focused on the impact it had through enabling commercial design, production and sale of synthetic siRNAs as reagents by biotechnology companies (*"Small interfering RNA – a change in the landscape of biotechnology"*). In the current case study, we are excited to be able to focus on a new set of significant, far-reaching impacts that the research has had since REF2014. Specifically, because RNAi can be used to silence individual genes in a targeted manner, **Baulcombe** and colleagues' pioneering discoveries have helped open up a completely new domain of innovation in drug development, namely a novel method for targeting genetic diseases in humans.

Many serious human diseases are genetic ones, being caused by abnormalities in the genome such as an altered chromosome number or gene mutations. So-called autosomal dominant diseases can be inherited from either parent acting as a carrier of the mutated gene and thereby contributing to the transmission and expression of the disorder in their children. The mutated genes result in the production of abnormal proteins that impair or alter their usual function within the cell in a harmful manner. Many such proteins were considered "undruggable", i.e. harmful proteins that cannot be targeted pharmacologically by classic methods such as the use of antibodies. RNAi has provided a means of treating such human diseases, previously considered intractable. Indeed, until now only the symptoms, not the causes, could be treated. In this way, RNAi has created an entirely new approach to improving the health and wellbeing of people.

Recognising the broader potential impact of their work, **Baulcombe** and colleagues filed for intellectual property on their discoveries on RNAi with Plant Biosciences Limited, an independent technology management company based on the Norwich Research Park, and this patent [R6] was then licensed to the US biopharmaceutical company Alnylam Pharmaceuticals Inc. to develop RNAi-based therapeutics.

*Image*: Argonaute protein (Argonaute homologue Aq 1447); *Credit*: Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute (ebi.ac.uk/), Public domain, via Wikimedia Commons (commons.wikimedia.org/wiki/File:PDB_1yvu_EBI.jpg).

## 3. References to the research

*Underpinning research:* Six key outputs report the underpinning research - five papers in competitive, international, peer-reviewed journals and one patent [R6]. Collectively, the papers have been cited over 3,870 times (citation numbers are from Google Scholar; UEA author names are in bold):


R1 **Dalmay T, Hamilton A**, Rudd S, Angell S, **Baulcombe DC** (**2000**) An RNA-dependent RNA polymerase gene in Arabidopsis is required for posttranscriptional gene silencing mediated by a transgene but not by a virus. *Cell* 101: 543-553. DOI: 10.1016/S0092-8674(00)80864-8 [1,317 citations]

R2 **Dalmay T, Horsefield R,** Braunstein TH, **Baulcombe DC** (**2001**) SDE3 encodes an RNA helicase required for post-transcriptional gene silencing in Arabidopsis. *EMBO Journal* 20: 2069-2078. DOI: 10.1093/emboj/20.8.2069 [455 citations]

R3 **Herr AJ**, Jensen MB, **Dalmay T**, **Baulcombe DC** (**2005**) RNA polymerase IV directs silencing of endogenous DNA. *Science* 308: 118-120. DOI: 10.1126/science.1106910 [759 citations]

R4 Baumberger N, **Baulcombe DC** (**2005**) Arabidopsis ARGONAUTE1 is an RNA Slicer that selectively recruits microRNAs and short interfering RNAs. *Proceedings of the National Academy of Sciences USA* 102: 11928-11933. DOI: 10.1073/pnas.0505461102 [1,073 citations]

R5 Mosher R, **Schwach F**, Studholme D, **Baulcombe DC** (**2008**) PolIVb influences RNA-directed DNA methylation independently of its role in siRNA biogenesis. *Proceedings of the National Academy of Sciences USA* 105: 3145-3150. DOI: 10.1073/pnas.0709632105 [271 citations]

R6 **Baulcombe DC**, Hamilton AJ. Gene silencing. US patent number: 8,097,710. Publication date: 4.11.04. Granted date: **17.1.12**. Available at: patents.google.com/patent/US8097710B2/en

*Funding:* Funding of the research has come from core funding to The Sainsbury Laboratory from the Gatsby Charitable Foundation and competitive, peer-reviewed sources including UKRI and the EU: Grant A: PI: **D Baulcombe** (lead). Title: *Composition of plant virus RNA replicase (COMREP)*. Funder: EU FP4-BIOTECH 2. Project dates: 1 October 1997 – 30 September 2000. Total value: GBP158,533; Grant B: PI: **D Baulcombe** (lead). Title: *Identification of foreign replicons and host genes naturally targeted by post-transcriptional gene silencing*. Funder: BBSRC. Project dates: 1 May 2001 – 30 April 2004. Total value: GBP173,580; Grant C: PI: **D Baulcombe** (lead). Title: *Factors affecting gene silencing in plants using tobacco rattle virus*. Funder: BBSRC. Project dates: 5 June 2001 – 4 June 2004. Total value: GBP204,336; Grant D: PI: **D Baulcombe** (lead). Title: *Silencing RNAs: organisers and coordinators of complexity in eukaryotic organisms (SIROCCO)*. Funder: EU FP6-LIFESCIHEALTH. Project dates: 1 January 2007 – 30 September 2011. Total value: EUR14,439,820 (GBP462,550 to UEA).

## 4. Details of the impact

**Baulcombe**'s research and its associated intellectual property have proved fundamental to the development of RNAi-based therapeutics that target previously intractable diseases [S1-S3]. Acting on behalf of **Baulcombe** and colleagues, Plant Bioscience Limited licensed **Baulcombe**'s patent to Alnylam Pharmaceuticals [R6], and this has ensured Alnylam's freedom to operate, since 2013, to develop, trial and release three RNAi-based drugs that target human genetic disorders, along with a fourth to treat inherited high cholesterol (familial hypercholesterolemia) [S4]. In particular, to target genetic disorders, Alnylam has registered and commercialised the two drugs ONPATTRO® and GIVLAARI®, and it has obtained permission for early release of a third drug, OXLUMO™, through the UK Medicines and Healthcare Products Regulatory Agency's Early Access to Medicines Scheme [S5] and the United States Food and Drug Administration (FDA) [S6]. It has also received approval of the familial hypercholesterolemia treatment drug LEQVIO® from the European Commission [S4].

As detailed below, these drugs are providing treatments that patients have described as transformative in their impact on individual lives [S4, S7-S9]. They have also helped underpin the growth of Alnylam Pharmaceuticals as a company and yielded important patent revenues. In this way, the research has had substantial impact on the health and wellbeing of people and on commerce and production in the health sector. As the Managing Director of Plant Bioscience Limited has stated, *"the impact of the discovery of siRNAs and understanding of their role in RNAi interference contributed by Sir David Baulcombe and Dr Andrew Hamilton has opened up a new generation of therapeutics. After pioneering development by PBL's licensing partners these are now having a huge impact across the world, in a wave of new and diverse treatments for previously intractable indications, treating millions of patients with a series of important life-threatening conditions."* [S3].

*ONPATTRO®* (patisiran): The disease hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a life-threatening, autosomal dominant neurodegenerative disease driven by the deposition of misfolded transthyretin protein (TTR protein) in the heart, nerves and gastrointestinal tract. Approximately 50,000 people, aged mainly between 20 and 40, suffer from the disease worldwide [S4]. Without treatment, sufferers typically die between 5 and 15 years after the onset of symptoms. Treatment options are limited, and many cases remain undiagnosed. RNAi therapeutics allow transcripts (messenger RNA) from the faulty gene to be silenced, thereby decreasing the amount of misfolded TTR protein in the body. ONPATTRO® has been approved by the European Union and United States, along with Brazil, Canada, Israel, Japan, Switzerland and Taiwan, for the treatment of hATTR amyloidosis [S4]. Based on a large-scale randomised clinical trial, ONPATTRO® significantly reduced patients' symptoms and improved their quality of life, such as walking ability, nutritional status and the ability to perform activities of daily living [S7, S8]. As a result, as at the third quarter of 2020, over 1,150 patients were taking ONPATTRO® [S4].

In terms of improvement in quality of life, a patient treated with ONPATTRO® stated, *"I'm so much more than this disease, and I can put it in its place and do the things that I love to do with the people who I most love and adore in my life."* [S4].

*GIVLAARI®* (givosiran): Acute hepatic porphyria (AHP) consists of a group of four inherited diseases of the liver with acute neurovisceral symptoms that are often missed or delayed in diagnosis because the clinical symptoms mimic those of other common disorders. Acute intermittent porphyria is the most severe of the set, with 20% of patients with recurrent symptoms developing chronic and ongoing pain. It occurs in about 1 in 1,600 people with a Western European genetic background and, in the EU and US, the patient population is estimated at 3,000 people [S4]. Previously, long-term solutions for treatment involved either infusion with blood products (e.g. IV hemin) or liver transplantation. GIVLAARI® was developed to treat adults with acute hepatic porphyria and was approved by the US Food and Drug Administration in November 2019 [S4]. It has also been approved for use in the European Union, Brazil and Canada [S4]. This drug significantly reduces the rate of porphyria attacks that require hospitalisations, urgent healthcare visits or infusion with blood products at home. A patient receiving the drug for acute intermittent porphyria stated, *"I've had pain for 10 years, I didn't expect that could go away. I'm seeing friends and they're [asking] 'you're not taking any painkillers?' and I was [saying] 'no!'."* [S9]. As at the third quarter of 2020, over 150 patients were being treated with GIVLAARI® [S4].

*OXLUMO™* (lumasiran): This drug is an RNAi therapeutic for the treatment of primary hyperoxaluria type 1 (PH1). In the EU and US, the patient population is estimated at 3,000 symptomatic individuals [S4]. The disease is caused by the build-up of oxalate, which is normally excreted in the urine. In affected people, the accumulated oxalate is deposited in the kidneys and urinary tract, where it combines with calcium to form the main component of kidney and bladder stones (calcium oxalate). Lumasiran is currently under approval and has been granted a "positive scientific opinion" (i.e. approved for use by the National Health Service) through the UK Medicines and Healthcare Products Regulatory Agency's Early Access to Medicines Scheme [S5].

*LEQVIO®* (inclisiran): LEQVIO® is the first siRNA drug that reduces low-density lipoprotein cholesterol (LDL-C) in patients with familial hypercholesterolemia. Approximately 3,900,000 people die annually in Europe from cardiovascular disease, of which high cholesterol (hypercholesterolemia) is a leading cause. While reducing low-density lipoprotein cholesterol levels using statins is a common treatment for high-risk patents, the majority of these patients (80%) do not experience reductions to below recommended levels. LEQVIO® conferred effective and sustained low-density lipoprotein cholesterol reduction of up to 52% in patients. It was approved by the European Commission in December 2020 [S4]. It is estimated that approximately 50,000,000 people with atherosclerotic cardiovascular disease or familial hypercholesterolemia could benefit from treatment with LEQVIO® in future [S4]. For example, in the UK, the Managing Director of Plant Bioscience Limited reported that: *"NHS projections estimate the drug will save 30,000 lives for every 300,000 patients treated"* [S3].

Overall, the scope of using RNAi for drug development is limited only by the identification of sequence targets relevant to a given disease. As such sequences are identified, drugs based on RNAi are being developed to target genes for an increasing range of diseases, including cancer (e.g. vascular endothelial growth factor, VEGF), and to target viruses underpinning viral diseases, including Hepatitis B and the recent pandemic disease COVID-19. Similarly, drugs targeting specific genes are being developed to treat diseases such as haemophilia, Alpha-1 liver disease, hypertension and cerebral amyloid angiopathy [S2, S4]. Hence, RNAi-based drug development has an extremely promising future.

*Economic impact of RNAi-based therapeutics.* As a young and rapidly growing development, the market in RNAi-based therapeutics has yet to realise its full economic potential. Nonetheless, in 2018, the global size of this market was already estimated to be approximately USD1,090,000,000 (12-2018) [S10]. RNAi drugs have also contributed substantially to the income and financial growth of Alnylam Pharmaceuticals. Specifically, for ONPATTRO®, the company's quarterly revenues increased from USD46,100,000 (12-2020) in the third quarter of 2019 to USD82,500,000 (12-

2020) in the third quarter of 2020 [S4]. In addition, in the third quarter of 2020, GIVLAARI® earned the company USD16,700,000 (12-2020) [S4]. For **Baulcombe** and colleagues, the patent [R6] issued for RNAi technology and managed by Plant Bioscience Limited has generated GBP10,000,000 in licensing income since 01-2014 [S3].

**5. Sources to corroborate the impact**


S1 Setten RL, Rossi JJ, Han S (2019) The current state and future directions of RNAi-based therapeutics. *Nature Reviews Drug Discovery* 18: 421-446. DOI: 10.1038/s41573-019-0017-4

S2 Hu B et al. (2020) Therapeutic siRNA: state of the art. *Signal Transduction and Targeted Therapy* 5: 101. DOI: 10.1038/s41392-020-0207-x

S3 Letter from the Managing Director, Plant Bioscience Limited (16.2.21).

S4 Alnylam Pharmaceuticals R&D Day 2020, Day 1 presentations (15.12.20). Available at: investors.alnylam.com (accessed 30.12.20). [PDF pages: pp. 6, 9, 18, 28, 55 (Intro.); pp. 10, 28, 31, 32 (ONPATTRO®); pp. 6, 18, 33, 34 (GIVLAARI®); pp. 12, 35, 36 (OXLUMO™); pp. 13, 23 (LEQVIO®); pp. 32, 34 (revenue)].

S5 UK Medicines and Healthcare Products Regulatory Agency (MHRA) scientific opinion through the Early Access to Medicines Scheme (EAMS) for Lumasiran (14.7.20) (accessed 30.12.20).

S6 News release from US Food and Drug Administration (from fda.gov) (23.11.20) (accessed 2.3.21).

S7 Adams D et al. (2018) Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *New England Journal of Medicine* 379: 11-21. DOI: 10.1056/NEJMoa1716153

S8 Obici L et al. (2020) Quality of life outcomes in APOLLO, the phase 3 trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. *Amyloid* 27: 153-162. DOI: 10.1080/13506129.2020.1730790

S9 BBC News article (2019) detailing the impact of a drug trial of givosiran on a UK patient (13.4.19). Available at: bbc.co.uk (accessed 30.12.20).

S10 Grand View Research market analysis report available at: grandviewresearch.com (June 2019) (accessed 30.12.20).