IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

Allele Biotechnology and Pharmaceuticals, Inc., Plaintiff, v. Regeneron Pharmaceuticals, Inc., Defendant.	Civil Action No. _____ Jury Trial Demanded

COMPLAINT

Plaintiff Allele Biotechnology and Pharmaceuticals, Inc. ("Allele" or "Plaintiff") brings this action for patent infringement against Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Defendant").

THE PARTIES

1. Plaintiff Allele is a California corporation having its principal place of business at 6404 Nancy Ridge Drive, San Diego, California. Allele focuses on developing and adapting cutting-edge technologies for clinical and therapeutic use and works on biological advancements that have been at the forefront of molecular biology research, including RNA interference, fluorescent proteins, induced pluripotent stem cells (iPSCs), genome editing, and camelid-derived single-domain antibodies.

2. Upon information and belief, defendant Regeneron is a New York corporation with its principal place of business at 777 Old Saw Mill River Road, Tarrytown, New York. Regeneron is primarily in the business of pharmaceutical preparations and commercializes products to treat various diseases.

JURISDICTION

3. This is a civil action for patent infringement under 35 U.S.C. § 271.

4. This action arises under the patent laws of the United States, 35 U.S.C. § 1, *et seq.* This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

5. Upon information and belief, this Court has personal jurisdiction over Regeneron because, *inter alia*, Regeneron is incorporated in New York; has substantial, continuous, and systematic contacts with the State of New York that render it at home in New York; markets, sells, and/or distributes pharmaceutical products to residents of the State of New York; and enjoys substantial income from sales of its pharmaceutical products in the State of New York.

6. Upon information and belief, Regeneron has engaged in and maintained systematic and continuous business contacts within the State of New York and has purposefully availed itself of the benefits and protections of the laws of New York.

7. Upon information and belief, Regeneron holds current and valid "Wholesaler" and "Manufacturer" licenses from the New York State Board of Pharmacy under Registration Nos. 034240, 022167, and 022168.

8. Upon information and belief, Regeneron consented to jurisdiction in New York by incorporating in New York and registering to conduct business with the State of New York and maintaining registered agent C T CORPORATION SYSTEM, 28 Liberty St., New York, New York.

9. This Court also has personal jurisdiction over Defendant because it has previously brought suit in this District and availed itself of this forum by asserting claims for the purpose of litigating patent infringement disputes. *See, e.g.*, Complaint, *Regeneron Pharm., Inc. v. Merus N.V.*, No. 1:14-cv-01650-KBF (S.D.N.Y. Mar. 11, 2014), ECF No. 1. This Court also has

personal jurisdiction over Defendant because it has previously been sued in this District without challenging this Court's assertion of personal jurisdiction and availed itself of this forum by asserting counterclaims for the purpose of litigating patent infringement disputes. *See, e.g.*, Answer and Countercls., *Novartis Vaccines and Diagnostics, Inc. v. Regeneron Pharm., Inc.*, No. 1:18-cv-02434-DLC (S.D.N.Y. Nov. 7, 2018), ECF No. 96.

VENUE

10. Venue is proper in this Judicial District under 28 U.S.C. §§ 1400 and 1391. Venue is proper in this Court at least because Regeneron is incorporated in the State of New York, maintains its principal place of business in this District, and maintains its registered office in this District and therefore "resides" in New York and in this District under 28 U.S.C. § 1400(b).

11. Venue also is proper in this Court because Defendant has previously brought suit in this District and availed itself of this forum by asserting claims for the purpose of litigating patent infringement disputes. *See, e.g.*, Complaint, *Regeneron Pharm., Inc. v. Merus N.V.*, No. 1:14-cv-01650-KBF (S.D.N.Y. Mar. 11, 2014), ECF No. 1. Venue is also proper in this Court because Defendant has previously been sued in this District without challenging that venue is proper in this Court and availed itself of this forum by asserting counterclaims for the purpose of litigating patent infringement disputes. *See, e.g.*, Answer and Countercls., *Novartis Vaccines and Diagnostics, Inc. v. Regeneron Pharm., Inc.*, No. 1:18-cv-02434-DLC (S.D.N.Y. Nov. 7, 2018), ECF No. 96.

BACKGROUND

12. Allele repeats and realleges the allegations of the foregoing paragraphs as though fully set forth herein.

13. Allele is a private, San Diego-based company that explores the mechanisms of biological processes to develop technologies and products for biomedical researchers and for clinical and therapeutic use. The company was founded by scientists with the goal of advancing discovery and innovation.

14. Fluorescent proteins (FPs) are a class of proteins capable of emitting light of one wavelength upon exposure to light of a different wavelength. FPs have numerous uses in biomolecular research. For example, biologists may introduce a gene (or a gene chimera) encoding an engineered FP into living cells and then visualize the expression and subcellular dynamics of the subsequently expressed gene product using fluorescence microscopy. FPs may also be used as readily detectable tags in various assays and reporter constructs.

15. The value of the discovery and development of FPs has been well recognized and appreciated across a wide spectrum of clinical and research fields. Research has continued in search of bright, photostable, and fast-maturing FPs in all spectral regions. Those that perform well as fusions or in fluorescent resonance energy transfer (FRET) applications see ever-increasing use as molecular markers. Recently, the emergence of novel microscopy techniques that can image with resolutions of ~10 nm have further emphasized the importance of fluorescent protein advancement.

16. For a span of 20 years, researchers had looked to *Aequorea victoria* Green Fluorescent Protein (avGFP) for their imaging and tracking needs. Over this time period, numerous refinements to avGFP have elicited variants capable of emitting in a wide spectrum of colors and have resulted in optimized versions of avGFP used for a multitude of applications. As imaging resolution increased, however, most common fluorescent proteins, including avGFP, did

not possess certain characteristics necessary for the most demanding high-resolution applications.

17. Allele first started offering FPs in 2006 with one guiding principle: to create the brightest truly monomeric FPs to enable and advance imaging technologies and research methods. Most naturally occurring FPs exist in oligomeric form, such dimers or tetramers. But oligomeric FPs have disadvantages as molecular biology tools. For example, their larger size and tendency to self-aggregate can limit their use in fusion studies to localize or functionally characterize a protein of interest, compromise their stability under demanding experimental conditions, reduce the resolution of fluorescence imaging with such proteins, and compromise the utility of such FPs in FRET applications. Monomeric FPs, by contrast, eliminate those problems inherent with traditional oligomeric FPs.

18. To meet the continuing need for smaller, brighter, more stable FPs in ever more demanding assays and imaging applications, particularly in the yellow and green segment of the emission spectrum, Allele developed a novel, high-performance monomeric yellow-green fluorescent protein, mNeonGreen, derived from a tetrameric yellow FP (YFP) found in a small marine invertebrate of the cephalochordate subphylum known as *Branchiostoma lanceolatum*.

19. Allele derived mNeonGreen by creating and introducing a series of specialized changes from the original tetrameric cephalochordate FP, which resulted in a novel, monomeric FP that still managed to exhibit sharp excitation and emission peaks with excellent brightness, quantum yield, and stability. The resulting monomeric mNeonGreen protein was blue-shifted relative to the original cephalochordate tetrameric FP, placing its emission wavelength between the traditional GFP and YFP classes. As a result, mNeonGreen fluorescence can be detected and

imaged using standard GFP and YFP filter sets with little to no reduction in detected fluorescence signal.

20. Allele's mNeonGreen is among the brightest monomeric green or yellow fluorescent protein produced to date and has proven to be an excellent fusion tag for traditional imaging as well as single-molecule super-resolution imaging.

21. Allele is the assignee and lawful owner of United States Patent No. 10,221,221 ("the '221 patent"), entitled "Monomeric Yellow-Green Fluorescent Protein from Cephalochordate," which duly and lawfully issued from the United States Patent and Trademark Office on March 5, 2019. A true and correct copy of the '221 patent is attached as Exhibit A and made a part hereof.

22. As the owner of the '221 patent by assignment, Allele is authorized and has standing to bring legal action to enforce all rights arising under the '221 patent.

23. The '221 patent describes and claims Allele's new and useful high performance monomeric yellow-green fluorescent proteins, one embodiment of which Allele has marketed under the name mNeonGreen. For ease of reference Allele herein will refer to the claimed proteins as "mNeonGreen."

24. Business Wire reported on the issuance of the '221 patent on April 23, 2019, and touted Allele's patented mNeonGreen protein as the "world's brightest monomeric fluorescent protein."

25. Hundreds of organizations and universities have active licenses to use Allele's mNeonGreen technology, which are listed at https://reagents.allelebiotech.com/fluorescent-protein-active-licenses/.

26. Regeneron does not have, and has never had, a license to use Allele's mNeonGreen technology. Upon information and belief, Regeneron has used and/or is currently using Allele's patented mNeonGreen technology, as demonstrated by multiple published articles and papers authored by Regeneron representatives, some of which are described below.

27. One such example is a paper first published in June 2020 in the academic journal *Science*, entitled "Studies in Humanized Mice and Convalescent Humans Yield a SARS-CoV-2 Antibody Cocktail," co-authored by Regeneron employees (Hansen, et al.).[1] A true and correct copy of that paper is attached as Exhibit B. The Hansen paper explains how neutralizing antibodies have become an important tool in treating infectious diseases and describes different approaches to generate antibodies against the "SARS-CoV-2 spike" protein. The paper explains that "[t]housands of antibodies were isolated and subsequently screened" for their ability to neutralize a viral reporter construct detected by its expression of mNeonGreen fluorescent protein ("pVSV-SARS-CoV-2-S(mNeon)"). During this process, "mNeon expression was measured 24 hours post-infection as a read-out for virus infectivity." For reference, the Regeneron paper directs readers to an article describing the original creation of the mNeonGreen protein, published by the inventors of the '221 patent (Shaner et al., *A bright monomeric green fluorescent protein derived from Branchiostoma lanceolatum*, NAT. METHODS 10, 407–409 (2013)).

28. Published with the above-described *Science* paper by Hansen et al. (Exhibit B) were "Supplementary Materials" disclosing additional data, processes, and other information. A true and correct copy of the published Supplementary Materials is attached as Exhibit C. The

[1] J. Hansen et al., *Studies in Humanized Mice and Convalescent Humans Yield a SARS-CoV-2 Antibody Cocktail*, SCIENCE 369, 1010-1014 (21 August 2020).

materials explain that "[n]on-replicative pseudoparticles were generated using a VSV genome encoding the mNeonGreen fluorescent reporter gene instead of the native viral glycoprotein (VSV-G). Infectious particles complemented with VSV-G ($VSV^{\Delta G:mNeon}$/VSV-G) were recovered and produced using standard techniques with minor modifications." Then, "[c]ells were monitored for mNeonGreen expression or cytopathic effect (CPE) indicative of virus replication." The supplementary materials again reference the same article published by the inventors of the '221 patent describing the creation of mNeonGreen (Shaner et al., *A bright monomeric green fluorescent protein derived from Branchiostoma lanceolatum*, NAT. METHODS 10, 407–409 (2013)).

29. Another example is a second paper first published in June 2020 in *Science*, entitled "Antibody Cocktail to SARS-CoV-2 Spike Protein Prevents Rapid Mutational Escape Seen with Individual Antibodies," authored by Regeneron employees (Baum, et al.).[2] A true and correct copy of that paper is attached as Exhibit D. The Baum paper similarly explains how anti-SARS-CoV-2 spike antibodies were tested in neutralization assays against spike protein variants encoded into pVSV-SARS-CoV-2-S(mNeon) viral pseudoparticle reporter constructs detected by their expression of mNeonGreen.

30. Published with the Baum *Science* paper (Exhibit D) were "Supplementary Materials." A true and correct copy of the published Supplementary Materials is attached as Exhibit E. These materials again explain the use of mNeonGreen in the generation of recombinant VSV, pseudotyping of VSV, and neutralization assays with VSV-based reporters.

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[2] A. Baum et al., *Antibody Cocktail to SARS-CoV-2 Spike Protein Prevents Rapid Mutational Escape Seen with Individual Antibodies*, 369 SCIENCE 1014-1018 (21 August 2020).

31. A third example is a paper published in July 2020 in *bioRxiv*, entitled "SARS-CoV-2 Spike Protein Variant D614G Increases Infectivity and Retains Sensitivity to Antibodies That Target the Receptor Binding Domain," co-authored by Regeneron employees.[3] A true and correct copy of that paper is attached as Exhibit F. The *bioRxiv* paper discusses that pseudoparticle generation and neutralization assays using mNeonGreen were performed as described in the Hansen and Baum papers. For example, neutralization assays were performed by mixing diluted serially antibodies with pVSV-SARS-CoV-2-S-mNeon pseudoparticles, using those mixtures to challenge Vero cells, and counting fluorescent foci resulting from mNeonGreen expression as a read-out for virus infectivity.

32. Regeneron's use of mNeonGreen is commercial in nature and has been undertaken in the development and production of commercial products.

33. Allele has consistently shown that it is willing to license its mNeonGreen technology on reasonable terms in order to help facilitate the use of that protein by third parties in their efforts to develop new and essential technologies.

34. After learning of Regeneron's infringement of '221 patent based on the evidence above, Allele sought on multiple occasions to discuss Regeneron's taking a license to that patent. All of Allele's overtures were ignored.

35. For example, on June 26, 2020, Allele completed an online contact form directed to Regeneron's business development group. Allele received no response.

36. On July 2, 2020, Allele called Regeneron's corporate headquarters and spoke to multiple employees who refused to connect Allele with Regeneron's business development

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[3] L. Yurkovetskiy et al., *SARS-CoV-2 Spike Protein Variant D614G Increases Infectivity and Retains Sensitivity to Antibodies That Target the Receptor Binding Domain*, BIORXIV (July 2020).

department and told Allele to send an email. Allele sent an email that afternoon. Allele received no response.

37. On July 9, 2020, Allele again called Regeneron's corporate headquarters, but multiple employees again refused to connect Allele with anyone in Regeneron's legal or business development departments. Eventually those employees hung up on Allele's representative. Allele sent a second email that afternoon. Allele has yet to receive any response.

38. Upon information and belief, Regeneron's use of Allele's mNeonGreen technology is directly covered by Allele's '221 patent and has no substantial, non-infringing use.

39. Regeneron therefore directly infringes the mNeonGreen technology claimed in the '221 patent. And, upon information and belief, Regeneron's publications, press releases, and other papers instruct others on how to use the patented technology, causing others to directly infringe the mNeonGreen technology claimed in the '221 patent.

40. Allele has not authorized Regeneron to use the mNeonGreen technology claimed in the '221 patent.

COUNT I: INFRINGEMENT OF THE '221 PATENT

41. Allele repeats and realleges each and every allegation of the foregoing paragraphs as though fully set forth herein.

42. Upon information and belief, Defendant's use of mNeonGreen is covered by one or more claims of the '221 patent.

43. Upon information and belief, the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of mNeonGreen by Defendant directly infringes one or more claims of the '221 patent.

44. Upon information and belief, Defendant has actual knowledge of the ’221 patent and actual knowledge that its activities constitute direct infringement of the ’221 patent, or has willfully blinded itself to the infringing nature of its activities, and yet continues its infringing activities.

45. Upon information and belief, the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of mNeonGreen by Defendant indirectly infringes through inducement and contributory infringement one or more claims of the ’221 patent.

46. Upon information and belief, Defendant has actual knowledge of the ’221 patent and actual knowledge that its activities constitute indirect infringement of the ’221 patent or has willfully blinded itself to the infringing nature of its activities, and yet continues its infringing activities.

47. Defendant engaged in the foregoing conduct with respect to the ’221 patent during the term of the patent and without authority from Allele.

48. Defendant’s infringement of the ’221 patent has been and will continue to be willful, deliberate, and intentional.

49. As a direct and proximate result of Defendant’s infringement of the ’221 patent, Plaintiff has been and will continue to be damaged and deprived of its rights in the ’221 patent, for which Plaintiff is entitled to relief.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

(a) a finding that the ’221 patent is valid and enforceable;

(b) a judgment that Defendant has infringed, actively induced infringement of, and/or contributed to the infringement of one or more claims of the ’221 patent;

(c) a judgment that Defendant's infringement of the '221 patent is willful;

(d) an award of Plaintiff's damages or other monetary relief to adequately compensate Plaintiff for Defendant's infringement of the '221 patent, and such damages be trebled under 35 U.S.C. § 284 and awarded to Plaintiff, with pre-judgment and post-judgment interest as allowed by law;

(f) a judgment that this is an exceptional case under 35 U.S.C. § 285 and awarding Plaintiff its attorneys' fees, expert witness fees, costs, and all expenses incurred in this action, with interest;

(g) an award of all of Plaintiff's actual and compensatory damages; and

(h) an award of any further and additional relief to Plaintiff as this Court deems just and proper.

JURY DEMAND

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Plaintiff demands a trial by jury on all issues triable by jury.

DATED: October 5, 2020

By: */s/ Martin E. Gilmore*
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