IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AGILENT TECHNOLOGIES, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. _____
	)	
SYNTHEGO CORPORATION,	)	**DEMAND FOR JURY TRIAL**
	)	
Defendant.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Agilent Technologies, Inc. ("Agilent"), for its Complaint against Defendant Synthego Corporation ("Synthego"), requests a trial by jury and alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement. Agilent alleges that Synthego infringes U.S. Patent No. 10,900,034 ("the '034 Patent") (Exhibit A) and U.S. Patent No. 10,337,001 ("the '001 Patent") (Exhibit B) (collectively, the "Asserted Patents"). The Asserted Patents are based on inventions of Agilent researchers, Daniel E. Ryan, Douglas J. Dellinger, Jeffrey R. Sampson, Robert Kaiser, and Joel Myerson.

2. Agilent alleges that Synthego directly and indirectly infringes the Asserted Patents by making, using, selling and/or offering for sale infringing products and methods for guide RNA with chemical modifications, including, without limitation, Synthego's Halo Platform Industrialized CRISPR Tools and Halo Platform Products, Eclipse Platform Products and Processes, including Industrialized CRISPR Cells and Cell Engineering Processes, and gRNA manufacturing at Synthego's "GMP facility." Agilent further alleges that Synthego induces the infringement of others. Agilent seeks damages and other relief for Synthego's infringement of the Asserted Patents.

3. Agilent invested substantial effort to invent chemically modified synthetic gRNAs and methods of synthesizing, delivering, and using chemically modified gRNAs to improve

CRISPR technologies. Agilent invented and synthesized chemical modifications of gRNAs, with specific modifications at particular nucleotide positions of the gRNA, which improved genome editing efficiency in all cell types, including in human primary cells. These inventions resolve the challenges that had previously prevented widespread application of CRISPR technologies. Agilent patented these inventions, and upon discovering Synthego's use of infringing products, set about trying to license its patented technology to Synthego. Agilent attempted to engage Synthego in licensing discussions, but Synthego has delayed and failed to substantively respond to Agilent's overtures. Synthego instead subsequently published a paper and issued advertisements and press releases in which it took credit for and championed the many benefits that Agilent researchers had worked so diligently to invent and did invent, relative to enhancing gene editing, improved gRNA, and expanded applications for CRISPR technologies.

THE PARTIES

4. Agilent is a corporation organized and existing under the laws of the State of Delaware with its principal place of business at 5301 Stevens Creek Boulevard, Santa Clara, California 95051.

5. Agilent is a world leading supplier in life sciences, diagnostics and applied chemical markets. Agilent advances quality of life with a broad range of high-quality solutions to customers in 110 countries. For example, Agilent provides laboratories with instruments, services, consumables, applications, and expertise, enabling customers to achieve their research, production, therapeutic, and discovery goals. Agilent instruments, software, and sample preparation solutions help scientists at top-tier universities conduct faster, more accurate research to learn more about cancer, cardiovascular diseases, diabetes, Alzheimer's, Parkinson's, autism, and other ailments. Agilent solutions further help pathology laboratories deliver fast, accurate information to the physicians, hospitals, and medical centers they serve. Agilent solutions also provide precise answers for every segment of the pharmaceutical industry, from disease research and drug discovery to drug development, manufacturing, and quality control.

6. Agilent owns the Asserted Patents and holds all rights necessary to bring this action.

7. On information and belief, Defendant Synthego is a corporation organized under the laws of the State of Delaware with a principal place of business at 3565 Haven Avenue, Suite A, Redwood City, California 94063. On information and belief, Defendant has committed and continues to commit acts of infringement throughout the United States, including in the District of Delaware, including but not limited to the sales of infringing products in this judicial district and active steps to induce the infringement of its customers in this district.

8. By incorporating in the State of Delaware, Defendant resides in the District of Delaware.

JURISDICTION AND VENUE

9. This is an action arising under the patent laws of the United States, 35 U.S.C. § 271, *et seq*. Accordingly, this Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

10. This Court has personal jurisdiction over Synthego due, *inter alia*, to its continuous presence in, and systematic contact with, this judicial district and its incorporation in Delaware and domicile in this judicial district. Synthego is subject to this Court's jurisdiction at least as a result of Synthego's domicile in the District of Delaware, its substantial business in this judicial district, including at least part of its past infringing activities, regularly doing or soliciting business in this judicial district, and engaging in persistent conduct and/or deriving substantial revenue from goods and services provided in the State of Delaware, including in the District of Delaware. Synthego, directly and/or through intermediaries, has committed and continues to commit acts of infringement in this judicial district by, among other things, using, offering for sale, and/or selling products and methods that infringe the Asserted Patents.

11. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b), (c), (d) and 1400(b) because Synthego is incorporated in the State of Delaware and has committed acts of infringement in this judicial district.

FACTUAL ALLEGATIONS

The Patented Inventions Improved and Expanded the Scope of CRISPR Applications and Technologies

12. CRISPR refers to "clusters of regularly interspaced **s**hort palindromic repeats." '034 Patent at 1:31-35. In the decades since these short repeats were first identified, CRISPR has often been used as shorthand to describe an array of gene editing technologies based on the native CRISPR-Cas system in bacteria and archaea, which also involves CRISPR-associated ("Cas") proteins, and which is further described below.

13. The naturally occurring CRISPR-Cas system includes components used by bacteria and archaea as an adaptive immune defense to attack and inactivate invading phages. Adaptations of this CRISPR-Cas system had been developed that presented a simpler and more cost-effective alternative to older gene editing techniques, such as protein-based technologies, which often required months to design a single, customized protein to target a specific gene.

14. This CRISPR technology offered promise to replace a lot of the more costly and less efficient gene editing alternatives, but existing CRISPR adaptations still suffered from limited effectiveness and efficiency, thereby preventing wide-scale application of the technology. For example, numerous research and therapeutic applications of CRISPR technology could not be achieved until CRISPR could be used for gene editing in human primary cells. As detailed below, Agilent addressed those limitations, inventing new gene editing tools and methods that improved CRISPR technologies applicable to all cell types, thereby rendering this technology more reliable, precise, and scalable across all applications. To do so, Agilent focused on a CRISPR-Cas component called *guide RNA*.

15. The native prokaryotic CRISPR-Cas system includes the aforementioned clusters of regularly interspaced short palindromic repeats, and between those CRISPRs are intervening "spacer" sequences of constant length. '034 Patent at 1:31-35. The "spacer" sequences between these CRISPRs are transcribed into RNA sequences and processed into small *guide RNAs* ("gRNA"). These guide RNAs are responsible for *guiding* CRISPR-associated ("Cas") proteins

to a specific location on the target polynucleotide – for example phage DNA – and enabling the Cas nuclease (an enzyme that cleaves nucleic acids) to bind and make a cut in that target DNA. *Id*. at 1:35-37, 41-44. These guide RNAs include CRISPR RNA ("crRNA") and trans-activating CRISPR RNA ("tracrRNA"), and each of these gRNA sequences has an important role in *guiding* the Cas nuclease to its target to cut the polynucleotide. For example, the sequence of the crRNA aids in targeting and binding the Cas protein to a specific location within an invading virus or plasmid, while the tracrRNA includes a protein binding segment capable of interacting with, and providing a scaffold for, the Cas nuclease. *Id*. at 4:7-21. Together, these guide RNAs form a complex with a Cas nuclease that enables that gRNA:Cas nuclease complex to recognize, bind and generate site-specific breaks in a target DNA sequence. *Id*. at 1:44-49.

16. Although the native CRISPR-Cas system is used by prokaryotes to defend against an exogenous phage or plasmid, for example, where the guide RNAs effectively *guide* the Cas nuclease to specific loci of the phage DNA to bind and cleave the exogenous genetic elements, variations of the CRISPR-Cas system can also be applied as tools for genome editing in an array of organisms and for common research endeavors.

17. For example, the crRNA and tracrRNA of the CRISPR-Cas system can be synthetically fused together to create a chimeric single guide RNA ("sgRNA") (*id.* at 1:57-59, 4:7-21), where the sgRNA is synthesized to hybridize to a desired polynucleotide target, and the sgRNA is delivered into cells as RNA or by using a DNA vector expressing the sgRNA. As an example, Figure 1, below, shows a schematic model of an exemplary CRISPR-Cas system using an sgRNA, with the guide sequence hybridized with the DNA target directly upstream of the protospacer adjacent motif ("PAM") sequence, and a Cas9 nuclease mediating a double-stranded break upstream of the PAM sequence, as indicated by arrows:

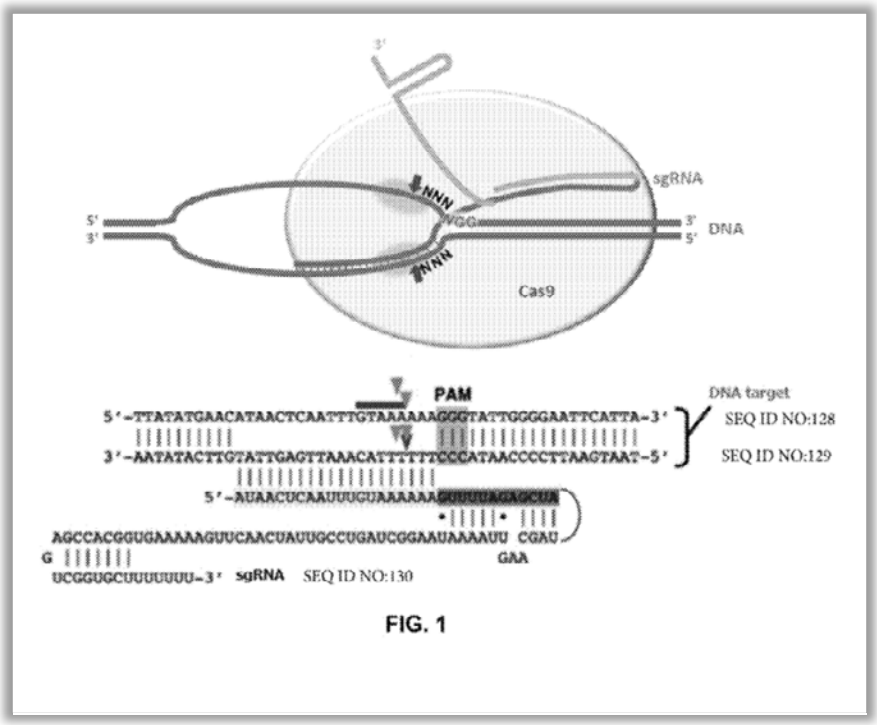


FIG. 1

'034 Patent at Figure 1, 2:22-34.

18. By synthesizing gRNA to mediate these site-specific DNA breaks, CRISPR technology can exploit DNA repair mechanisms to edit a gene of interest. For example, a gene can be disrupted or "knocked-out" by inserting or deleting a nucleotide during DNA repair, preventing the gene from making a functional protein, and thereby opening a variety of investigative doors, such as the study of a gene's function, cellular pathway research, and using knockout organisms for disease research. As another example, CRISPR technology can also be used to "knock-in" a gene after a DNA break, where the gene is edited by inserting genetic material into the gene. Such knock-in gene edits can be useful, for example, in studying the effects of specific gene variants, investigating genome regulation, using reporter genes to track gene products, and even repairing defective genes or disease-causing mutations.

19. Prior to the Agilent inventions set forth in the Asserted Patents, however, CRISPR technology could not be relied upon to accurately or effectively achieve gene editing across all cell types, thereby halting the progress of a wide array of biotechnological and therapeutic applications, such as those available from knock-out or knock-in gene editing techniques.

20. Agilent had been working on improving upon the prior art for years, and ultimately invented synthetic chemically modified gRNAs, with specific chemical modifications of nucleotides that provide identifiable advantages over unmodified gRNAs, showing enhanced properties at particular identified nucleotide locations, and still provide gRNA functionality.

21. These synthetic chemically modified gRNA inventions advanced genome editing applications, for example, by improving upon the stability (*e.g.*, '034 Patent at 2:1-8, 31:47-32:43, 35:31-41, 44:38-45:2, 63:53-67), functionality (*e.g.*, *id*. at 63:36-52, 134:40-52), transfectability (*e.g.*, *id*. at 3:60-4:2), and effective delivery of gRNA, including sgRNA, into cells, especially into the nuclei of eukaryotic cells (*e.g.*, *id*. at 34:39-41, 35:31-41, 44:8-12, 62:38-63:32), and minimizing their immunostimulatory response in cells after transfection (*e.g.*, *id*. at 134:29-39).

22. Agilent also invented novel methods of using and successfully transfecting such synthetic chemically modified gRNAs into cells to effect enhanced CRISPR-Cas system functionality, for example, by co-delivering the invented sgRNAs with mRNA encoding the Cas nuclease. *See, e.g.*, '034 Patent at 62:65-63:10, 36-52, 134:40-52.

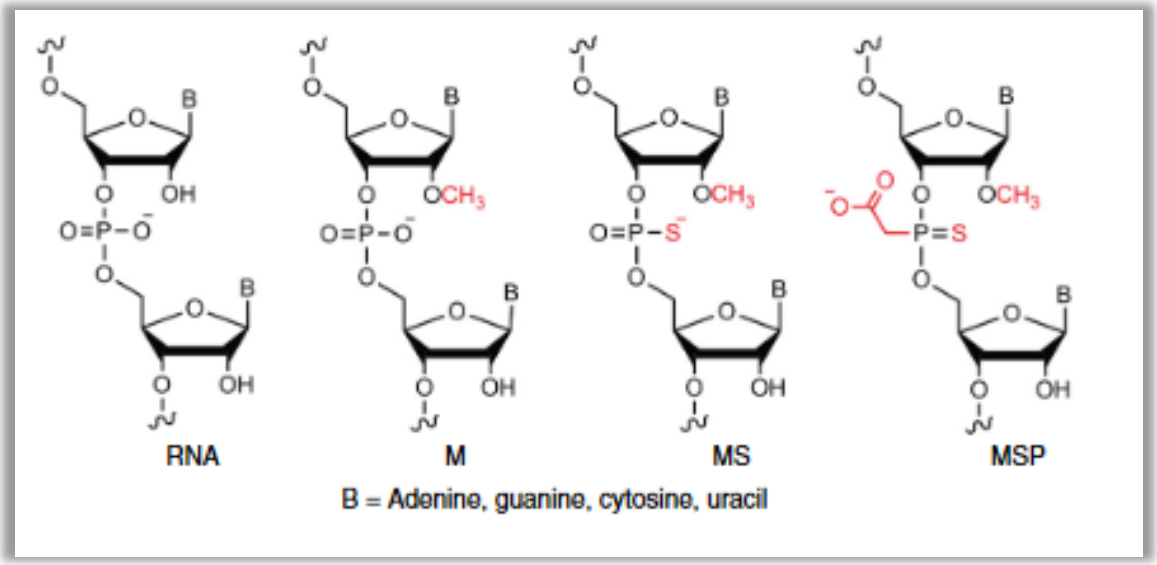
23. Agilent's inventions also included chemically modified gRNAs and methods of use in which gRNAs were synthesized with chemically modified nucleotides at specific positions to *improve* stability and functionality, while *reducing* immunostimulatory responses. For example, immunostimulatory responses could be minimized with gRNA modifications on the 5′ and 3′ ends of a synthetic gRNA. *See, e.g.*, '034 Patent at 134:29-39.

24. Agilent worked to patent these valuable inventions. Agilent filed its first provisional application related to the Asserted Patents in December 2014. Further provisional applications related to the Asserted Patents were filed in April 2015 and November 2015. The patent application that ultimately led to the issuance of the '034 Patent was filed in December 2015, and the patent application that ultimately led to the issuance of the '001 Patent was filed in May 2017, which was a continuation of the December 2015 application.

25. With the invention firm in hand, Agilent inventors teamed up with researchers at

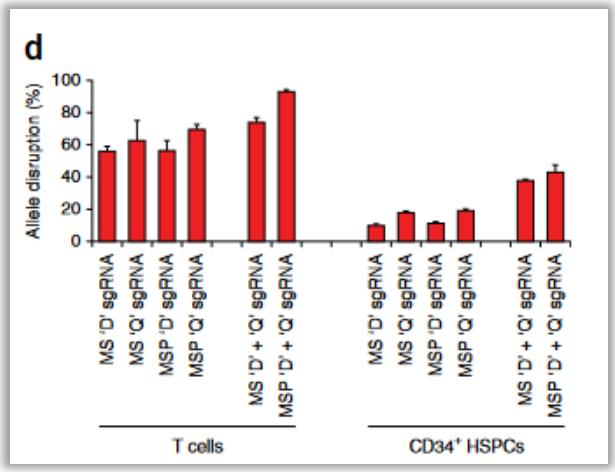
Stanford University to further demonstrate the efficacy of the inventions in human primary cells. The results of that work were published in June 2015. *Nat. Biotechnol.* 33:9, 985-9 ("Hendel et al. (2015)" or "the Hendel paper").

26. Hendel et al. (2015) includes a description of technology Agilent invented and that is covered by the two Asserted Patents. For example, the Hendel paper describes successful gene editing in human primary cells using three of the chemically modified gRNAs Agilent invented: synthesized sgRNAs with chemical modifications comprising 2′-O-methyl ("M"), 2′-O-methyl 3′ phosphorothioate ("MS"), or 2′-O-methyl 3′ thiophosphonoacetate ("MSP"), each at three terminal nucleotides at both the 5′ and 3′ ends. Hendel et al. (2015); *see, e.g., id.*:



(Figure 1(b), depicting structures of M, MS and MSP chemical modifications incorporated during chemical synthesis of sgRNAs).

27. Agilent's modified sgRNAs achieved high frequencies of gene disruption or targeted genome editing in human primary cells, for example, as shown below:



Hendel et al. (2015) (Figure 2(d); *see also* '034 Patent at Figure 12D, 3:40-46.

The Asserted Patents

28. Agilent sought and obtained patent protection for its inventions in the field of guide RNA with chemical modifications, and genome editing using chemically modified guide RNAs. The inventions claimed in the patents have broad application in a variety of CRISPR-mediated functions, including but not limited to editing genes, regulating gene expression, cleaving target sequences, and binding to target sequences, in vitro or in vivo, such as in cell-free assays, in intact cells, or in whole organisms.

29. United States Patent Nos. 10,900,034 and 10,337,001 are asserted here. The Asserted Patents derive from Appl. No. 14/757,204 and 15/607,295, respectively, and share patent specification disclosures.

30. U.S. Patent No. 10,900,034, entitled "Guide RNA with Chemical Modifications," was duly and lawfully issued by the USPTO on January 26, 2021. Agilent is the assignee and owner of all right to enforce and has full rights to sue and recover damages from all past, present, and future infringements of the '034 Patent. Daniel E. Ryan, Douglas J. Dellinger, Jeffrey R. Sampson, Robert Kaiser, and Joel Myerson are the sole inventors of the inventions claimed in the '034 Patent. A true and correct copy of the '034 Patent is attached as Exhibit A.

31. The ’034 Patent describes “modified guide RNAs and their use in clustered, regularly interspaced, short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems” in which certain claimed chemical modifications to synthetic gRNA expand the scope of CRISPR-associated technologies and functions. ’034 Patent at Abstract, 3:54-4:2. The inventions of the ’034 Patent presented an important advance from existing gene editing products and methods at the time. *Id*. at 1:60-2:18.

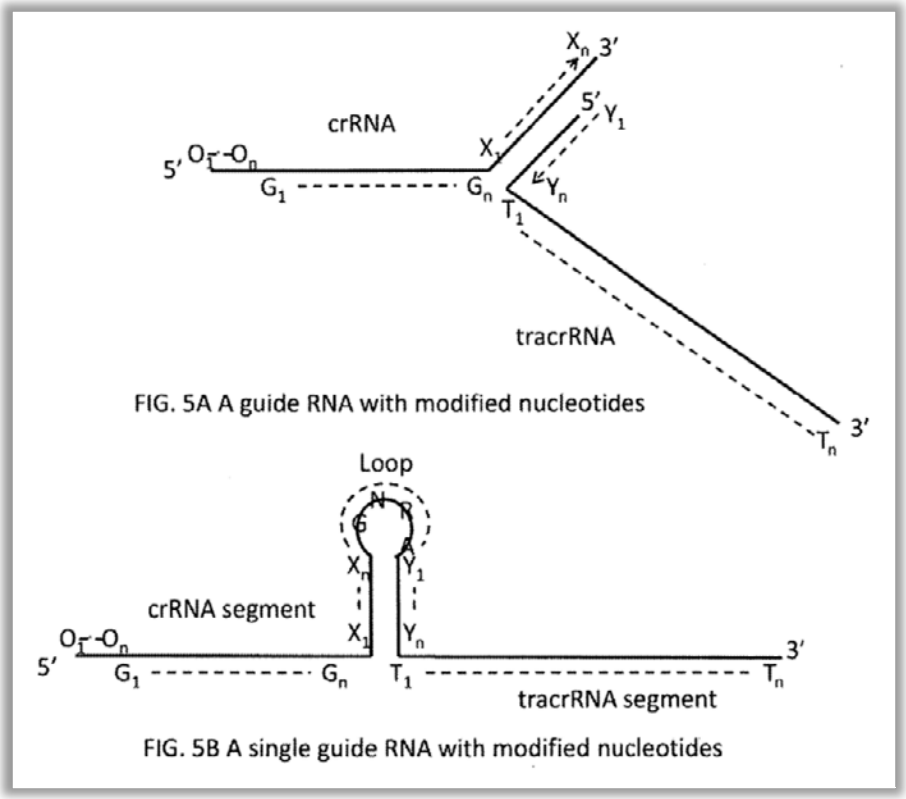
32. The ’034 Patent describes and claims inventions related to chemical modifications to synthetic gRNA to enhance gene editing and overall methods of using these chemically modified gRNAs described above, and includes specific claims directed to specific chemical modifications.

33. For example, as described in paragraphs 12-27 above, the chemical modifications of synthetic gRNA and their use in CRISPR-Cas systems and technologies disclosed and claimed in the ’034 Patent provide significant advantages in CRISPR-mediated functions, including genome editing efficiencies in cells, such as human cells (*e.g.*, ’034 Patent at 57:27-30 (“the modified guide RNA significantly enhanced genome editing efficiencies in human cells, including human primary T cells and $CD34_+$ HSPCs”)), increasing the frequency of nucleotide insertions or deletions (“indels”) in the genome (*e.g.*, ’034 Patent at 63:36-52 (“modified gRNA increases the frequency of insertions or deletions (indels)”), stimulating higher levels of gene targeting (*e.g.*, ’034 Patent at 64:1-8 (“modified gRNA stimulates gene targeting, which, in turn, allows for gene editing by, for example, homologous recombination or NHEJ”)), enhancing functionality, by for example, preventing misfolded structures (*e.g.*, ’034 Patent at 134:40-52), and minimizing immunostimulatory response in transfected cells (*e.g.*, ’034 Patent at 134:29-39).

34. The chemical modifications and methods disclosed and claimed in the ’034 Patent further expand the scope of CRISPR applications, for example, by improving gRNA stability, including increased thermostability and protection from nuclease activity (*e.g.*, ’034 Patent at 63:53-67 (“modified gRNA improves stability … gRNA having 2′-O-methyl-3′-thioPACE

(MSP) incorporated at three terminal nucleotides at both the 5′ and 3′ ends, dramatically improves stability against nucleases")).

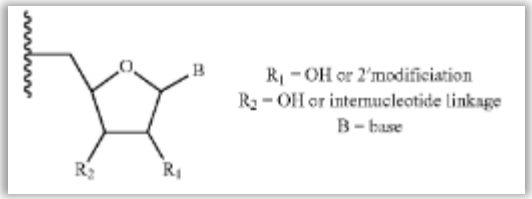
35. Exemplary gRNA and sgRNA with modified nucleotides are shown in Figures 5A and 5B below:



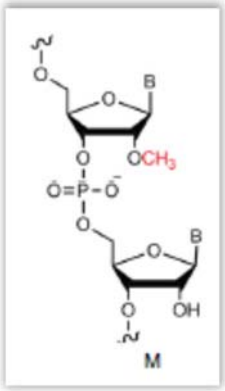
'034 Patent at Figures 5A-5B, 2:51-54.

36. An example configuration of the invented synthetic CRISPR guide RNA includes one or more modifications in the guide sequence, wherein the one or more modifications comprises a 2′-O-methyl. *See, e.g.*, '034 Patent at 8:61-64. The '034 Patent discloses hundreds of exemplary modified nucleotides contained in the synthetic guide sequence, where R_1 may be

an OH group or a 2′ modification, R_2 may be an OH group or internucleotide linkage, and B is a base, as depicted below:

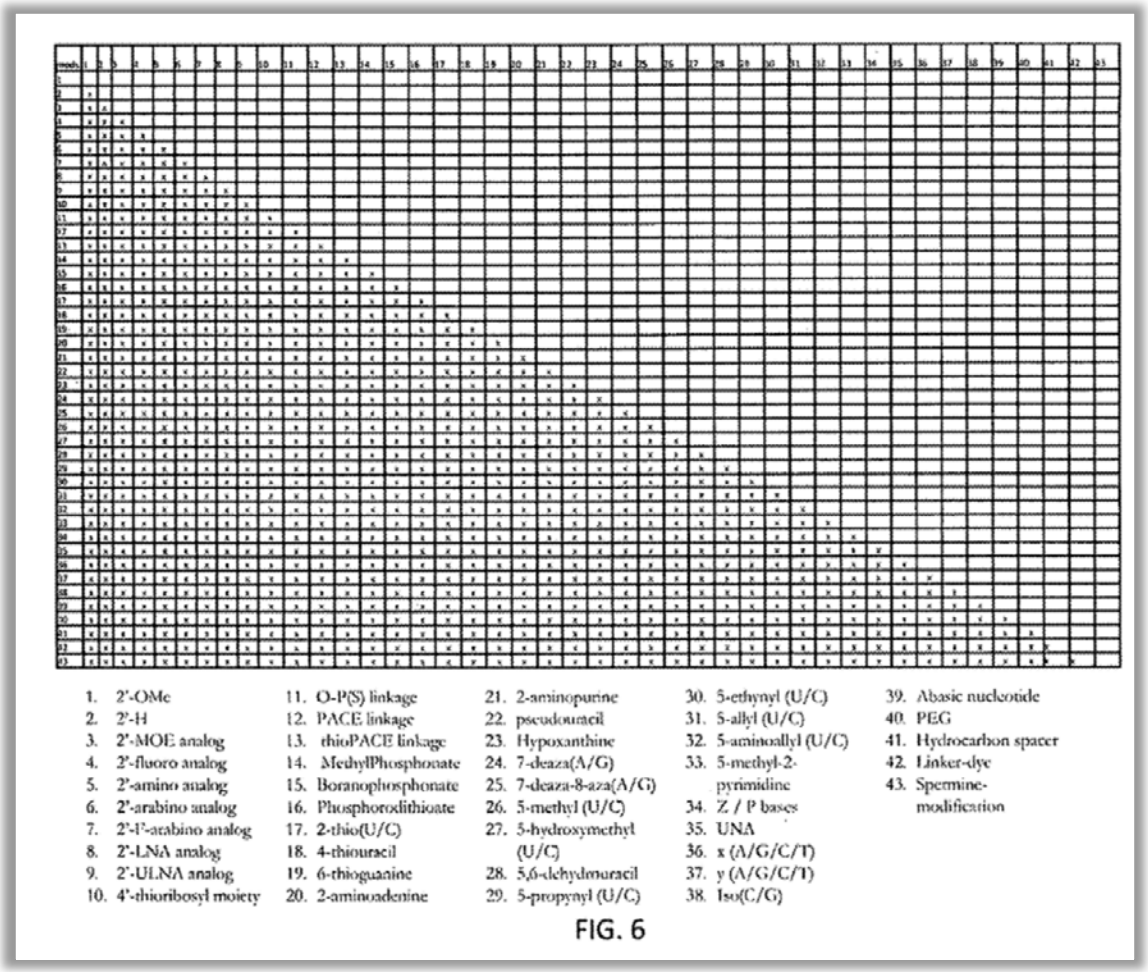


'034 Patent at 12:24-24:15. The figure below depicts one such nucleotide modification, a 2′-O-methyl:



Hendel et al. (2015) (Figure 1(b)) ; *see, e.g.*, '034 Patent at 8:61-9:12.

37. Exemplary synthetic gRNAs with at least two chemical modifications are shown in Figure 6, below, with each number representing a modification as indicated and each "x" indicating the combination of modifications in a guide RNA:



1. 2'-OMe
2. 2'-H
3. 2'-MOE analog
4. 2'-fluoro analog
5. 2'-amino analog
6. 2'-arabino analog
7. 2'-F-arabino analog
8. 2'-LNA analog
9. 2'-ULNA analog
10. 4'-thioribosyl moiety
11. O-P(S) linkage
12. PACE linkage
13. thioPACE linkage
14. MethylPhosphonate
15. Boranophosphonate
16. Phosphorodithioate
17. 2-thio(U/C)
18. 4-thiouracil
19. 6-thioguanine
20. 2-aminoadenine
21. 2-aminopurine
22. pseudouracil
23. Hypoxanthine
24. 7-deaza(A/G)
25. 7-deaza-8-aza(A/G)
26. 5-methyl (U/C)
27. 5-hydroxymethyl (U/C)
28. 5,6-dehydrouracil
29. 5-propynyl (U/C)
30. 5-ethynyl (U/C)
31. 5-allyl (U/C)
32. 5-aminoallyl (U/C)
33. 5-methyl-2-pyrimidine
34. Z / P bases
35. UNA
36. x (A/G/C/T)
37. y (A/G/C/T)
38. Iso(C/G)
39. Abasic nucleotide
40. PEG
41. Hydrocarbon spacer
42. Linker-dye
43. Spermine-modification

FIG. 6

'034 Patent at Figure 6, 2:55-62.

38. Exemplary types of synthetic guide RNAs with at least three chemical modifications are shown in Figure 7, below:

Single mod / Double mod	Sugar	Phosphorus Linkage	Base modification*	Other
Sugar/Sugar	X	X	X	X
Sugar/ P link	X	X	X	X
Sugar/Base	X	X	X	X
Sugar/other	X	X	X	X
P link/ Plink	X	X	X	X
P link/ base	X	X	X	X
P link/other	X	X	X	X
Base/ Base	X	X	X	X
Base/other	X	X	X	X
other/other	X	X	X	X

*Base modifications includes Base Pair Modifications

Sugar modifications ("Sugar"): 2'-O-Methyl (=2'-OMe) (2'-OC_1-C_4 alkyl), 2'-H, 2'-MOE (2'- OC_1-C_3 alkyl-OC_1-C_3 alkyl), 2'-F, 2'-amino, 2'-arabino, 2'-F-arabino, 2'-LNA, 2'-UNLA, 4'-thioribosyl nucleotide.
Internucleotide linkage and 3' and/or 5' terminal nucleotide modifications ("Phosphorus Linkage" or "P link"): -P(S) (phosphorothioate), -PACE (phosphonoacetate, phosphonocarboxylate), -thioPACE (thiophosphonoacetate, thiophosphonocarboxylate), $-P(CH_3)$ (methylphosphonate, alkylphosphonate), $-P(BH_3)$ (boranophosphonate), $-P(S)_2$ (phosphorodithioate)
Base modifications: 2-thiouracil, 2-thiocytosine, 4-thiouracil, 6-thioguanine, 2-aminoadenine, 2-aminopurine, pseudouracil, hypoxanthine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deazaadenine, 7-deaza-8-azaadenine, 5-methylcytosine, 5-methyluracil, 5-hydroxymethylcytosine,5-hydroxymethyluracil, 5,6-dehydrouracil, 5-propynylcytosine, 5-propynyluracil, 5-ethynylcytosine, 5-ethynyluracil,5-allyluracil, 5-allylcytosine, 5-aminoallyl-uracil, 5-aminoallyl-cytosine and abasic nucleotides.
Base Pair modifications: Z/P nucleotides, UNA, isoC/isoG, 6-thioG/5-methyl-pyrimidine, x(A,G,C,T) and y(A,G,C,T).
Other: End modifications and/or spacer/linker (ends or internal) modifications: PEG, hydrocarbon spacer, (including: heteroatom (O,S,N)-substituted hydrocarbon spacers, halo-substituted-hydrocarbon spacers, (keto,carboxy,amido,thionyl,carbamoyl,thionocarbamaoyl)-containing hydrocarbon spacers), spermine, dyes linkers including: 6-Fluorescein-phosphoramidite and the like, squarate conjugation, Diels-Alder conjugation, or "Click" chemistry conjugation.

FIG. 7

'034 Patent at Figure 7, 2:63-3:3.

39. The inventions of the '034 Patent presented an important advance from existing, unmodified gRNAs, as Agilent's synthetic chemically modified gRNAs, including sgRNAs, can be used effectively to enhance targeted and multiplexed genome editing by improving gRNA properties without compromising gRNA functionality in gene editing. '034 Patent at 3:51-59. The claimed chemically modified synthetic gRNAs also improve a wide range of CRISPR-associated technologies such as the CRISPRi/CRISPRa systems for inhibition and activation of gene expression, the CRISPR imaging tool for dynamic visualization of genomic loci, and CRISPR-mediated RNA recognition and cleavage. *See, e.g.*, '034 Patent at 50:46-51:4. Additionally, these synthetic chemically modified gRNAs and methods could be used to improve

intracellular delivery to target cells or tissues, and enable conjugation to various molecules for imaging and biochemical studies. *Id*. at 10:60-28.

40. Agilent is the assignee and owner of all right to enforce U.S. Patent No. 10,337,001, entitled "Guide RNA with Chemical Modifications," and has full rights to sue and recover damages from all past, present and future infringements of the '001 Patent. The United States Patent and Trademark Office duly and legally issued the '001 Patent on July 2, 2019. Daniel E. Ryan, Douglas J. Dellinger, Jeffrey R. Sampson, Robert Kaiser, and Joel Myerson are the sole inventors of the inventions claimed in the '001 Patent. A true and correct copy of the '001 Patent is attached as Exhibit B.

41. The '001 Patent describes and claims inventions related to the chemically modified synthetic gRNA products and overall methods described above and includes specific claims relating to locations of chemical modifications on the gRNA, which enable the improvement(s) of the modification while still retaining functionality of the gRNA for forming a gRNA:Cas complex and performing gene editing and/or gene activation or repression. *See, e.g.*, '001 Patent at 243:10-18 (claim 1 (*e.g.*, "… one or more modified nucleotides within five nucleotides from said 5′ end," or "from said 3′ end," or "both")); *id*. at 24:61-25:27.

42. The inventions claimed in the '001 Patent improved on the prior art and provided the same benefits as discussed above with respect to the '034 Patent, and further included the specific locations at which chemical modifications of synthetic gRNA retained and/or improved gRNA functionality and gene editing efficiency. Individually and together, the claimed inventions provide new and unconventional techniques for chemically modifying synthetic gRNAs to improve the and functionality of gRNA, improving gene editing efficacy and efficiency, and improving titratability and transfectability, and enhancing the overall CRISPR technologies and tools for gene editing.

43. In summary, the claimed inventions of the Asserted Patents provide significant benefits to CRISPR component manufacturers, suppliers, and users like Synthego—as can be seen in Synthego's own advertisements of its infringing products discussed below. Those

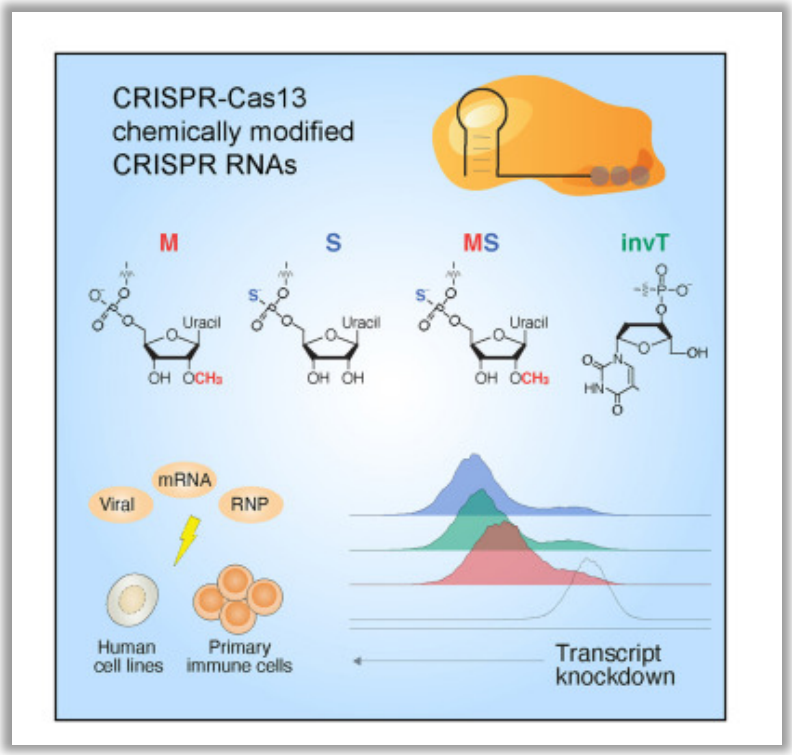
benefits include enhanced genome editing efficacy and genome editing efficiencies for CRISPR technology applied to all cell types.

Synthego's Knowledge of the Patented Technology

44. Synthego has known of the Agilent patents, including the Asserted Patents and the inventions therein, since at least June 24, 2021. At that time, Agilent contacted Synthego and provided to Synthego information identifying the patents, their benefits and the broad adoption and use of this patented technology.

45. Subsequently, and without license from Agilent, Synthego began and continued the manufacture, use, sale, offer of sale, supply, and advertisement of synthetic gRNA with chemical modifications that infringe the Asserted Patents, as described more fully below. For example, Synthego manufactured, used, tested, sold, and benefited from infringing products and methods after Agilent's June 24, 2021 identification of the Asserted Patents, and advertised the benefits thereof, championing the benefits of the infringing products and methods, as shown in an academic paper published on August 2, 2021, co-authored by Synthego employees and shareholders Anastasia Kadina, John Walker, and Kevin Holden, entitled, "Chemically modified guide RNAs enhance CRISPR-Cas13 knockdown in human cells." *See* Méndez-Mancilla, et al. (2021). Chemically modified guide RNAs enhance CRISPR-Cas13 knockdown in human cells. *Cell Chem. Biol*. 29, 1-7 (detailing use, tests, test results, and benefits of infringing products, in which Synthego employees and shareholders synthesized infringing chemically modified gRNAs, and did so "using solid-phase phosphoramidite chemistry (Synthego CRISPRevolution platform)"). Synthego's manufacture, use of and benefit from chemically modified synthetic gRNAs included Agilent's inventions for synthesis of chemically modified gRNA, as well as specifically claimed chemically modified synthetic gRNAs and claimed methods for gene editing

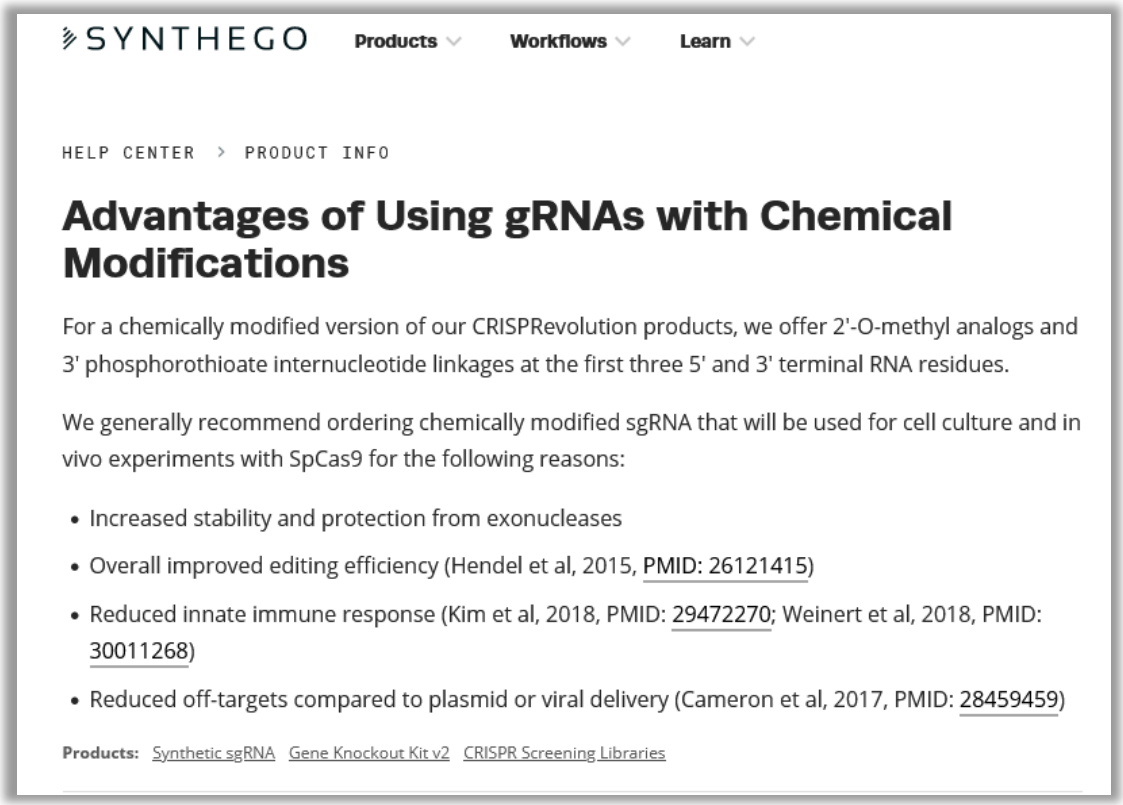
using these modified gRNAs – as can be seen for example, in diagrams of Synthego's chemical modifications to gRNA at the 3′ end, ***including 2'-O-methyl modifications***:



Méndez-Mancilla, et al. (2021) (graphical abstract) (showing chemical modifications incorporated during synthesis of gRNAs, including 2′-O-methylation (M) and 2′-O-methylation and phosphorothiate linkage (MS)). Synthego manufactured, used, and touted the benefits of chemically modified synthetic gRNAs, including M and MS modified gRNAs within five nucleotides from the 3′ end. *Id*. (*e.g.*, the figure above shows three modifications at the 3′).

46. After Synthego published the Méndez-Mancilla, et al. (2021) paper, Agilent again contacted Synthego about the patent portfolio in August 2021 and in September 2021, and specifically offered to continue licensing discussions about the patent portfolio, as well as its usefulness to Synthego. Synthego did not substantively respond to Agilent's overtures to license the patented technology.

47. On information and belief, before and during the communications described above between Agilent and Synthego, and at least as early as September 2019, Synthego had synthesized, employed, and was benefiting from products and methods that infringe the Asserted Patents. Synthego executives well understood the benefits of Agilent's inventions, and indeed were praising those benefits in advertisements about Synthego's infringing products. For example, Synthego's website advertises "advantages" to using its infringing products and recommends use of infringing chemically modified gRNAs (***"we offer 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues"***) for cell culture and in vivo experiments for the "following reasons: "increased stability and protection from exonucleases," "overall improved editing efficiency," "reduced innate immune response," and "reduced off-targets compared to plasmid or viral delivery," as shown below:



SYNTHEGO Products Workflows Learn

HELP CENTER > PRODUCT INFO

Advantages of Using gRNAs with Chemical Modifications

For a chemically modified version of our CRISPRevolution products, we offer 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues.

We generally recommend ordering chemically modified sgRNA that will be used for cell culture and in vivo experiments with SpCas9 for the following reasons:

- Increased stability and protection from exonucleases
- Overall improved editing efficiency (Hendel et al, 2015, PMID: 26121415)
- Reduced innate immune response (Kim et al, 2018, PMID: 29472270; Weinert et al, 2018, PMID: 30011268)
- Reduced off-targets compared to plasmid or viral delivery (Cameron et al, 2017, PMID: 28459459)

Products: Synthetic sgRNA Gene Knockout Kit v2 CRISPR Screening Libraries

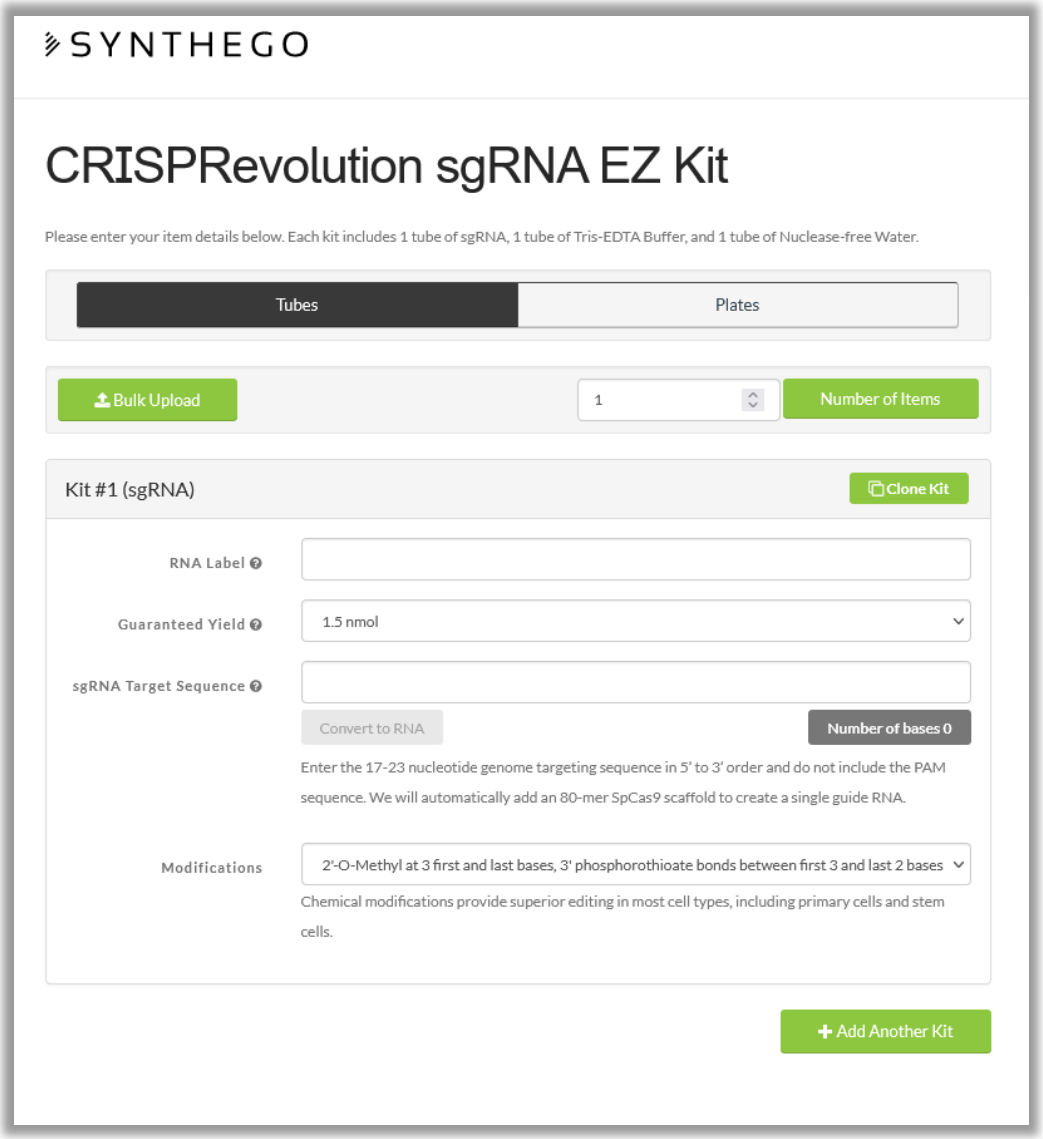
See Synthego, Help Center - Product Info, "Advantages of Using gRNAs with Chemical Modifications", *available at* https://www.synthego.com/help/grnas-chemical-modifications (citing and providing a hyperlink to Hendel et al. (2015)).

48. Synthego had specific knowledge of the Agilent patents, including the Asserted Patents, and knew of the application and usefulness of Agilent's inventions to Synthego's manufacturing, use, supply, sale, offers of sale, and advertisement of chemically modified gRNAs.

Synthego's Infringing Use of the Patented Technology

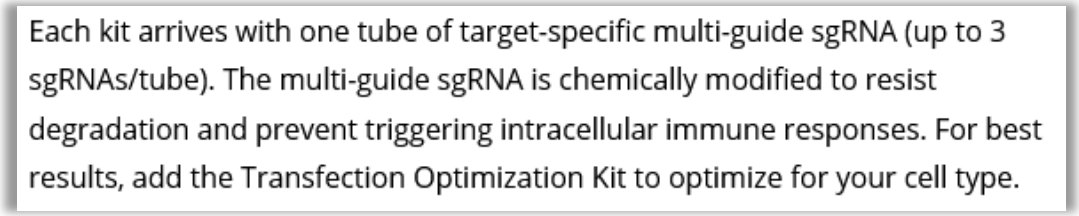
49. Beginning at least as early as 2019, Synthego began using and marketing infringing products under the Halo Platform, which includes the following "CRISPRevolution" and/or "Halo-powered products": Synthetic sgRNA Kit, Gene Knockout Kit v2, Arrayed CRISPR Screening Libraries, Advanced RNA and CRISPR GMP sgRNA Manufacturing.

50. For example, Synthego's sgRNA Kit includes synthetic chemically modified gRNA, wherein one or more modifications comprises a "2′-O-methyl" chemical modification at the "3 first and last bases" and "3′ phosphorothioate bonds between first 3 and last 2 bases":



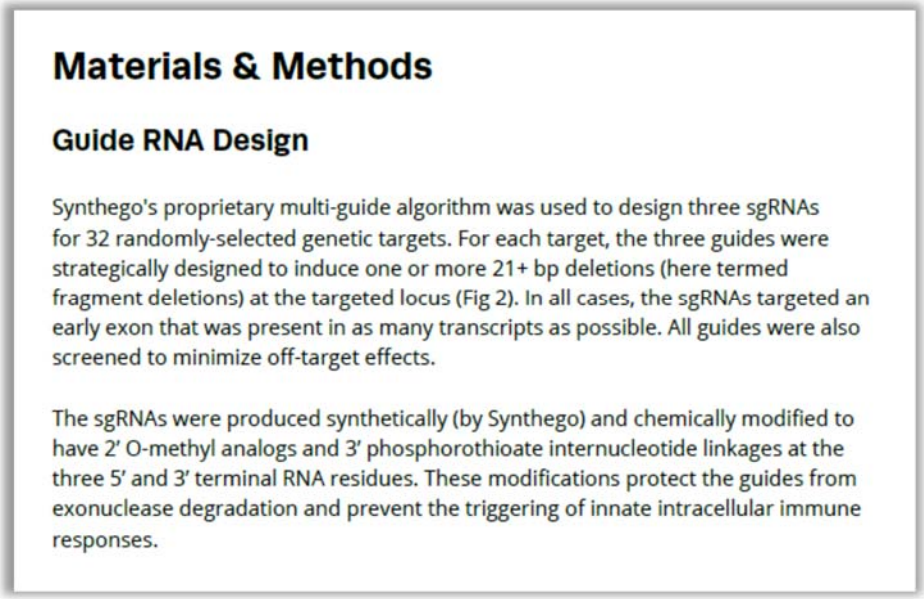
See Synthego, Orders, "CRISPRevolution sfRNA EZ Kit", *available at* https://orders.synthego.com/products/crisprevolution-sgrna-ez-kit-13/#/tubes?mod_code=1. Just as Agilent had described in the Asserted Patents, Synthego's order form for the CRISPRevolution sgRNA EZ Kit praises these infringing synthetic chemically modified gRNAs as providing "superior editing in most cell types, including primary cells and stem cells." *Id.*

51. Synthego also manufactures, offers for sale, and sells a Gene Knockout Kit v2, which includes infringing synthetic chemically modified sgRNAs:



Each kit arrives with one tube of target-specific multi-guide sgRNA (up to 3 sgRNAs/tube). The multi-guide sgRNA is chemically modified to resist degradation and prevent triggering intracellular immune responses. For best results, add the Transfection Optimization Kit to optimize for your cell type.

See Synthego, Products, CRISPR Kits, "Gene Knockout Kit v2", *available at* https://www.synthego.com/products/crispr-kits/gene-knockout-kit. Synthego's "multi-guide sgRNAs" include sgRNAs that ***"were produced synthetically (by Synthego) and chemically modified to have 2' O-methyl analogs and 3' phosphorothioate internucleotide linkages at the three 5'and 3' terminal RNA residues."*** *See* Synthego, Resources, Application Note, "Multi-guide sgRNA improves CRISPR Knockout Efficiency by Generating Fragment Deletions", *available at* https://www.synthego.com/resources/multiplexed-sgrna-application-note (emphases added). Synthego describes these modifications as offering benefits described and claimed by the Asserted Patents:



Materials & Methods

Guide RNA Design

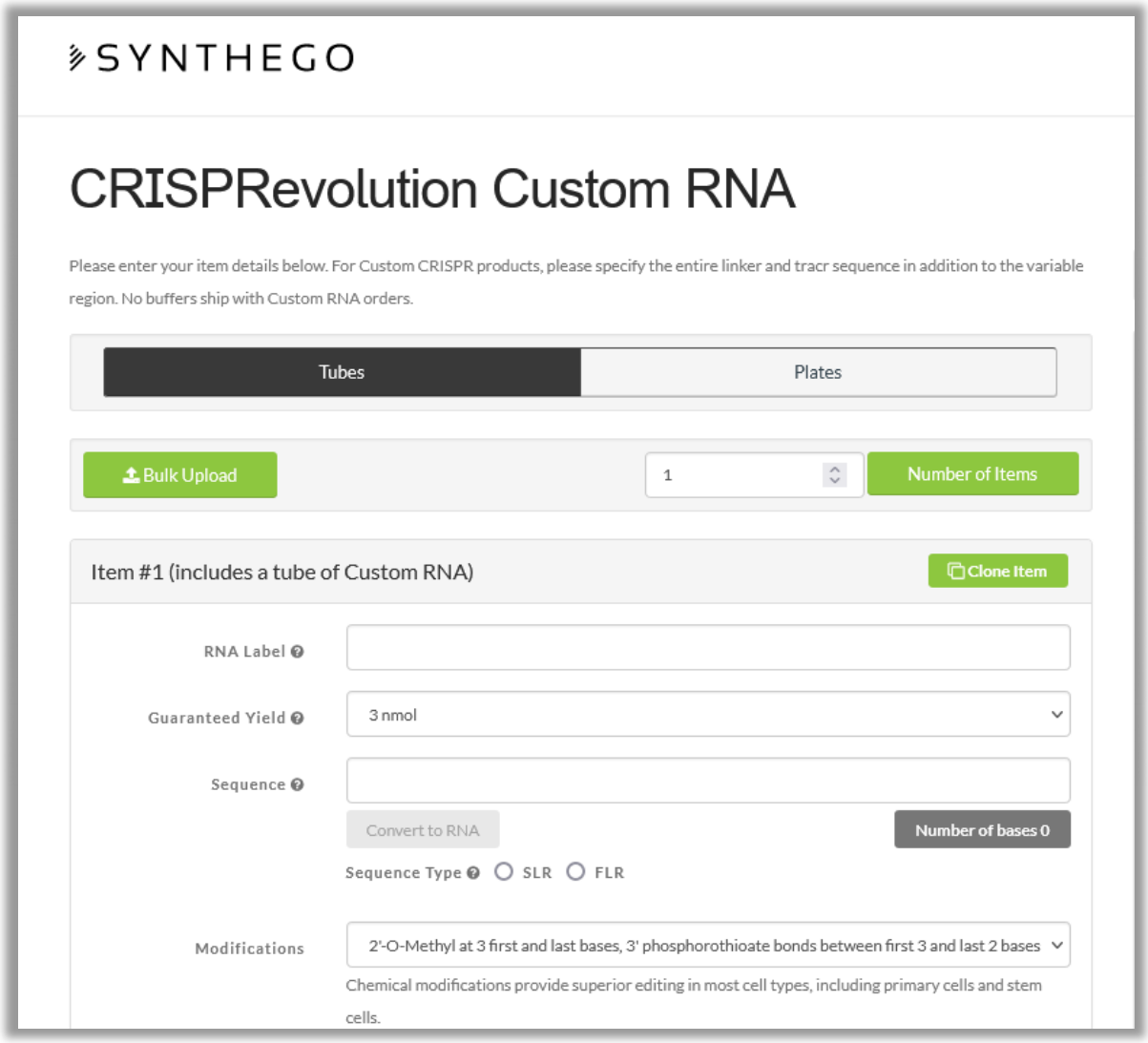
Synthego's proprietary multi-guide algorithm was used to design three sgRNAs for 32 randomly-selected genetic targets. For each target, the three guides were strategically designed to induce one or more 21+ bp deletions (here termed fragment deletions) at the targeted locus (Fig 2). In all cases, the sgRNAs targeted an early exon that was present in as many transcripts as possible. All guides were also screened to minimize off-target effects.

The sgRNAs were produced synthetically (by Synthego) and chemically modified to have 2′ O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the three 5′ and 3′ terminal RNA residues. These modifications protect the guides from exonuclease degradation and prevent the triggering of innate intracellular immune responses.

Id. at 4.

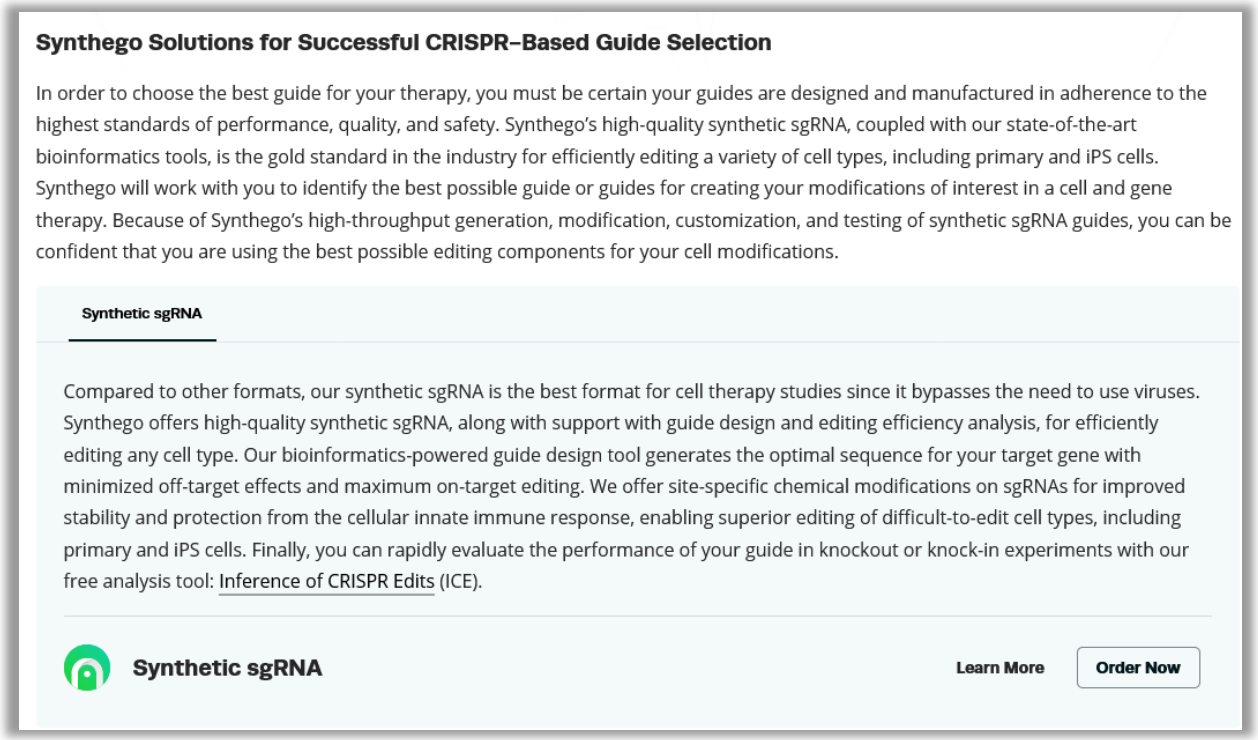
52. Synthego manufactures, offers for sale, and sells Arrayed CRISPR Screening Libraries, which include infringing "multi-guide modified sgRNAs." As described in paragraph 51 above, Synthego's multi-guide sgRNA includes sgRNAs that were produced synthetically by Synthego and chemically modified to have 2′ O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the three 5′ and 3′ terminal RNA residues. *See id.; and see* Synthego, Products, CRISPR Kits, "CRISPR Screening Libraries", *available at* https://www.synthego.com/products/crispr-kits/screening-libraries

53. Synthego manufactures, offers for sale, and sells Advanced RNA, which includes synthetic chemically modified gRNA, wherein one or more modifications comprises a ***"2'-O-Methyl"*** chemical modification at the ***"3 first and last bases" and "3' phosphorothioate bonds between first 3 and last 2 bases"***:



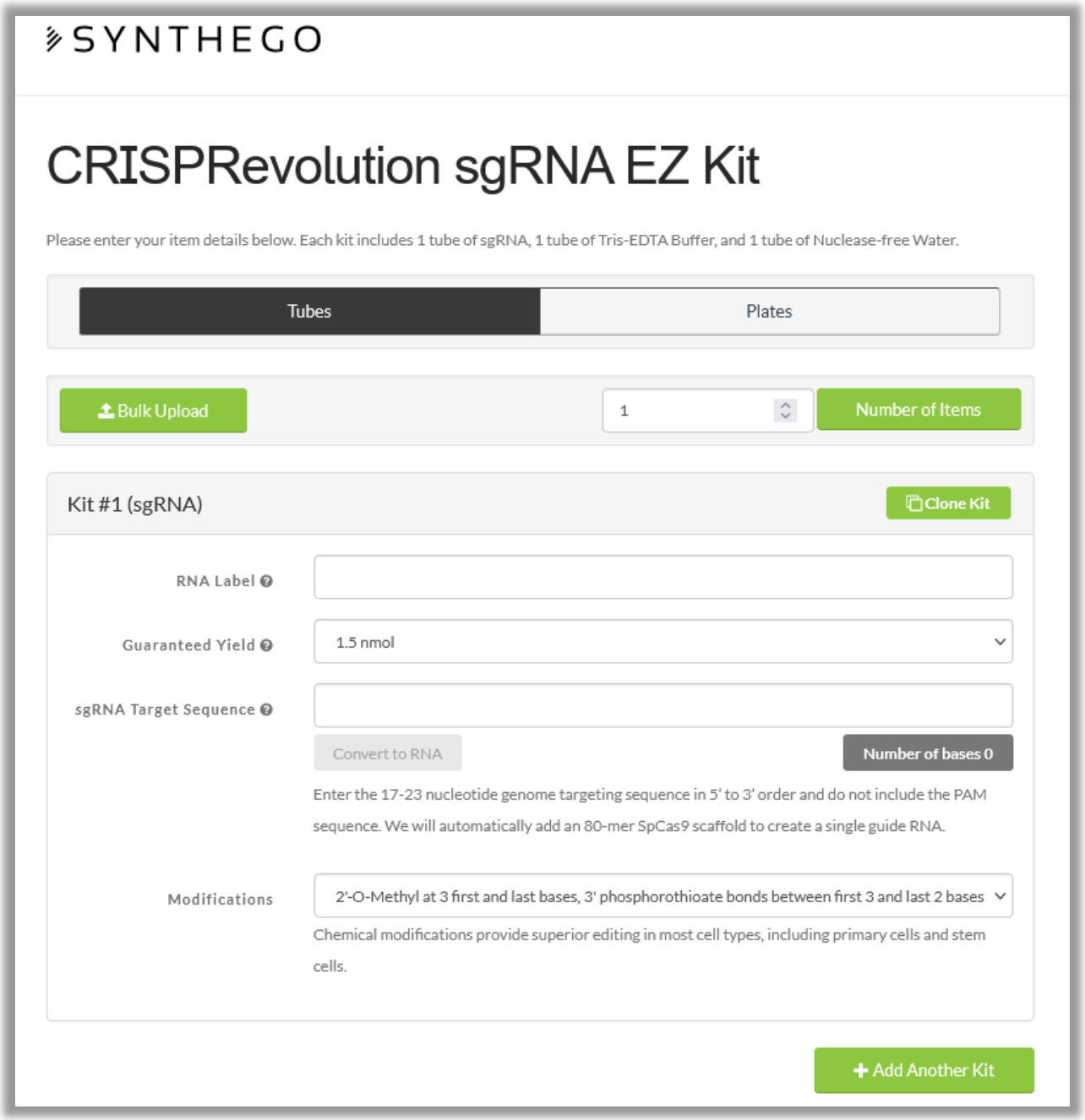
See Synthego, Products, Crispr Kits, "Advanced RNA", Orders, *available at* https://orders.synthego.com/products/crisprevolution-custom-rna-9/#/tubes (emphases added). Mimicking the benefits described in the Asserted Patents, here also Synthego touts these synthetic chemically modified gRNAs as providing "superior editing in most cell types, including primary cells and stem cells." *Id.*

54. Synthego's GMP facility operates a synthetic sgRNA manufacturing system that offers large scale research use-only sgRNA synthesis, GMP-like sgRNA synthesis, and GMP sgRNA manufacturing. *See* Synthego, Products, CRISPR Kits, "GMP sgRNA Manufacturing", *available at* https://www.synthego.com/products/crispr-kits/gmp-sgrna. For each type of large scale sgRNA synthesis, Synthego offers "site-specific chemical modifications on sgRNAs for improved stability and protection from the cellular innate immune response, enabling superior editing of difficult to edit cell types, including primary and iPS cells," for example, as described below:



See Synthego, Workflows, Cell and Gene Therapies, *available at* https://www.synthego.com/workflows/cell-gene-therapy. And, by clicking on the "Synthetic sgRNA" "**Order Now**" button, the customer is automatically redirected to the "CRISPRevolution sgRNA EZ Kit" order page depicted below, which defaults to synthetic sgRNA with chemical modifications, including an infringing modified gRNA with a ***"2'-O-***

Methyl" modification at the ***"3 first and last bases" and "3'phosphorothioate bonds between first 3 and last 2 bases"***:



See Synthego, Products, "CRISPRevolution sfRNA EZ Kit", *available at* https://orders.synthego.com/products/crisprevolution-sgrna-ez-kit-13/#/tubes?mod_code=1

(emphasis added). Again, Synthego praises these infringing synthetic chemically modified gRNAs as providing "superior editing in most cell types, including primary cells and stem cells." *Id*.

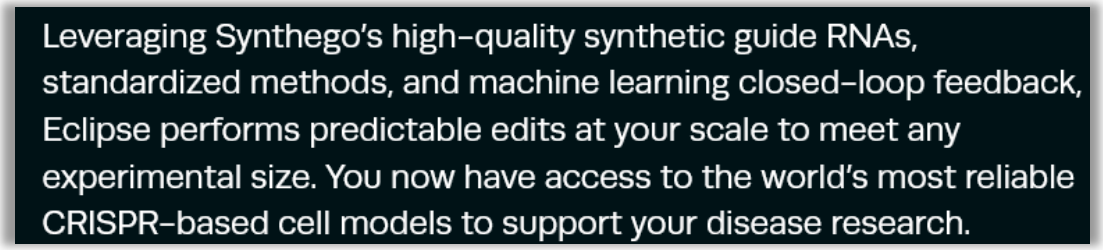
55. On information and belief, beginning at least as early as April 2021, Synthego began using and marketing infringing products and processes under the Eclipse Platform, a "CRISPR-editing platform" which includes at least the following "Eclipse-powered products": Knock-In iPS Cells, Knockout iPS Cells, CRISPR Knockout Cell Clone, and Knockout Cell Pool. *See* Synthego, Platform/Eclipse, *available at* https://www.synthego.com/platforms/eclipse. Synthego's Halo platform products, as detailed above, include sgRNAs that "were produced synthetically (by Synthego) and chemically modified to have 2′ O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the three 5′ and 3′ terminal RNA residues." *See* Synthego, Resources, Application Note, "Multi-guide sgRNA improves CRISPR Knockout Efficiency by Generating Fragment Deletions." These Halo platform products are "vertically integrated with the Eclipse platform," such that "the two platforms are related and they learn from each other." *See* Synthego, Eclipse, Engineered Cells Webinar, "Introducing Industrialized CRISPR Cells, Powered by the Eclipse Platform", *available at* https://www.synthego.com/thanks/eclipse-industrialized-crispr-webinar?submissionGuid=148e638b-7918-40cd-b8b5-20dca95127f9. For example, Synthego's Chief Strategy Officer, Jason Steiner, Ph.D. described Halo's platform ("tools platform") integration with the Eclipse platform, stating:

> We have a protocol that we implement across the company on all of our platforms which we call Closed- Loop CRISPR. It links our platforms for generating engineered tools and our platform for generating engineered cells. ***Our tools platforms provide reagents to engineer cells***, our engineered cells outputs provide data back to our tools platform.
>
> ***By combining these two platforms we're able to produce a whole suite of products and these products support the utilization of genome engineering technologies across the entire discovery to clinical manufacturing spectrum,***

including everything from target identification through again GMP manufacturing.

Id. Synthego used and continues to use infringing synthetic chemically modified sgRNAs in its Eclipse platform products and processes, including for example its engineered cell products, and cell engineering processes, such as modular design, optimized transfection, clones with integrity, end-to-end tracking, and predictive CRISPR design. *See* Synthego, Platform/Eclipse (Synthego's CRISPR engineered cell products include at least "Knock-In iPS Cells, Knockout iPS Cells, CRISPR Knockout Cell Clone, and Knockout Cell Pool"); *and see, e.g.*, Synthego, Eclipse, Engineered Cells Webinar, "Introducing Industrialized CRISPR Cells, Powered by the Eclipse Platform" (showing "Halo Integration" with Eclipse cell engineering processes); *see also* Synthego, Platforms, Eclipse, "Technology-Fueled Genome Engineering", *available at* https://www.synthego.com/platforms/eclipse:

56. For example, Synthego uses its "high-quality synthetic sgRNA, powered by the Halo Platform," to generate "genome-engineered human iPSC lines harboring ADRD-associated mutations at scale across 22 gene targets." *See* Synthego, Case Study, "Industrialized CRISPR iPS Cells Enable NIH Large Scale Alzheimer's Disease Research Effort", *available at* https://www.synthego.com/platforms/eclipse/indi. Synthego also advertises that customers can "leverage[] Synthego's high-quality synthetic guide RNAs" for Eclipse platform engineered cells and cell engineering processes. *See, e.g.*, Synthego, Platforms, Eclipse, "Technology-Fueled Genome Engineering":



57. Since receiving notice of Agilent's patent portfolio, including the Asserted Patents, at least as early June 24, 2021, Synthego has continued to make, use, sell, and offer for sale infringing products, including advertising and championing the many benefits of the patented inventions described in the Asserted Patents.

58. And each of these benefits was obvious to Synthego when it used and advertised the advantages of the Asserted Patents' synthetic chemically modified guide RNA. *See, e.g.*, Synthego, Help Center - Product Info, "Advantages of Using gRNAs with Chemical Modifications."

59. After receiving notice of Agilent's patent portfolio and the Asserted Patents in particular, Synthego has continued to use, take advantage of, and profit from the benefits of the patented inventions highlighted in the Asserted Patents. Synthego continues to recommend the use of their infringing products for cell culture and in vivo experiments due to: "increased stability and protection from exonucleases," "overall improved editing efficiency," "reduced innate immune response," and "reduced off-targets compared to plasmid or viral delivery." *Id.*

60. Synthego's publications and advertisements show its understanding of the many benefits of Agilent's patented inventions. For example, Synthego's "Newsroom" includes a press release regarding a *Genetic Engineering & Biotechnology News* article, dated August 4, 2021, which details a Synthego-co-authored paper, "Chemically modified guide RNAs enhance CRISPR-Cas13 knockdown in human cells," in which Synthego employees and shareholders synthesized, used and touted many of the same benefits from using infringing chemically modified sgRNAs as were described by the Asserted Patents. *See* Synthego, Newsroom, News

& Releases, "Modified RNA Guides Improve RNA Targeting Ability of CRISPR-Cas13", *available at* https://www.synthego.com/press; *see also* Genetic Engineering & Biotechnology News, August 4, 2021, *available at* https://www.genengnews.com/topics/genome-editing/modified-rna-guides-improve-rna-targeting-ability-of-crispr-cas13/ (citing and detailing Méndez-Mancilla et al. (2021)).

61. The Méndez-Mancilla et al. (2021) publication expressly cited the benefits of Agilent's patented inventions, for example, stating:

> We tested three different modifications of the 3xU bases that ***have been reported before to improve RNA stability and evade secondary immune responses (Hendel et al. 2015)*** … 2′-O-methylation (M), phosphorothioate linkage (S), and 2′-O-methylation and phosphorothioate linkage (MS).

Id. (emphases added).

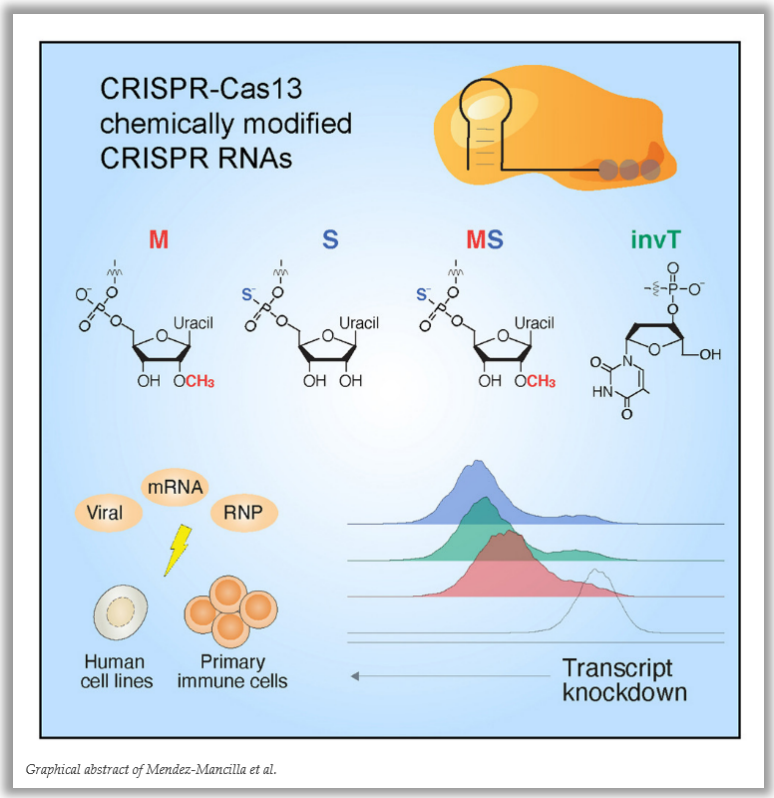
62. One of the co-authors of the Méndez-Mancilla et al. (2021) paper stated to *Genetic Engineering & Biotechnology News*:

> "CRISPR RNA guide delivery can be challenging, with knockdown time limited due to rapid guide degradation. We were inspired by the guide modifications developed for other DNA-targeting CRISPRs and wanted to test if chemically modified guides could improve knockdown time for RNA-targeting CRISPR-Cas13 in human cells," said Alejandro Méndez-Mancilla, PhD, a postdoc at New York Genome Center (NYGC) and co-first author of the study.

See Genetic Engineering & Biotechnology News, August 4, 2021. Additionally, the "research team, which included collaborators at Synthego and New England BioLabs," touted the benefits of the patented inventions in improving Cas13 activity, as well as characterizing "***the placement of these modified RNA bases []as crucial***":

> The team found that certain methylation and inverted terminator modifications also improved Cas13 activity. For all modifications, the placement of these modified RNA bases was crucial. When placed incorrectly, the modifications resulted in guide RNAs that did not function.

Id. (emphases added); *and see* Méndez-Mancilla, et al. (2021) (detailing use of, tests with, and touting results from chemical modifications incorporated during synthesis of gRNAs, including 2′-O-methylation (M) and 2′-O-methylation and phosphorothiate linkage (MS), within five nucleotides from the 3′ end). The Genetic Engineering & Biotechnology News article even reproduced the graphical abstract from Méndez-Mancilla, et al. (2021), depicting the infringing synthetic chemically modified gRNAs used, tested, and touted by Synthego:



Graphical abstract of Mendez-Mancilla et al.

See Genetic Engineering & Biotechnology News, August 4, 2021.

63. In summary, Agilent informed Synthego of the inventions claimed in the Asserted Patents; also, the Asserted Patents detailed the many substantial benefits and applications of these inventions. Synthego did not take a license. And since receiving notice of the Asserted Patents, Synthego has continued to make, use, sell, offer to sell, benefit from, and advertise the benefits of infringing synthetic chemically modified sgRNA products, uses and methods. Synthego has also published a paper and re-published press articles illustrating its infringing use after being on notice of the Asserted Patents. Synthego never compensated Agilent for the use of

Agilent's valuable and important inventions. Instead, Synthego has continued its willful infringement of Agilent's Asserted Patents.

FIRST COUNT

(INFRINGEMENT OF U.S. PATENT NO. 10,900,034)

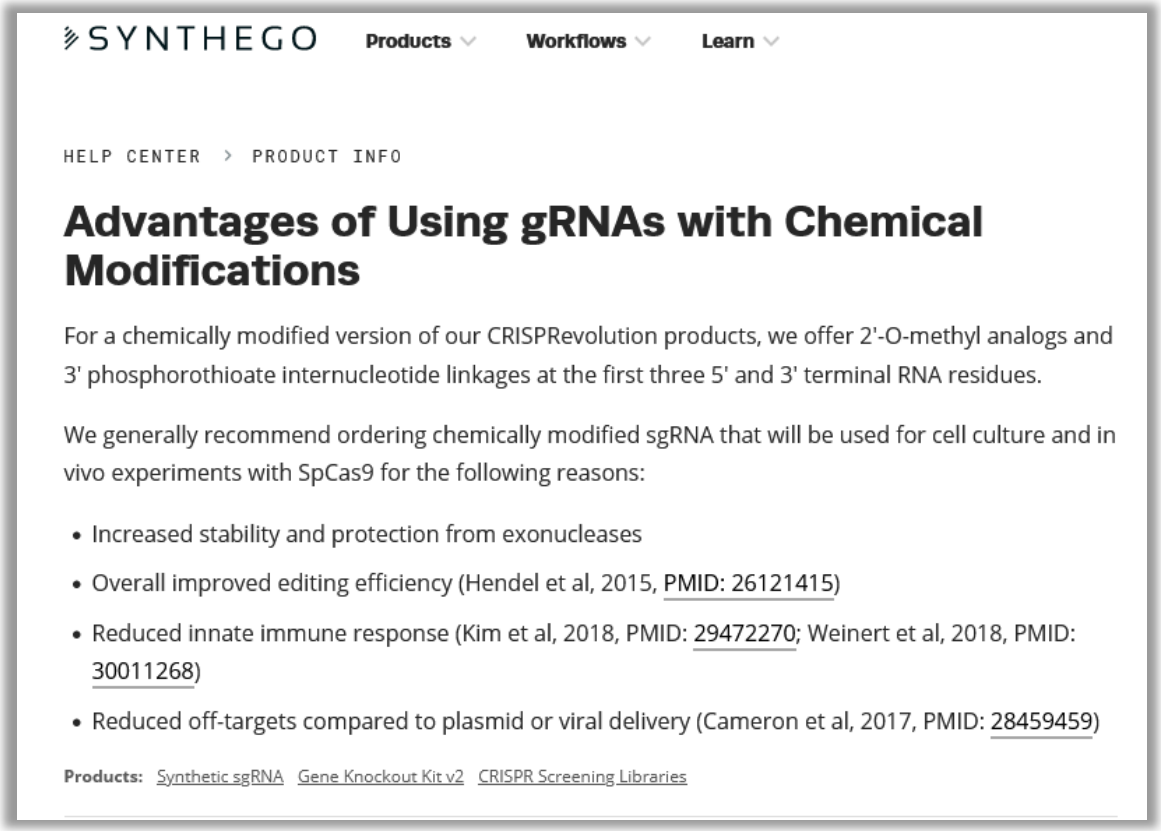
64. Agilent incorporates by reference the allegations set forth in the above paragraphs 1-63 of this Complaint as though fully set forth herein.

65. Synthego has directly infringed and continues to directly infringe one or more claims of the '034 Patent, including at least claim 1 of the '034 Patent, in the state of Delaware, in this judicial district, and elsewhere in the United States by, among other things, making, using, selling, offering for sale, and/or importing into the United States products that embody one or more of the inventions claimed in the '034 Patent, including but not limited to the above-identified Halo Platform products, which includes but is not limited to at least the following "CRISPRevolution" and/or "Halo-powered products": Synthetic sgRNA Kit, Gene Knockout Kit v2, Arrayed CRISPR Screening Libraries, Advanced RNA and CRISPR GMP sgRNA Manufacturing, including Synthego's sgRNA manufacturing system that offers large scale research use-only sgRNA synthesis, GMP-like sgRNA synthesis, and GMP sgRNA manufacturing; Eclipse Platform products and processes, which includes but is not limited to at least the following "Eclipse-powered products": Knock-In iPS Cells, Knockout iPS Cells, CRISPR Knockout Cell Clone, and Knockout Cell Pool, as well as Eclipse Platform cell engineering processes, such as modular design, optimized transfection, clones with integrity, end-to-end tracking, and predictive CRISPR design; and all reasonably similar products ("the '034 Accused Products"), in violation of 35 U.S.C. § 271(a).

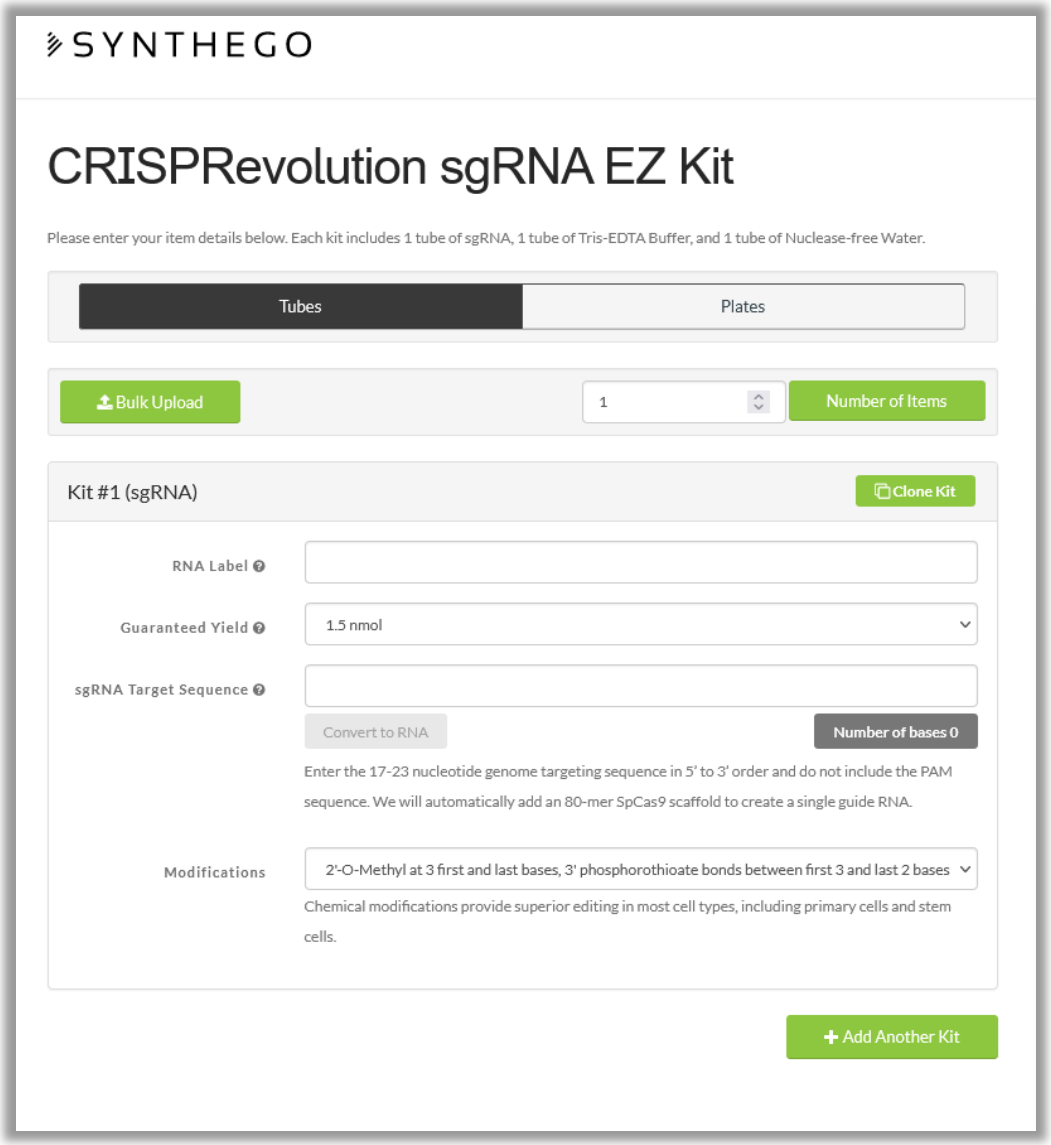
66. As an example, the '034 Accused Products, including Synthetic sgRNA Kit, Gene Knockout Kit v2, Arrayed CRISPR Screening Libraries, Advanced RNA and CRISPR GMP sgRNA Manufacturing, each use a synthetic chemically modified guide RNA that has gRNA functionality and comprises a 2′-O-methyl modification. '034 Patent at 257:34-47 (claim 1). Synthego Eclipse Platform products and processes are "integrated" with Halo Platform products,

including platform tools which use infringing synthetic chemically modified guide RNA that has gRNA functionality and comprises a 2′-O-methyl modification. *Id*.

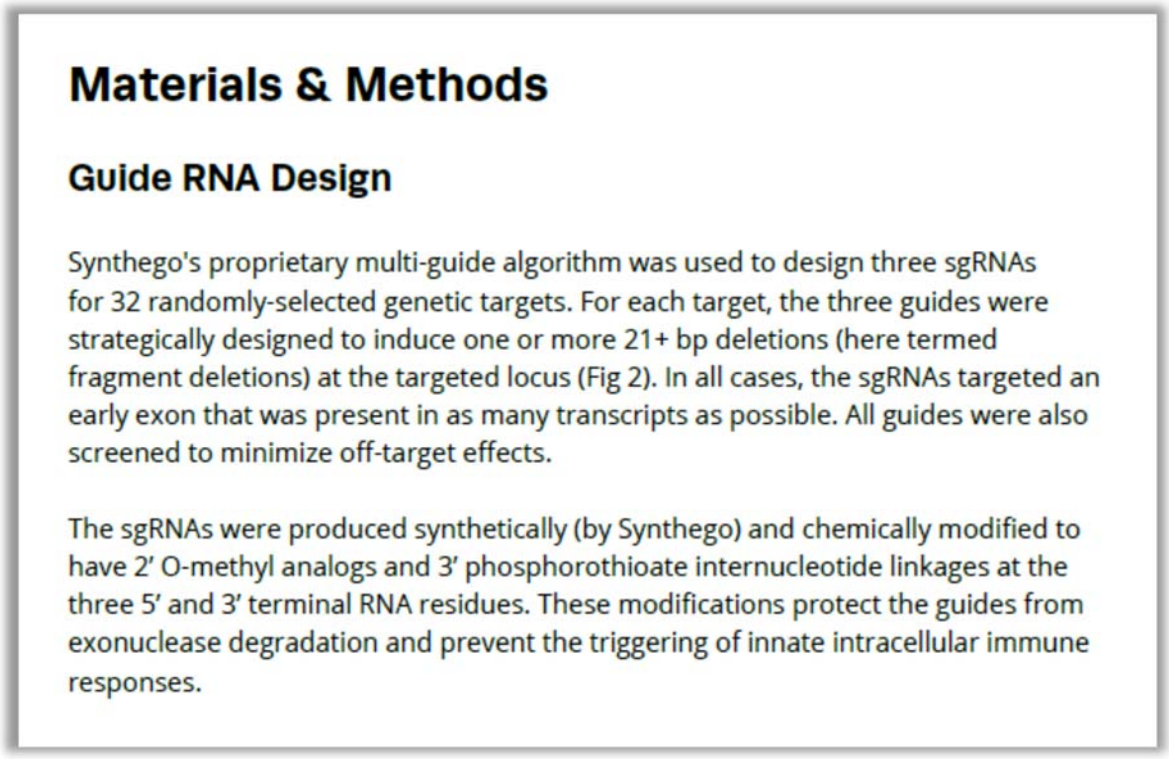
67. In each of the ’034 Accused Products, Synthego uses a synthetic CRISPR guide RNA with gRNA functionality to associate with a Cas protein and target the gRNA:Cas protein complex to the target sequence, and has one or more modifications including a 2′-O-methyl. For example, Synthego’s synthesis, use, offer for sale and sale of infringing synthetic chemically modified sgRNA is depicted in its own advertisements, order forms, “product info,” instruction manuals, and publication, as shown below:



See Synthego, Help Center - Product Info, “Advantages of Using gRNAs with Chemical Modifications.”



See Synthego, Products, "CRISPRevolution sfRNA EZ Kit."



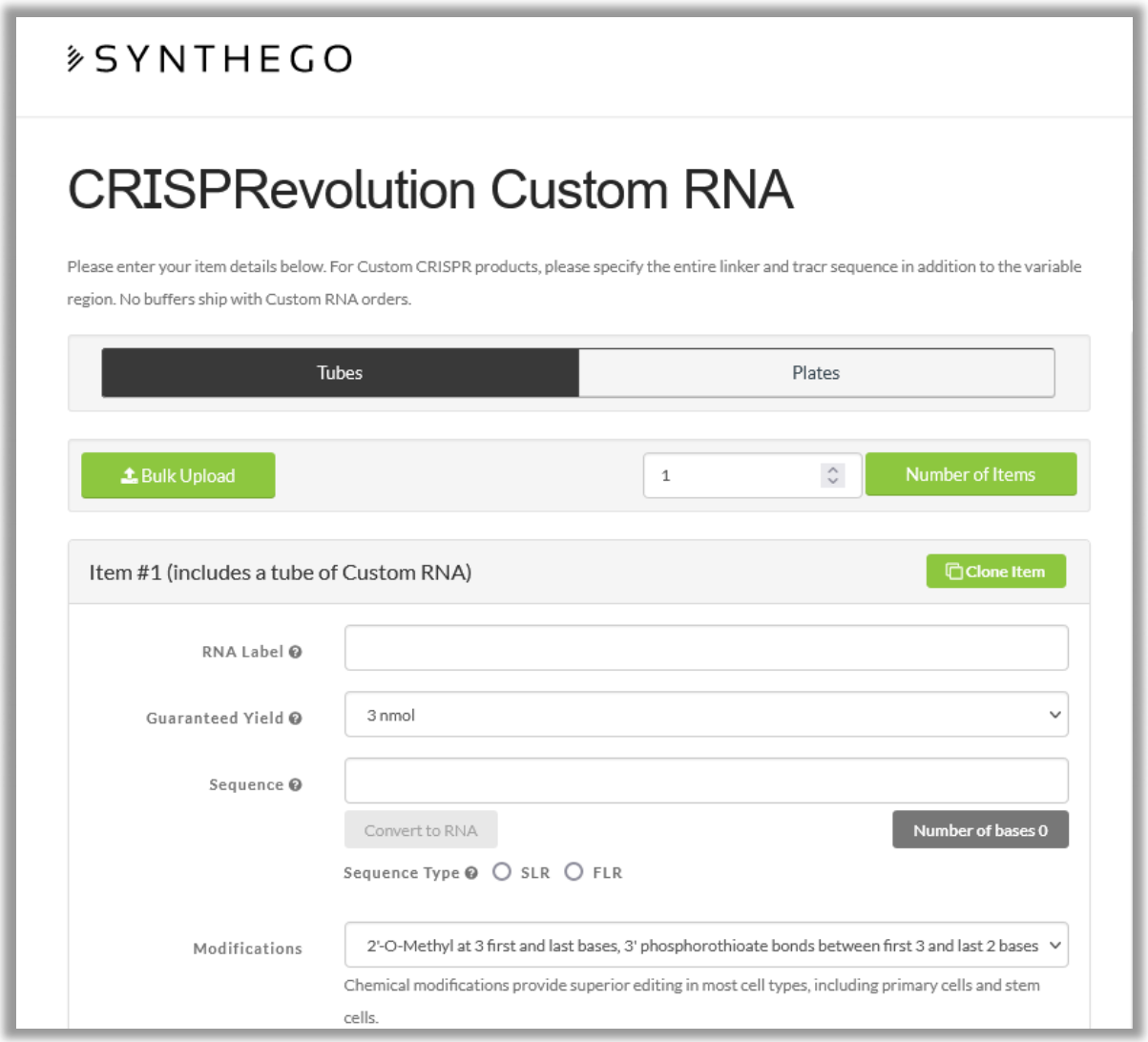
Materials & Methods

Guide RNA Design

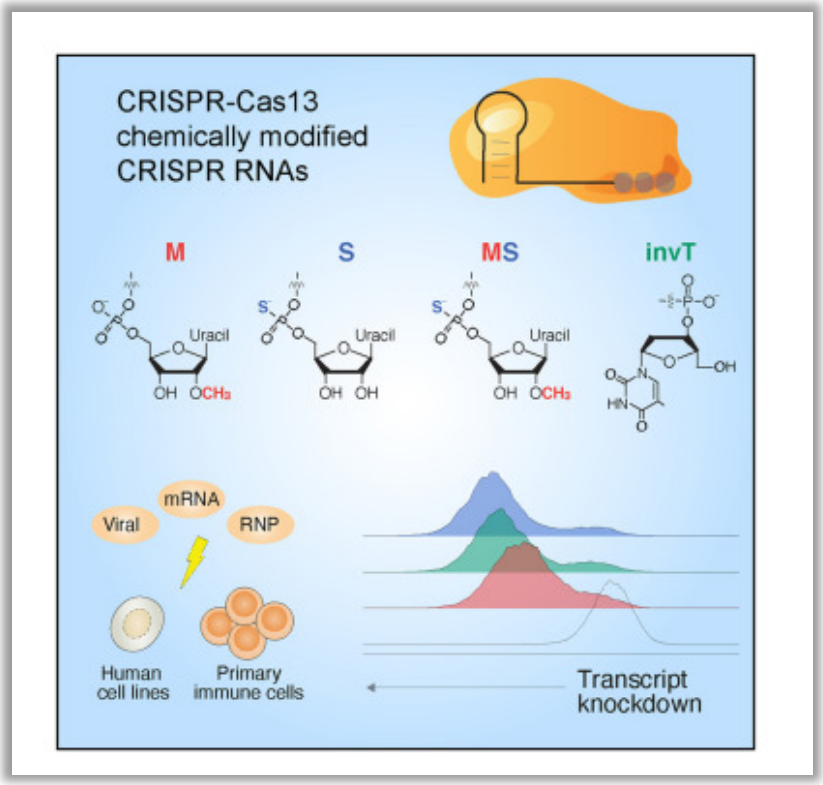
Synthego's proprietary multi-guide algorithm was used to design three sgRNAs for 32 randomly-selected genetic targets. For each target, the three guides were strategically designed to induce one or more 21+ bp deletions (here termed fragment deletions) at the targeted locus (Fig 2). In all cases, the sgRNAs targeted an early exon that was present in as many transcripts as possible. All guides were also screened to minimize off-target effects.

The sgRNAs were produced synthetically (by Synthego) and chemically modified to have 2′ O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the three 5′ and 3′ terminal RNA residues. These modifications protect the guides from exonuclease degradation and prevent the triggering of innate intracellular immune responses.

See Synthego, Resources, Application Note, "Multi-guide sgRNA improves CRISPR Knockout Efficiency by Generating Fragment Deletions" at 4.



See Synthego, Products, Crispr Kits, "Advanced RNA", Orders.

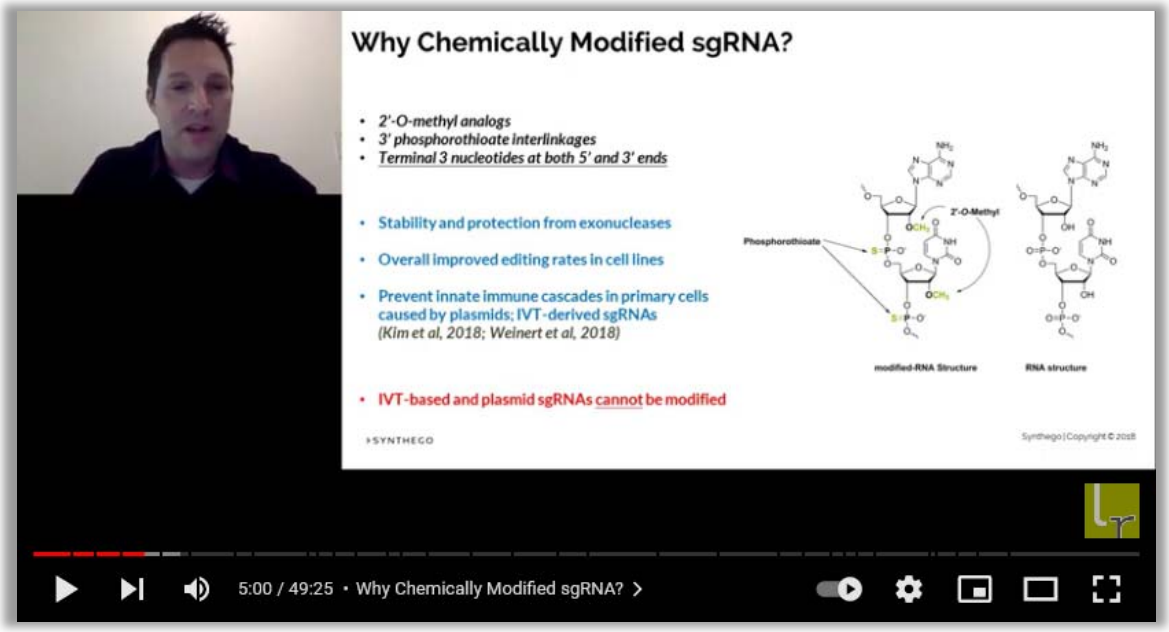


See Méndez-Mancilla, et al. (2021) (graphical abstract).

68. Synthego advertises its infringing use of synthetic sgRNA with chemical modifications including 2′-O-methyl modifications at the first and last three terminal nucleotides in "all" of its projects. For example, Kevin Holden, Head of Synthetic Biology at Synthego, explained:

> When we're talking about the guide RNA format to use, at Synthego we are a cell engineering company and ***all of our projects involve the use of these chemically modified synthetic single guide RNAs*** that we use for generating indels in cells, knockouts and knock-ins. …
>
> ***Why do we use these single guide RNAs in a chemically modified format?*** Well, several years ago now there was a landmark paper that came out of Matthew Porteus' lab at Stanford University showing that you could utilize these chemically modified guide RNAs to effectively edit many different types of human primary cells, specifically in this case, primary human T cells and hematopoietic stem cells. And these chemical modifications that exist on the guide RNAs they're important for several reasons. ***They actually are these 2'-***

O-methyl analogs and these sulfur interlinkages on the terminal 3 nucleotides of both ends of the guide RNA molecule.

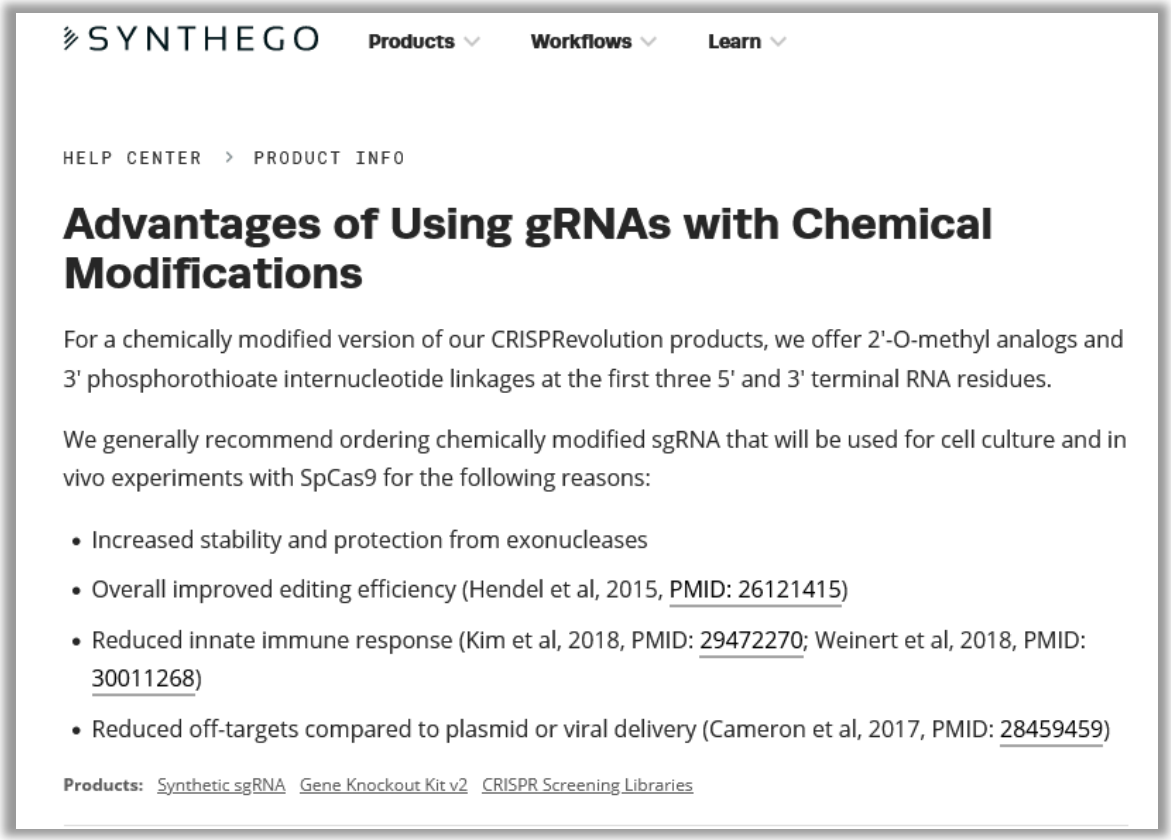


See Synthego, "Design, Edit, Analyze and Maximize Your CRISPR-Cas9 Editing Efficiency," Kevin Holden, October 15, 2018, *available at* https://www.youtube.com/watch?v=mc0ioq23Ugw

69. By making, using, offering for sale, and/or selling products in the United States and/or importing products into the United States, including but not limited to the '034 Accused Products, Synthego has injured Agilent and is liable to Agilent for directly infringing one or more claims of the '034 Patent, including without limitation claim 1, pursuant to 35 U.S.C. § 271(a).

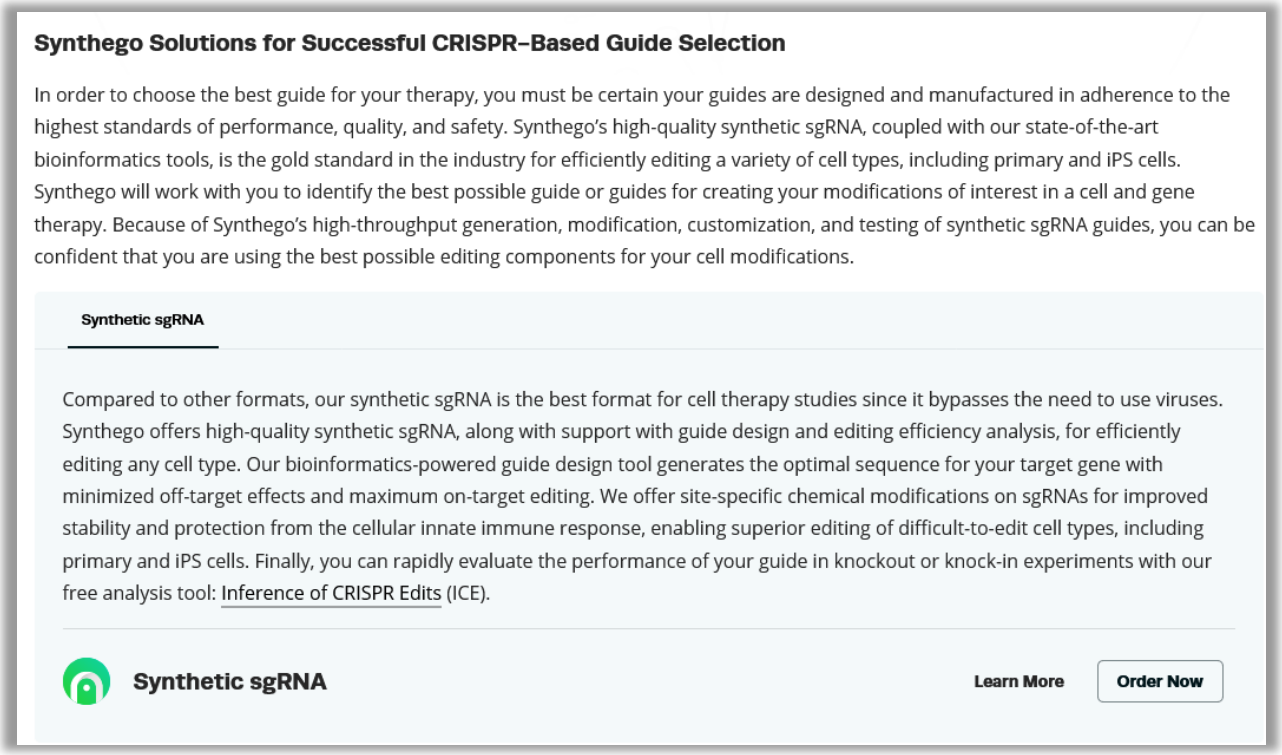
70. On information and belief, Synthego is inducing and/or has induced infringement of one or more claims of the '034 Patent, including at least claim 1, as a result of, among other activities, instructing, encouraging, recommending, and directing its customers on the use of '034 Accused Products in an infringing manner in violation of 35 U.S.C. § 271(b). Through its website, instructional guides, manuals, case studies, publications, press releases, and advertisements, Synthego provides its customers with detailed explanations, instructions, and

information on how to use and implement the '034 Accused Products which demonstrate active steps taken to encourage direct infringement. *See, e.g.*, Synthego, Help Center - Product Info, "Advantages of Using gRNAs with Chemical Modifications", wherein Synthego not only "offer[s] 2′-O-methyl analogs" at the "first three 5′ and 3′ terminal RNA residues," Synthego also "recommend[s] ordering chemically modified sgRNA that will be used for cell culture and in vivo experiments with SpCas9" for several specified reasons, including those benefits described and claimed by the inventions of the Asserted Patents:



As another example, Synthego advertises the benefits of its GMP facility for the synthesis of chemically modified sgRNA, and, by clicking on the "Synthetic sgRNA" "**Order Now**" button (*see* Synthego, Workflows, Cell and Gene Therapies), the customer is automatically redirected to the "CRISPRevolution sgRNA EZ Kit" order page which ***defaults to sgRNA with chemical modifications***, including ***an infringing synthetic gRNA with 2'-O-methyl chemical***

modification at the "3 first and last bases", which states, ***"chemical modifications provide superior editing in most cell types, including primary and stem cells":***



Synthego Solutions for Successful CRISPR–Based Guide Selection

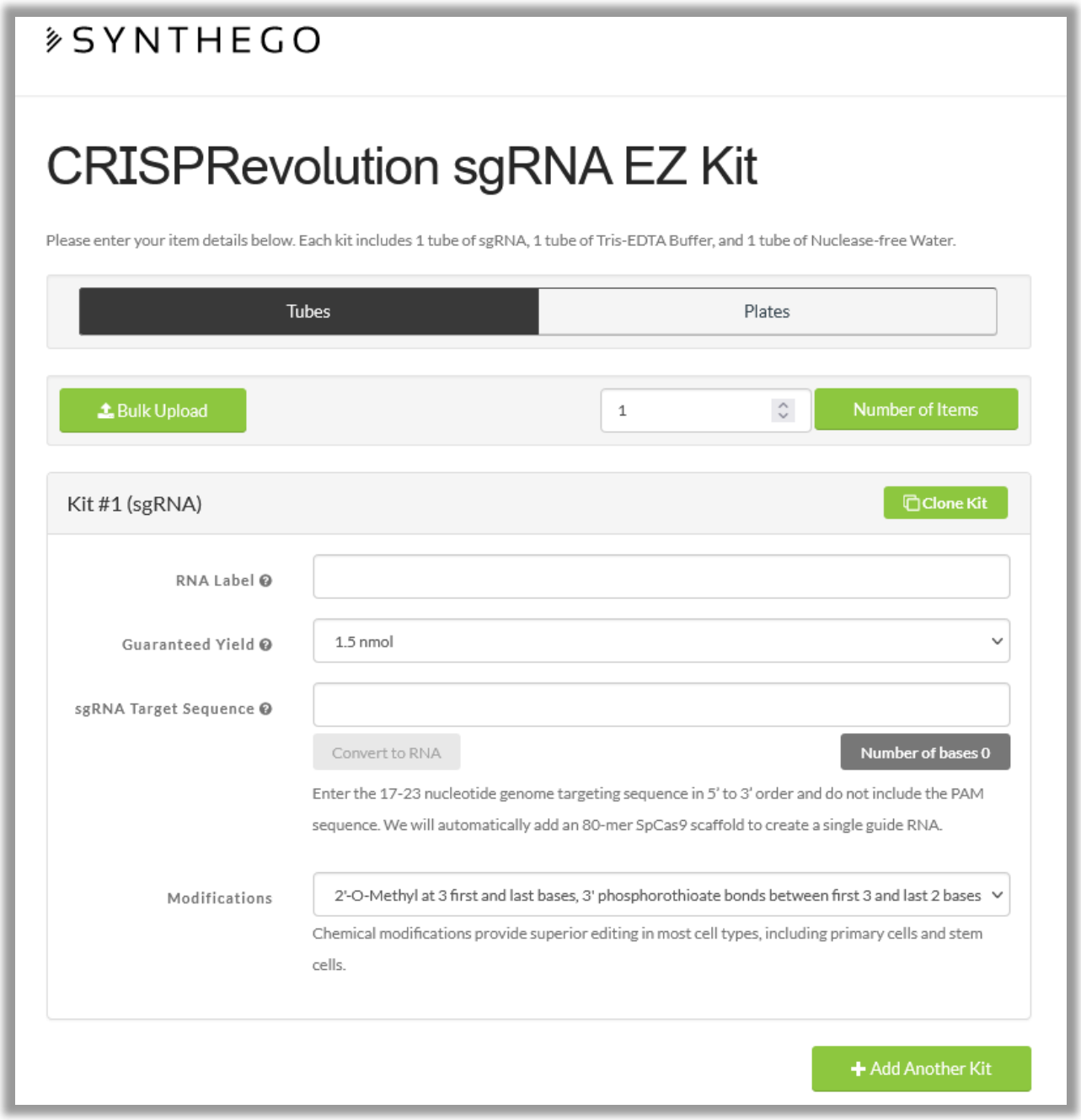
In order to choose the best guide for your therapy, you must be certain your guides are designed and manufactured in adherence to the highest standards of performance, quality, and safety. Synthego's high-quality synthetic sgRNA, coupled with our state-of-the-art bioinformatics tools, is the gold standard in the industry for efficiently editing a variety of cell types, including primary and iPS cells. Synthego will work with you to identify the best possible guide or guides for creating your modifications of interest in a cell and gene therapy. Because of Synthego's high-throughput generation, modification, customization, and testing of synthetic sgRNA guides, you can be confident that you are using the best possible editing components for your cell modifications.

Synthetic sgRNA

Compared to other formats, our synthetic sgRNA is the best format for cell therapy studies since it bypasses the need to use viruses. Synthego offers high-quality synthetic sgRNA, along with support with guide design and editing efficiency analysis, for efficiently editing any cell type. Our bioinformatics-powered guide design tool generates the optimal sequence for your target gene with minimized off-target effects and maximum on-target editing. We offer site-specific chemical modifications on sgRNAs for improved stability and protection from the cellular innate immune response, enabling superior editing of difficult-to-edit cell types, including primary and iPS cells. Finally, you can rapidly evaluate the performance of your guide in knockout or knock-in experiments with our free analysis tool: Inference of CRISPR Edits (ICE).

Synthetic sgRNA Learn More Order Now

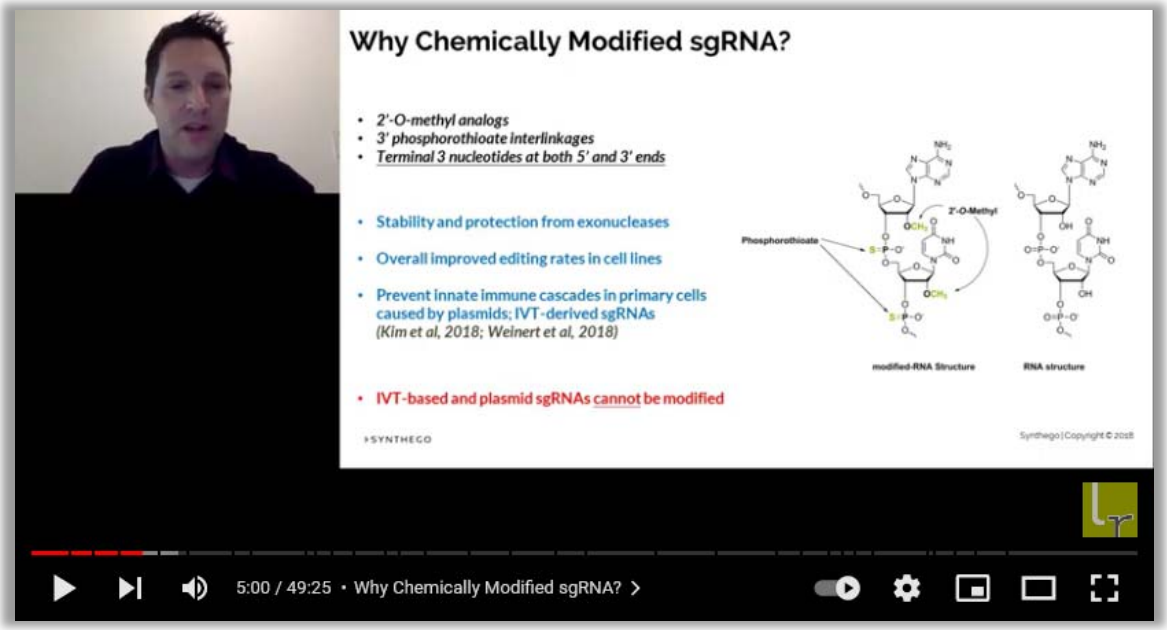
See Synthego, Workflows, Cell and Gene Therapies.



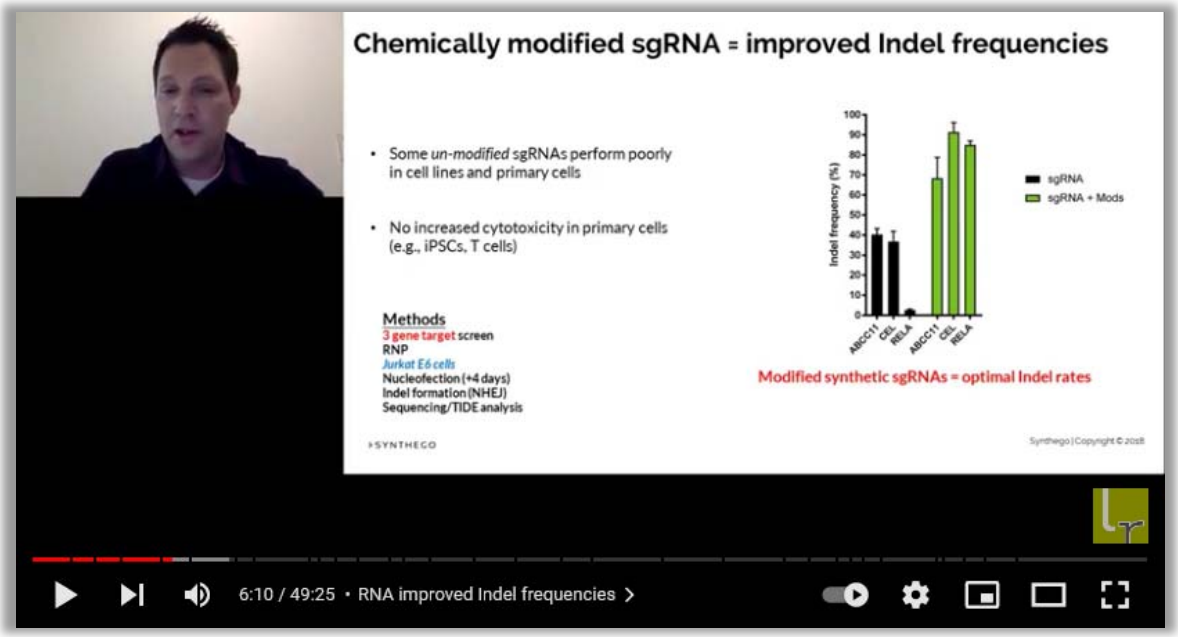
See Synthego, Products, "CRISPRevolution sfRNA EZ Kit." As yet another example, Synthego instructs customers which "guide RNA format to use," explaining that synthetic chemically modified gRNA with 2′-O-methyl analogs on the terminal three nucleotides of both ends of the guide RNA molecule are "important for several reasons," including increased

stability, protection from exonucleases, overall improved editing rates in both cell lines and primary cells, prevention of innate immune responses, and improved indel frequency:

> When we're talking about the guide RNA format to use, at Synthego we are a cell engineering company and ***all of our projects involve the use of these chemically modified synthetic single guide RNAs*** that we use for generating indels in cells, knockouts and knock-ins. …
>
> ***Why do we use these single guide RNAs in a chemically modified format?*** Well, several years ago now there was a landmark paper that came out of Matthew Porteus' lab at Stanford University showing that you could utilize these chemically modified guide RNAs to effectively edit many different types of human primary cells, specifically in this case, primary human T cells and hematopoietic stem cells. And these chemical modifications that exist on the guide RNAs they're important for several reasons. ***They actually are these 2'-O-methyl analogs and these sulfur interlinkages on the terminal 3 nucleotides of both ends of the guide RNA molecule.***
>
> And ***these are important because they provide stability and protection from exonucleases inside the cell***. We also see that ***they also give overall improved editing rates in both cell lines and particularly primary cells*** as I mentioned. And this is because ***they prevent some of these innate immune cascades that can occur in primary cells*** that have been shown to be triggered by utilizing plasmid delivery systems or in vitro transcribed single guide RNAs …



…So utilizing the modified version of the single guides really does improve your indel frequencies.



See Synthego, "Design, Edit, Analyze and Maximize Your CRISPR-Cas9 Editing Efficiency."

71. Synthego has had actual knowledge of the '034 Patent at least as of June 24, 2021. Despite this knowledge of the '034 Patent, Synthego has continued to engage in activities

to encourage and assist its customers in the use of the '034 Accused Products, as depicted in the aforementioned examples. Thus, on information and belief, Synthego (1) had actual knowledge of the patent; (2) knowingly induced its customers to infringe the patent; and (3) had specific intent to induce the patent infringement.

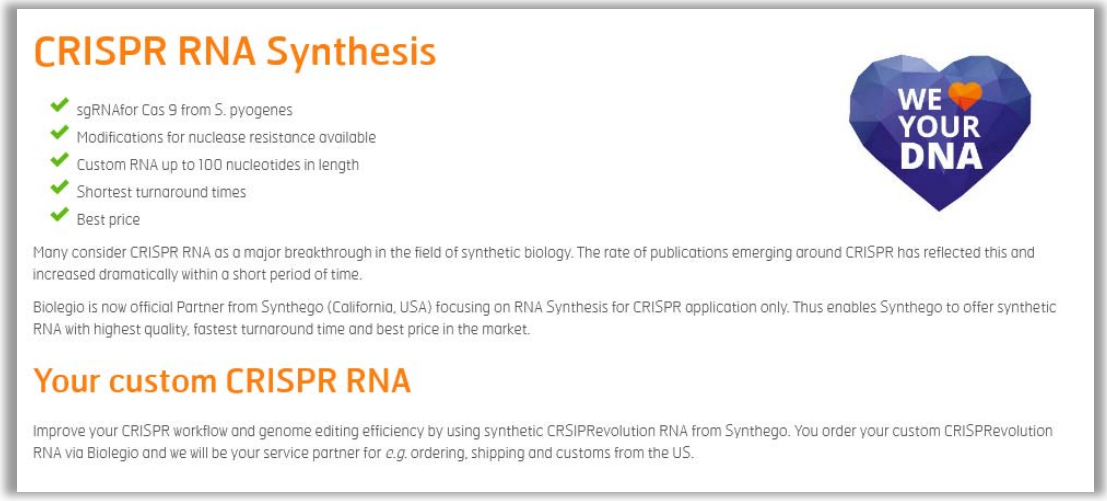
72. On information and belief, by using the '034 Accused Products as encouraged, recommended and assisted by Synthego, Synthego's customers have directly infringed and continue to directly infringe one or more claims of the '034 Patent, including at least claim 1.

73. On information and belief, Synthego is actively inducing and/or has actively induced the combination of components of the patented inventions of the '034 Patent outside of the United States in a manner that would infringe the '034 Patent if such combination occurred within the United States, in violation of 35 U.S.C. § 271(f)(1). Synthego infringes one or more claims of the '034 Patent, including at least claim 1, by supplying or causing to be supplied in or from the United States a substantial portion of the components of the '034 patented inventions, including without limitation, components of at least claim 1, such as a synthetic CRISPR guide RNA that has gRNA functionality, including a crRNA segment with a guide sequence capable of hybridizing to a target sequence in a polynucleotide and a stem sequence, as well as a tracrRNA segment with a nucleotide sequence that is partially or completely complementary to the stem sequence, wherein the guide sequence has one or more modifications including a 2′-O-methyl, so as to, on information and belief, intentionally and with knowledge, actively induce the combination of such components outside of the United States in a manner that would infringe the '034 Patent if such combination occurred within the United States.

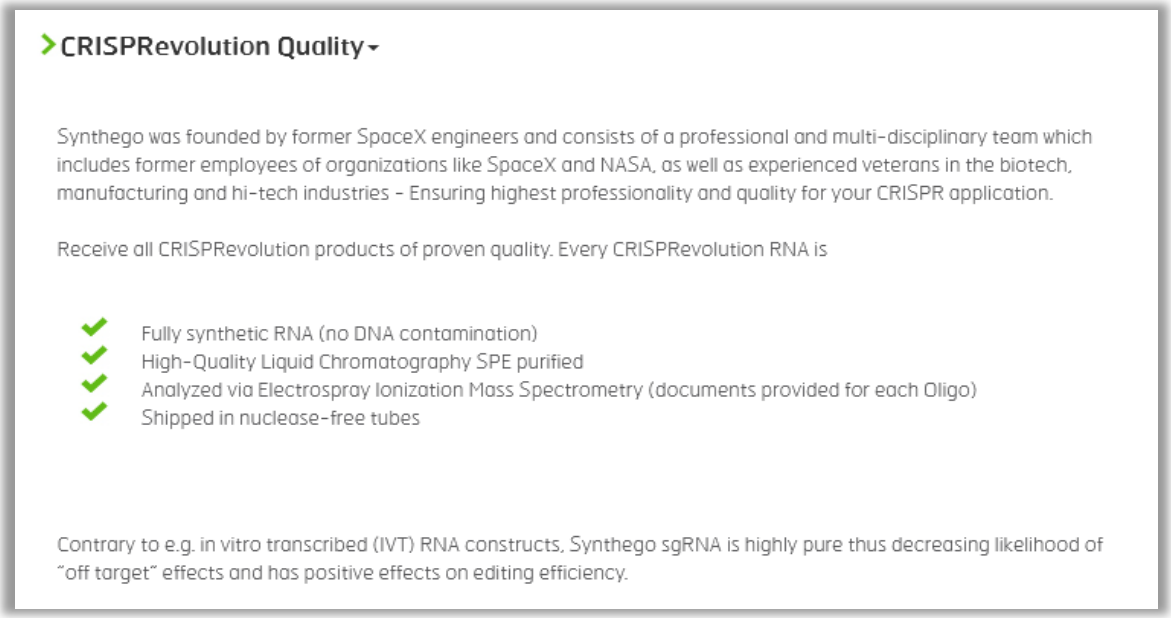
74. As an example of Synthego's infringing acts in violation of 35 U.S.C. § 271(f)(1), Synthego has partnered with at least 23 different "global distributors" to supply infringing products and/or components of infringing products outside the United States, such that the combination of such components would infringe the '034 Patent, including at least claim 1, if such combination occurred within the United States. *See, e.g.*, Synthego, Worldwide Directory, *available at* https://www.synthego.com/contact/worldwide. Synthego supplies these global

distributors with synthetic CRISPR guide RNA that has gRNA functionality, including a crRNA segment with a guide sequence capable of hybridizing to a target sequence in a polynucleotide and a stem sequence, as well as a tracrRNA segment with a nucleotide sequence that is partially or completely complementary to the stem sequence, wherein the guide sequence has one or more modifications including a 2′-O-methyl modification. Synthego advertises its partnership with Biolegio, for example, to distribute its products in The Netherlands:

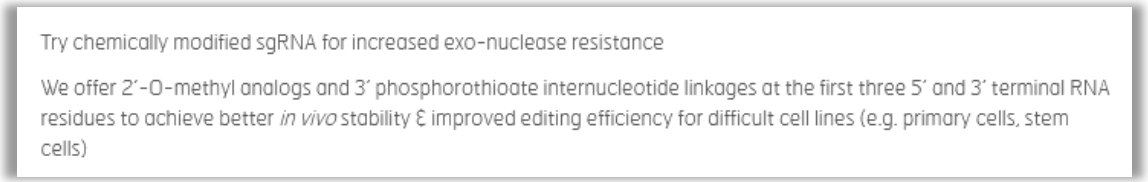
See id. Biolegio advertises that it is the "official partner from Synthego (California, USA)" enabling its customers to order Synthego's infringing products and components, wherein Biolegio is the "service partner for *e.g*. ordering, shipping and customs from the US." *See, e.g.*, Biolegio, Products-Services, CRISPR RNA Synthesis, *available at* https://www.biolegio.com/products-services/crispr-rna-synthesis/:

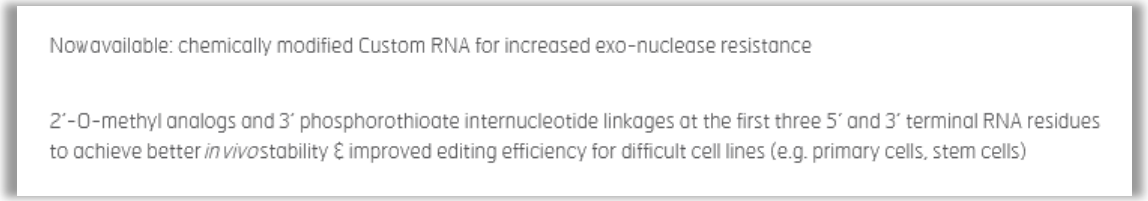


Biolegio advertises its use of Synthego sgRNA products, such as "CRISPRevolution products," *see, e.g.*: Biolegio, Products-Services, CRISPRevolution Quality, *available at* https://www.biolegio.com/products-services/crispr-rna-synthesis/#tab_2:



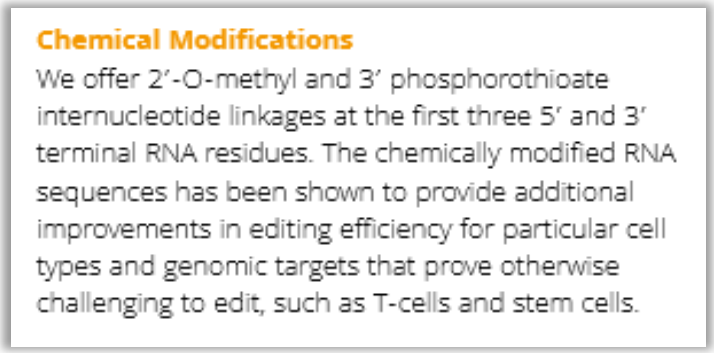
Biolegio sells Synthego-supplied synthetic chemically modified gRNA with one or more 2′-O-methyl modifications, including sgRNA for use with Cas9, as well as "custom RNA" for use with "CPF1 or other Cas systems," as shown in Biolegio advertisements below:



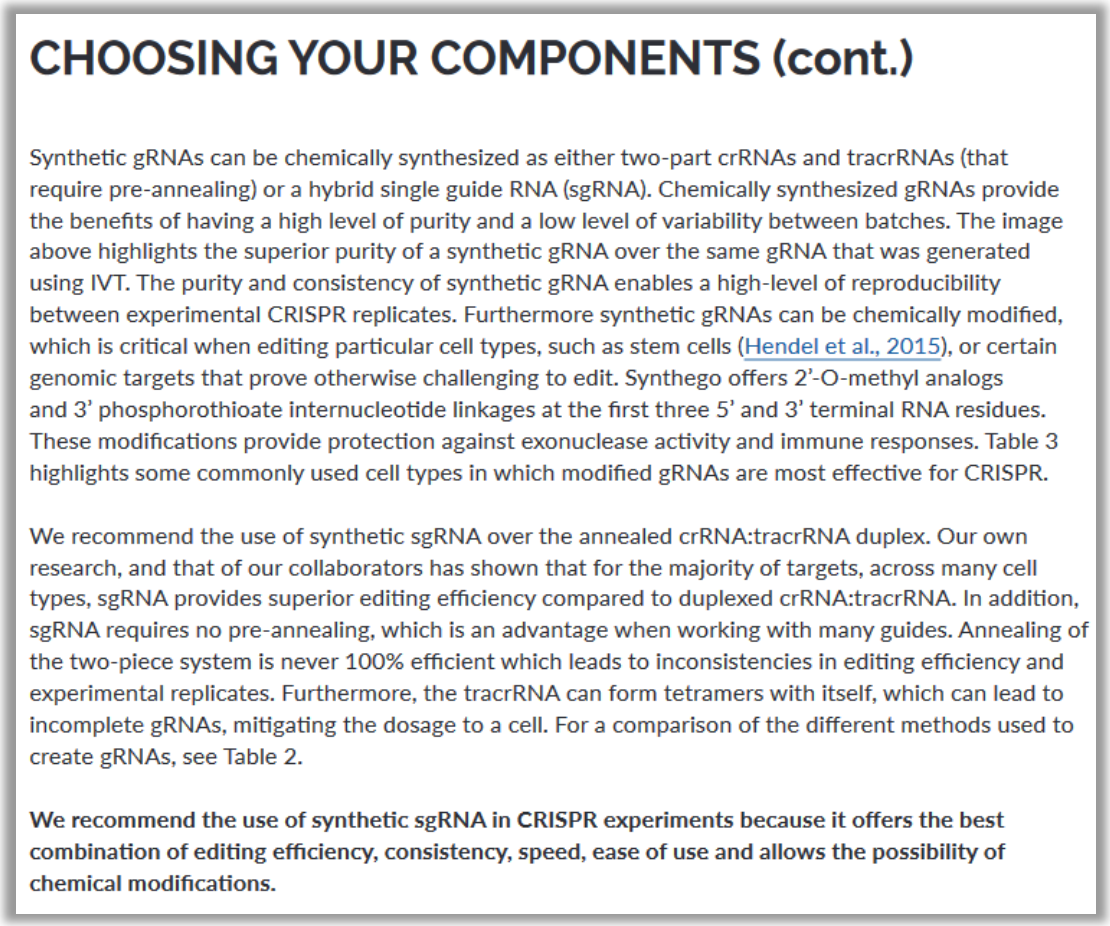


See Biolegio, Products-Services, CRISPR RNA Synthesis, Overview, *available at* https://www.biolegio.com/products-services/crispr-rna-synthesis/#tab_1

75. Biolegio's website offers various materials which instruct how to engage in infringing use of the '034 Patent, including at least claim 1, including advertisements, instruction manuals, guides, posters, and a video prepared, authored, and/or co-authored by Synthego, including but not limited to: (1) a Synthego and Biolegio co-authored Whitepaper, titled "Transforming Life Science: CRISPR-Cas9," which provides instructions, recommendations and guides for infringing "applications" of synthetic chemically modified RNA sequences, such as use of such sequences with 2′-O-methyl modifications at the first three 5′ and 3′ terminal RNA residues, as shown below:



(see Biolegio, Products-Services, CRISPR RNA Synthesis, Downloads and Links, Whitepaper, "Transforming Life Science: CRISPR-CAS9", *available at* https://www.biolegio.com/media/4193/biolegio-application-note-crispr-mail.pdf); (2) a Synthego-authored "guide," titled "How to Perform Successful CRISPR Experiments, a Step-by-Step Guide," which provides instructions, recommendations and guides for the infringing use of chemically modified synthetic gRNAs, such as 2′-O-methyl modifications at the first three 5′ and 3′ terminal RNA residues, as shown below:



CHOOSING YOUR COMPONENTS (cont.)

Synthetic gRNAs can be chemically synthesized as either two-part crRNAs and tracrRNAs (that require pre-annealing) or a hybrid single guide RNA (sgRNA). Chemically synthesized gRNAs provide the benefits of having a high level of purity and a low level of variability between batches. The image above highlights the superior purity of a synthetic gRNA over the same gRNA that was generated using IVT. The purity and consistency of synthetic gRNA enables a high-level of reproducibility between experimental CRISPR replicates. Furthermore synthetic gRNAs can be chemically modified, which is critical when editing particular cell types, such as stem cells (Hendel et al., 2015), or certain genomic targets that prove otherwise challenging to edit. Synthego offers 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues. These modifications provide protection against exonuclease activity and immune responses. Table 3 highlights some commonly used cell types in which modified gRNAs are most effective for CRISPR.

We recommend the use of synthetic sgRNA over the annealed crRNA:tracrRNA duplex. Our own research, and that of our collaborators has shown that for the majority of targets, across many cell types, sgRNA provides superior editing efficiency compared to duplexed crRNA:tracrRNA. In addition, sgRNA requires no pre-annealing, which is an advantage when working with many guides. Annealing of the two-piece system is never 100% efficient which leads to inconsistencies in editing efficiency and experimental replicates. Furthermore, the tracrRNA can form tetramers with itself, which can lead to incomplete gRNAs, mitigating the dosage to a cell. For a comparison of the different methods used to create gRNAs, see Table 2.

We recommend the use of synthetic sgRNA in CRISPR experiments because it offers the best combination of editing efficiency, consistency, speed, ease of use and allows the possibility of chemical modifications.

(*see* Biolegio, Products-Services, CRISPR RNA Synthesis, Downloads and Links, Guide: "How to Perform Successful CRISPR Experiments", *available at* https://www.biolegio.com/media/4148/how-to-perform-successful-crispr-experiments.pdf); and (3) a Synthego-authored "poster" titled "Use of Synthetic sgRNAs for Improved CRISPR Editing in Various Cell Types," which provides instructions, recommendations and guides for the infringing use of chemically modified synthetic gRNAs, including use such sgRNAs with 2′-O-methyl modifications at the first three 5′ and 3′ terminal RNA residues, as shown below:

Chemically modified synthetic sgRNA enables efficient CRISPR-Cas9 editing in K562 cells

K562 cells were electroporated using 4D-Nucleofector (Lonza) with *S.aureus* Cas9 or *S.pyogenes* Cas9 expression plasmids along with CRISPRevolution synthetic RNA (Synthego). Guide RNAs were supplied as either: unmodified sgRNA; modified-sgRNA; modified annealed crRNA:tracrRNA (Synthego). Modified sgRNA and crRNA:tracrRNA were chemically synthesized to contain 2'-O-methyl analogs and 3' phosphorothioate nucleotide interlinkages in the terminal three nucleotides at both 5' and 3' ends of the RNA molecule. All guide RNAs targeted the *CCR5* gene. Average editing efficiency was determined four days post-electroporation by cell lysis, PCR and GeneArt cleavage detection (Thermo).

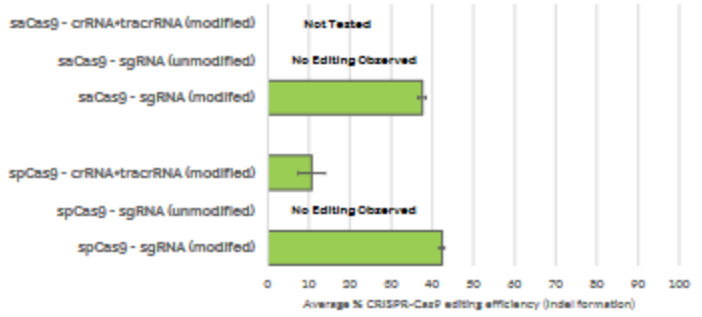


Figure 5. Chemically modified synthetic sgRNA enables reproducible CRISPR-Cas9 DNA editing in K562 cells with both *S.aureus* Cas9 (saC9) or *S.pyogenes* Cas9 (spC9) nucleases, with superior editing efficiency to a 2-part annealed synthetic crRNA:tracrRNA.

Improved editing of CD34+ hematopoietic stem cells using chemically modified synthetic sgRNA

Primary human CD34+ hematopoietic stem cells were electroporated using a 10µl Neon tip (Thermo) with *S.pyogenes* mRNA Cas9 (Trilink) and CRISPRevolution modified synthetic sgRNA (Synthego) or modified annealed crRNA:tracrRNA (IDT). Modified sgRNA were chemically synthesized to contain 2'-O-methyl analogs and 3' phosphorothioate nucleotide interlinkages in the terminal three nucleotides at both 5' and 3' ends of the RNA molecule. Modified crRNA:tracrRNA contained proprietary chemical modifications. The sgRNA targeted the *TCRα* gene in order to knockdown CD3 expression. Editing efficiency was determined seven days post-electroporation by staining with anti-human CD3 (BioLegend) and analysis by flow cytometry, with a mock-treated sample as a control input.

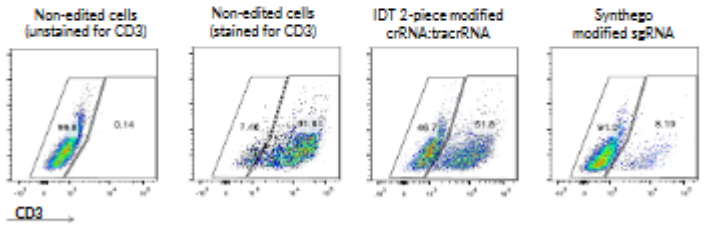


Figure 7. FACS analysis of CD34+ hematopoietic stems cells electroporated with modified synthetic sgRNA or modified crRNA:tracrRNA targeting *TCRα*. Knockdown of *TCRα* yields a CD3-negative phenotype, as seen in 46.7% of modified cr:tracrRNA-transformed cells and 91.0% of modified sgRNA-transformed cells.

(*see* Biolegio, Products-Services, CRISPR RNA Synthesis, Downloads and Links, Poster: "Use of synthetic gRNA for improved CRISPR genome editing", *available at* https://www.biolegio.com/media/4147/poster_use-of-synthetic-sgrnas-for-improved-crispr-editing-in-various-cell-types.pdf).

76. Synthego has had actual knowledge of the '034 Patent at least as of June 24, 2021. Despite this knowledge of the '034 Patent, Synthego has continued to engage in activities to actively induce the infringement of others, including advertising infringing products and/or instructing how to engage in an infringing use of the '034 Accused Products, as depicted in the aforementioned examples. Thus, on information and belief, Synthego (1) had actual knowledge of the patent; (2) knowingly induced international customers and/or those of its global distributors to infringe the patent; and (3) had specific intent to induce the patent infringement.

77. Synthego's infringement of the '034 Patent has been and continues to be deliberate and willful, and this is therefore an exceptional case warranting an award of enhanced damages and attorneys' fees and costs pursuant to 35 U.S.C. § 284-285.

78. On information and belief, Synthego will continue to infringe the '034 Patent unless enjoined by this Court.

79. As a result of Synthego's infringement of the '034 Patent, Agilent has suffered monetary damages, and seeks recovery, in an amount to be proven at trial, adequate to compensate for Synthego's infringement, but in no event less than a reasonable royalty with interest and costs. Synthego's infringement of Agilent's rights under the '034 Patent will continue to damage Agilent, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

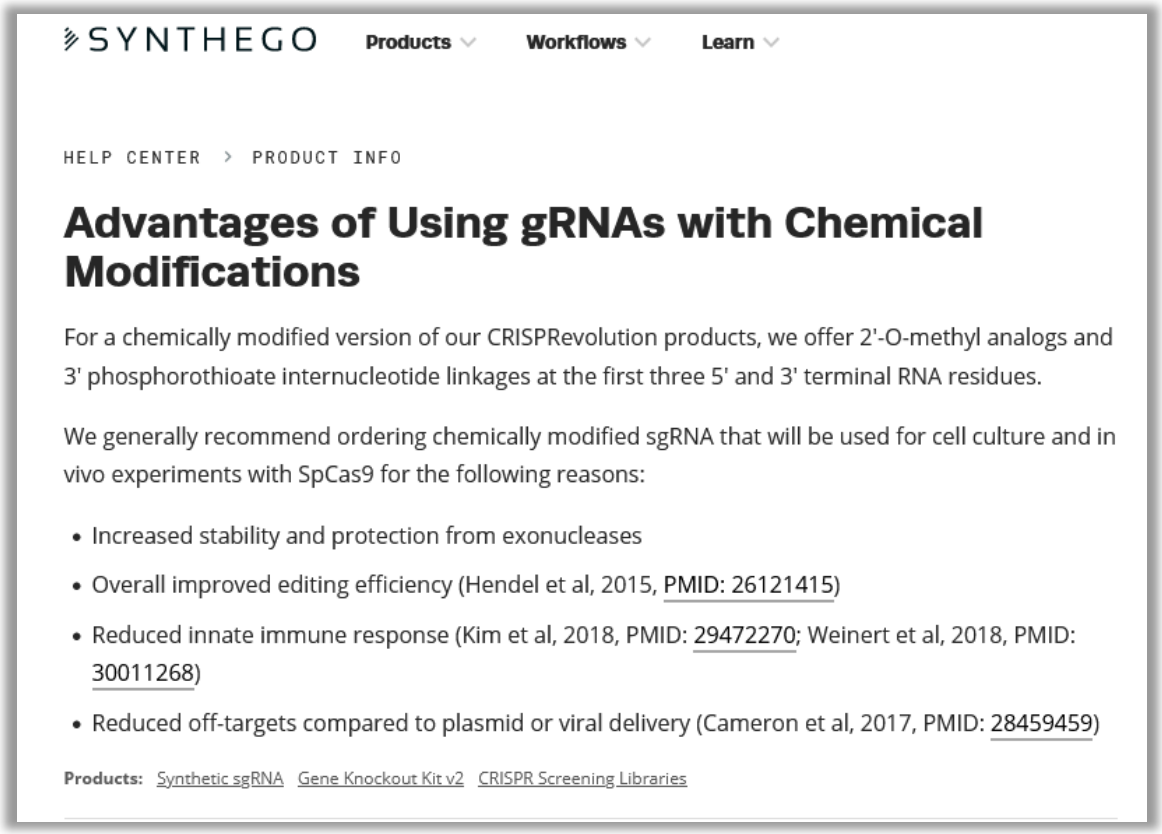
SECOND COUNT

(INFRINGEMENT OF U.S. PATENT NO. 10,337,001)

80. Agilent incorporates by reference the allegations set forth in the above paragraphs 1-79 of this Complaint as though fully set forth herein.

81. Synthego has directly infringed and continues to directly infringe one or more claims of the ’001 Patent, including at least claim 1 of the ’001 Patent, in the state of Delaware, in this judicial district, and elsewhere in the United States by, among other things, making, using, selling, offering for sale, and/or importing into the United States products that embody one or more of the inventions claimed in the ’001 Patent, including but not limited to the above-identified Halo Platform products, which includes but is not limited to at least the following “CRISPRevolution” and/or “Halo-powered products”: Synthetic sgRNA Kit, Gene Knockout Kit v2, Arrayed CRISPR Screening Libraries, Advanced RNA and CRISPR GMP sgRNA Manufacturing, including Synthego’s sgRNA manufacturing system that offers large scale research use-only sgRNA synthesis, GMP-like sgRNA synthesis, and GMP sgRNA manufacturing; Eclipse Platform products and processes, which includes but is not limited to at least the following “Eclipse-powered products”: Knock-In iPS Cells, Knockout iPS Cells, CRISPR Knockout Cell Clone, and Knockout Cell Pool, as well as Eclipse Platform cell engineering processes, such as modular design, optimized transfection, clones with integrity, end-to-end tracking, and predictive CRISPR design; and all reasonably similar products (“the ’001 Accused Products”), in violation of 35 U.S.C. § 271(a).

82. In each of the ’001 Accused Products, Synthego uses a synthetic CRISPR guide RNA with gRNA functionality to associate with a Cas protein and target the gRNA:Cas protein complex to the target sequence, and has one or more modified nucleotides within five nucleotides from the 5′ end or within five nucleotides from the 3′ end or both. *See, e.g.*, ‘001 Patent at 243:11-24 (claim 1). For example, Synthego’s synthesis, use, offer for sale and sale of infringing synthetic chemically modified sgRNA is depicted in its own advertisements, order forms, “product info,” instruction manuals, publication and webinar, as shown below:



SYNTHEGO Products Workflows Learn

HELP CENTER > PRODUCT INFO

Advantages of Using gRNAs with Chemical Modifications

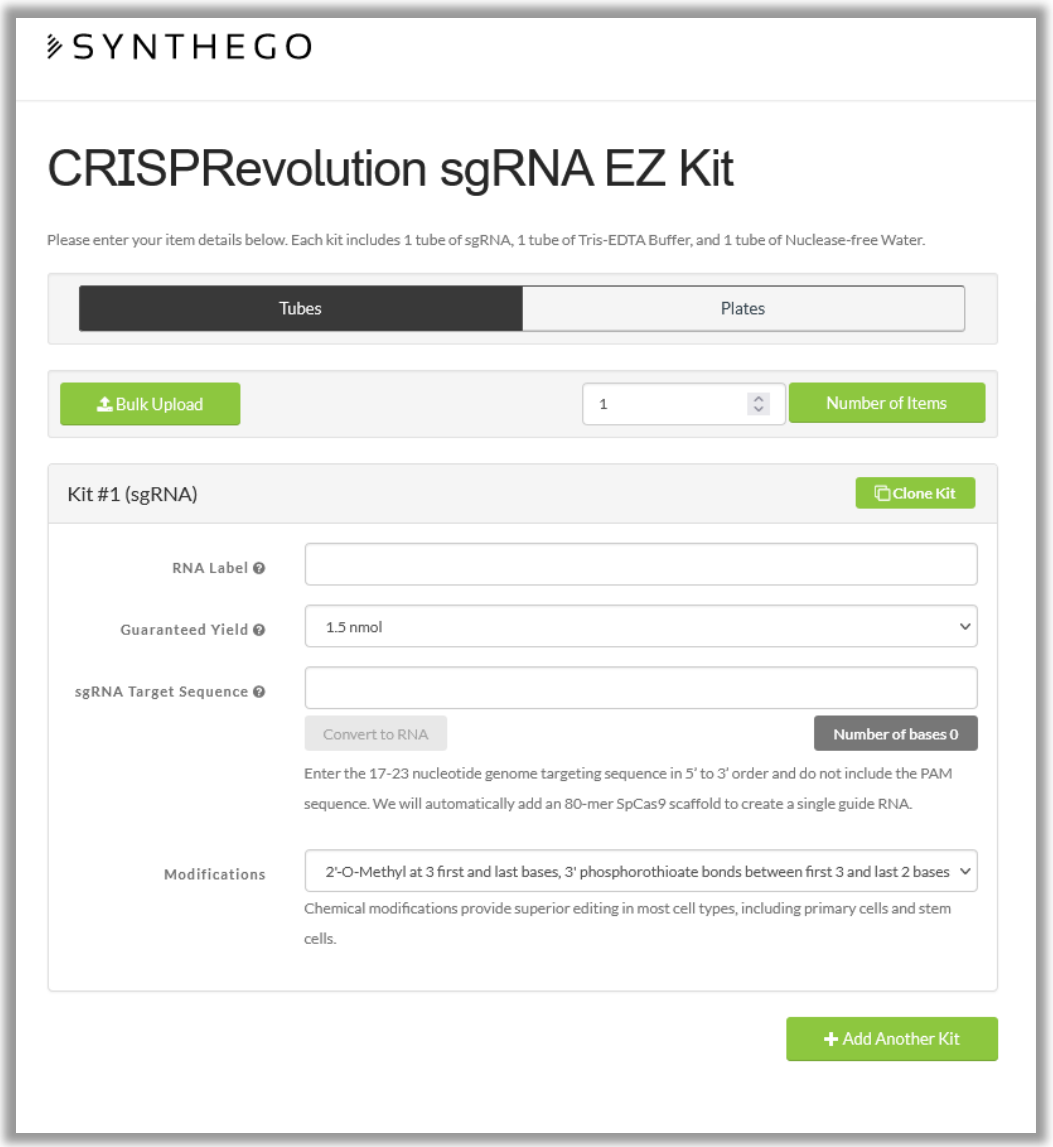
For a chemically modified version of our CRISPRevolution products, we offer 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues.

We generally recommend ordering chemically modified sgRNA that will be used for cell culture and in vivo experiments with SpCas9 for the following reasons:

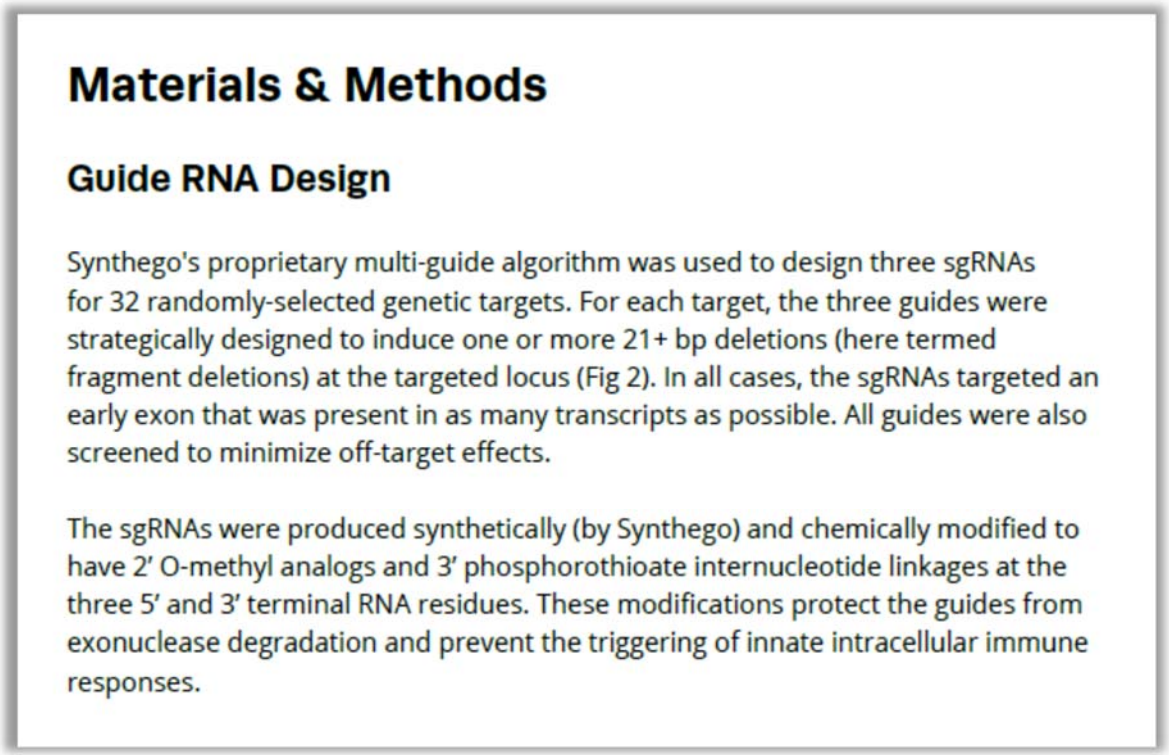
- Increased stability and protection from exonucleases
- Overall improved editing efficiency (Hendel et al, 2015, PMID: 26121415)
- Reduced innate immune response (Kim et al, 2018, PMID: 29472270; Weinert et al, 2018, PMID: 30011268)
- Reduced off-targets compared to plasmid or viral delivery (Cameron et al, 2017, PMID: 28459459)

Products: Synthetic sgRNA Gene Knockout Kit v2 CRISPR Screening Libraries

See Synthego, Help Center - Product Info, "Advantages of Using gRNAs with Chemical Modifications."



See Synthego, Products, "CRISPRevolution sfRNA EZ Kit."



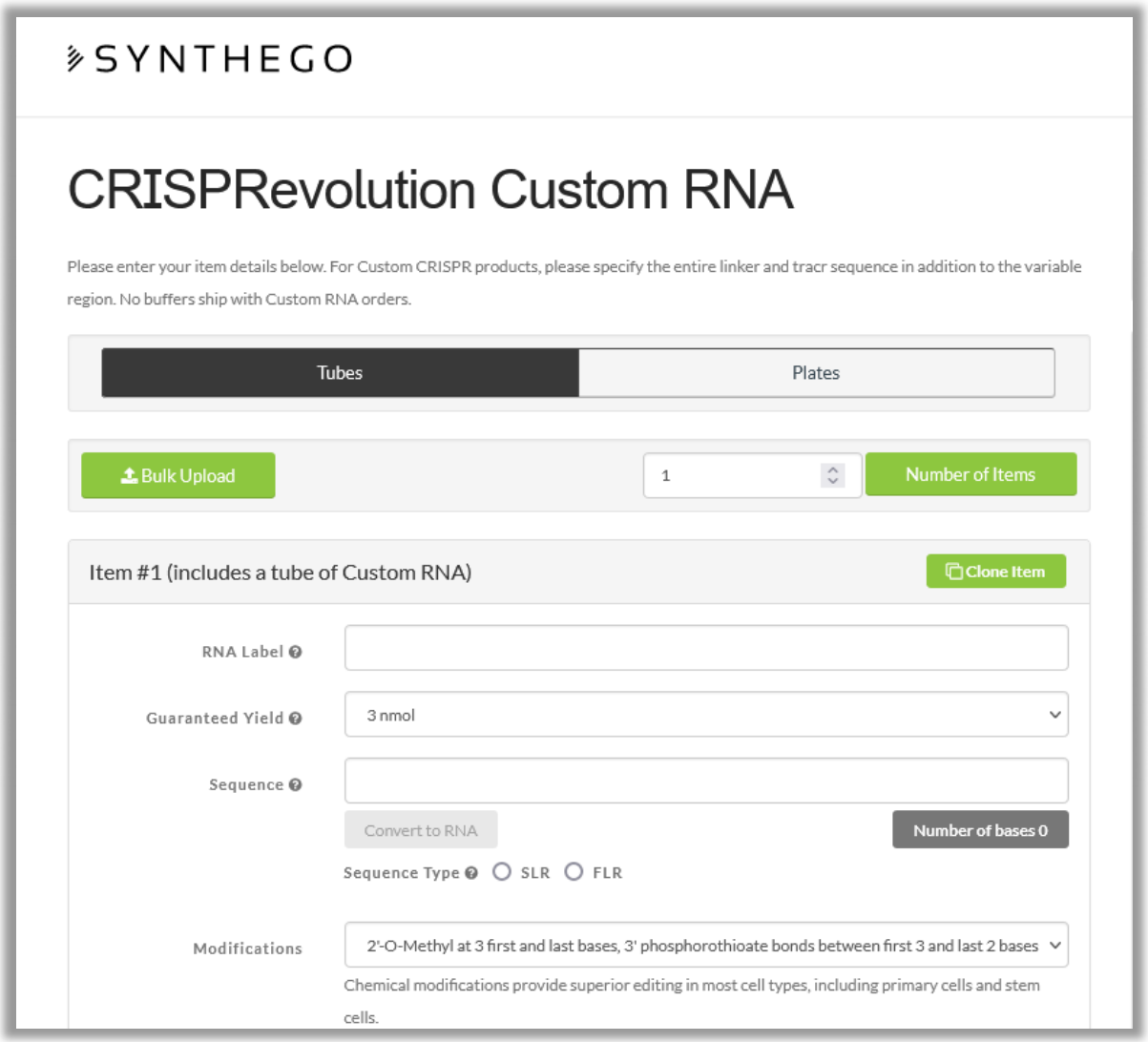
Materials & Methods

Guide RNA Design

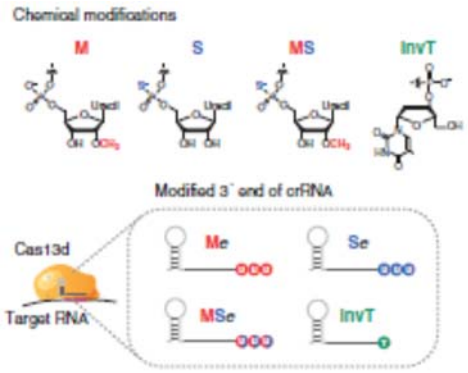
Synthego's proprietary multi-guide algorithm was used to design three sgRNAs for 32 randomly-selected genetic targets. For each target, the three guides were strategically designed to induce one or more 21+ bp deletions (here termed fragment deletions) at the targeted locus (Fig 2). In all cases, the sgRNAs targeted an early exon that was present in as many transcripts as possible. All guides were also screened to minimize off-target effects.

The sgRNAs were produced synthetically (by Synthego) and chemically modified to have 2′ O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the three 5′ and 3′ terminal RNA residues. These modifications protect the guides from exonuclease degradation and prevent the triggering of innate intracellular immune responses.

See Synthego, Resources, Application Note, "Multi-guide sgRNA improves CRISPR Knockout Efficiency by Generating Fragment Deletions" at 4.

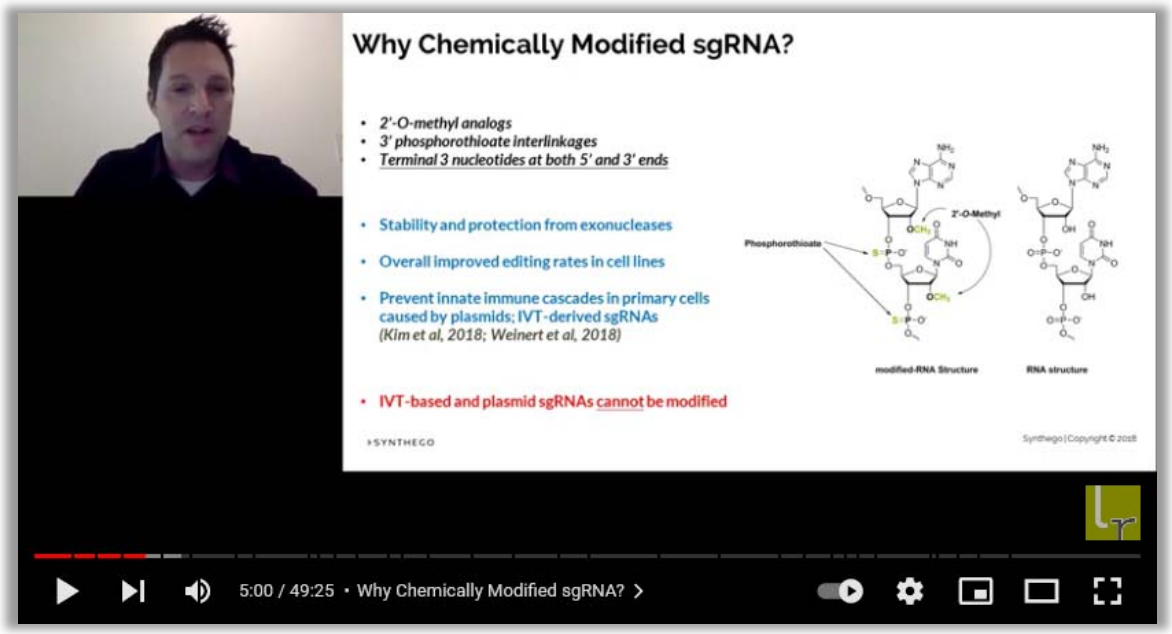


See Synthego, Products, Crispr Kits, "Advanced RNA", Orders; *and see* Méndez-Mancilla, et al. (2021) (Figure 1(A) depicting chemically modified sgRNAs, where the "modified crRNAs add extra bases at the crRNA 3′ end"):



See Synthego, "Design, Edit, Analyze and Maximize Your CRISPR-Cas9 Editing Efficiency", wherein Kevin Holden, Head of Synthetic Biology at Synthego, explained:

> When we're talking about the guide RNA format to use, at Synthego we are a cell engineering company and ***all of our projects involve the use of these chemically modified synthetic single guide RNAs*** that we use for generating indels in cells, knockouts and knock-ins. …
>
> ***Why do we use these single guide RNAs in a chemically modified format?*** Well, several years ago now there was a landmark paper that came out of Matthew Porteus' lab at Stanford University showing that you could utilize these chemically modified guide RNAs to effectively edit many different types of human primary cells, specifically in this case, primary human T cells and hematopoietic stem cells. And these chemical modifications that exist on the guide RNAs they're important for several reasons. ***They actually are these 2'-O-methyl analogs and these sulfur interlinkages on the terminal 3 nucleotides of both ends of the guide RNA molecule.***



83. By making, using, offering for sale, and/or selling products in the United States and/or importing products into the United States, including but not limited to the '001 Accused Products, Synthego has injured Agilent and is liable to Agilent for directly infringing one or more claims of the '001 Patent, including without limitation claim 1, pursuant to 35 U.S.C. § 271(a).

84. On information and belief, Synthego is inducing and/or has induced infringement of one or more claims of the '001 Patent, including at least claim 1, as a result of, among other activities, instructing, encouraging, recommending, and directing its customers on the use of '001 Accused Products in an infringing manner in violation of 35 U.S.C. § 271(b). Through its website, instructional guides, manuals, case studies, publications, press releases, and advertisements, Synthego provides its customers with detailed explanations, instructions, and information on how to use and implement the '001 Accused Products which demonstrate active steps taken to encourage direct infringement. (*See, e.g.*, examples set forth in paragraph 70).

85. Synthego has had actual knowledge of the '001 Patent at least as of June 24, 2021. Despite this knowledge of the '001 Patent, Synthego has continued to engage in activities

to encourage and assist its customers in the use of the '001 Accused Products. Thus, on information and belief, Synthego (1) had actual knowledge of the patent; (2) knowingly induced its customers to infringe the patent; and (3) had specific intent to induce the patent infringement.

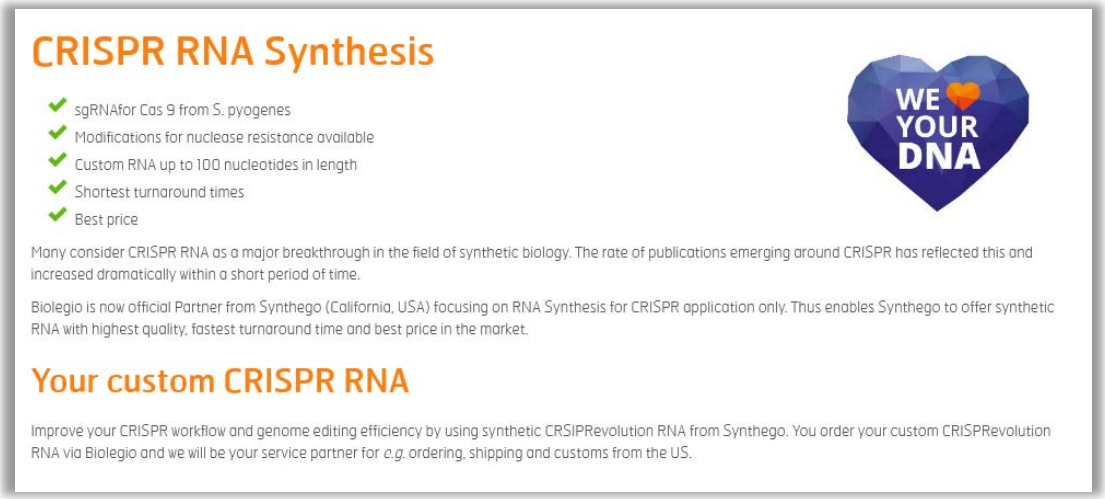
86. On information and belief, by using the '001 Accused Products as encouraged, recommended and assisted by Synthego, Synthego's customers have directly infringed and continue to directly infringe one or more claims of the '001 Patent, including at least claim 1.

87. On information and belief, Synthego is actively inducing and/or has actively induced the combination of components of the patented inventions of the '001 Patent outside of the United States in a manner that would infringe the '001 Patent if such combination occurred within the United States, in violation of 35 U.S.C. § 271(f)(1). Synthego infringes one or more claims of the '001 Patent, including at least claim 1, by supplying or causing to be supplied in or from the United States a substantial portion of the components of the '001 patented inventions, including without limitation, components of at least claim 1, such as a synthetic CRISPR guide having at least one 5′-end and at least one 3′-end, where the synthetic guide RNA has one or more modified nucleotides within five nucleotides from said 5′-end, or one or more modified nucleotides within five nucleotides from said 3′-end, or both, and the guide RNA has one or more RNA molecules and has gRNA functionality, and the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both, so as to, on information and belief, intentionally and with knowledge, actively induce the combination of such components outside of the United States in a manner that would infringe the '001 Patent if such combination occurred within the United States.

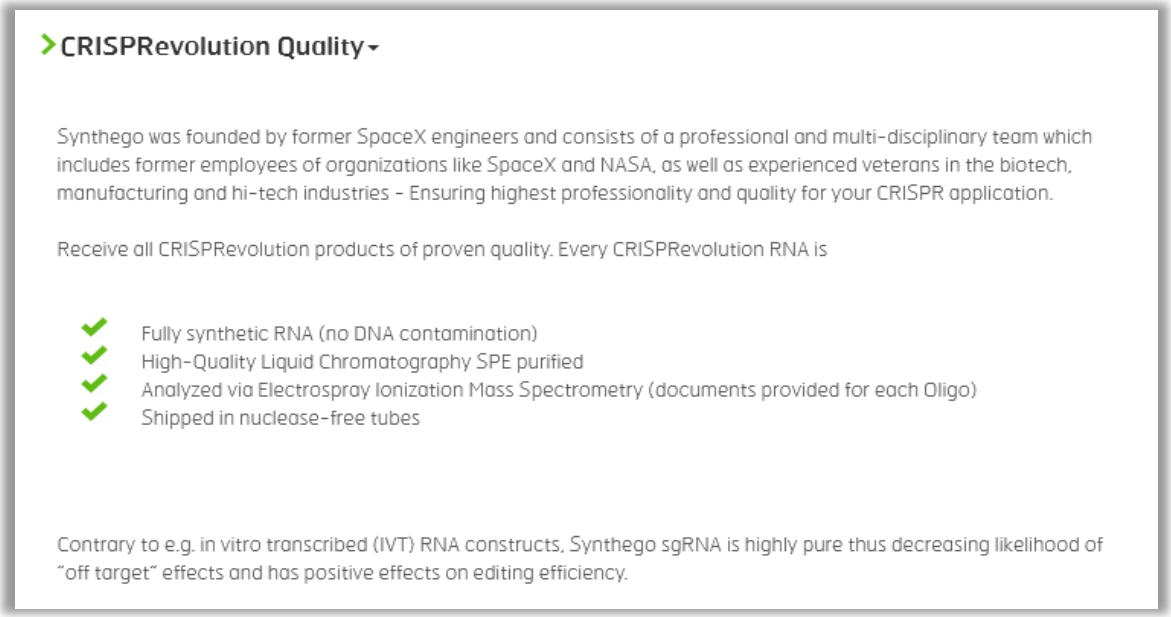
88. As an example of Synthego's infringing acts in violation of 35 U.S.C. § 271(f)(1), Synthego has partnered with at least 23 different "global distributors" to supply infringing products and/or components of infringing products outside the United States, such that the combination of such components would infringe the '001 Patent, including at least claim 1, if such combination occurred within the United States. *See, e.g.*, Synthego, Worldwide Directory. Synthego supplies these distributors with synthetic CRISPR guide RNA having at least one 5′-

end and at least one 3′-end, where the synthetic guide RNA has one or more modified nucleotides within five nucleotides from said 5′-end, or one or more modified nucleotides within five nucleotides from said 3′-end, or both, and the guide RNA has one or more RNA molecules and has gRNA functionality, and the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both. Synthego advertises its partnership with Biolegio, for example, to distribute its products in The Netherlands:

See id. Biolegio advertises that it is the "official partner from Synthego (California, USA)" enabling its customers to order Synthego's infringing products and components, wherein Biolegio is the "service partner for *e.g*. ordering, shipping and customs from the US." *See, e.g.*, Biolegio, Products-Services, CRISPR RNA Synthesis:



Biolegio advertises its use of Synthego sgRNA products, such as "CRISPRevolution products," *see, e.g.*: Biolegio, Products-Services, CRISPRevolution Quality:



CRISPRevolution Quality

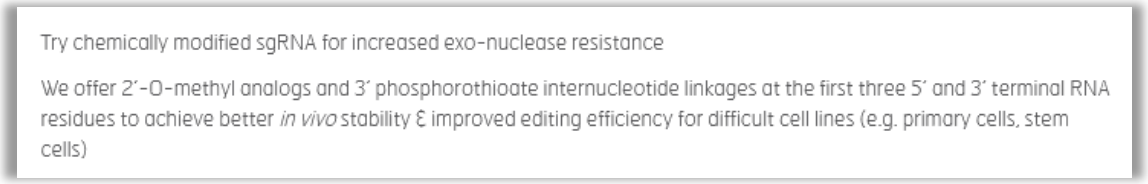
Synthego was founded by former SpaceX engineers and consists of a professional and multi-disciplinary team which includes former employees of organizations like SpaceX and NASA, as well as experienced veterans in the biotech, manufacturing and hi-tech industries - Ensuring highest professionality and quality for your CRISPR application.

Receive all CRISPRevolution products of proven quality. Every CRISPRevolution RNA is

- Fully synthetic RNA (no DNA contamination)
- High-Quality Liquid Chromatography SPE purified
- Analyzed via Electrospray Ionization Mass Spectrometry (documents provided for each Oligo)
- Shipped in nuclease-free tubes

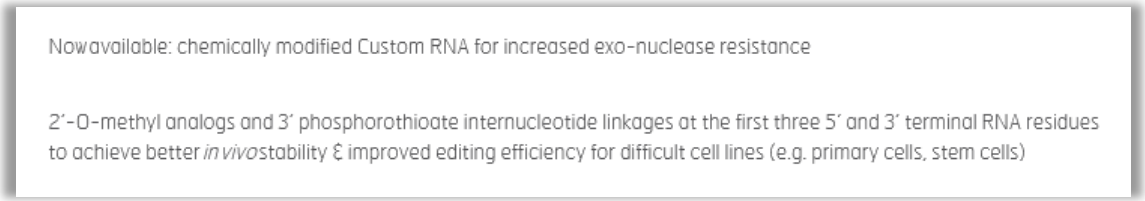
Contrary to e.g. in vitro transcribed (IVT) RNA constructs, Synthego sgRNA is highly pure thus decreasing likelihood of "off target" effects and has positive effects on editing efficiency.

Biolegio sells Synthego-supplied synthetic gRNA with 2′-O-methyl modifications, including synthetic chemically modified sgRNA for use with Cas9, as well as "custom RNA" for use with "CPF1 or other Cas systems," with such modifications ***"at the first three 5′ and 3′ terminal RNA residues,"*** as shown in its advertisements below:



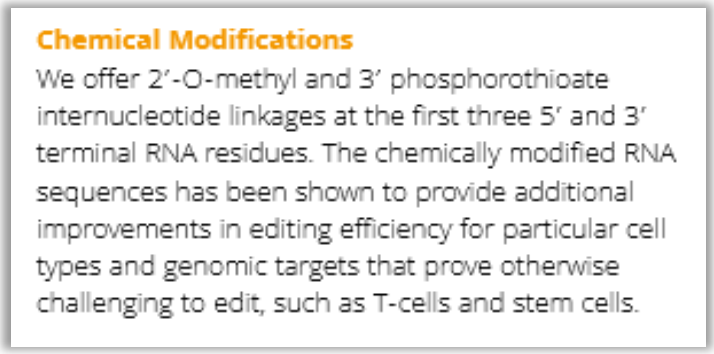
Try chemically modified sgRNA for increased exo-nuclease resistance

We offer 2′-O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the first three 5′ and 3′ terminal RNA residues to achieve better *in vivo* stability & improved editing efficiency for difficult cell lines (e.g. primary cells, stem cells)

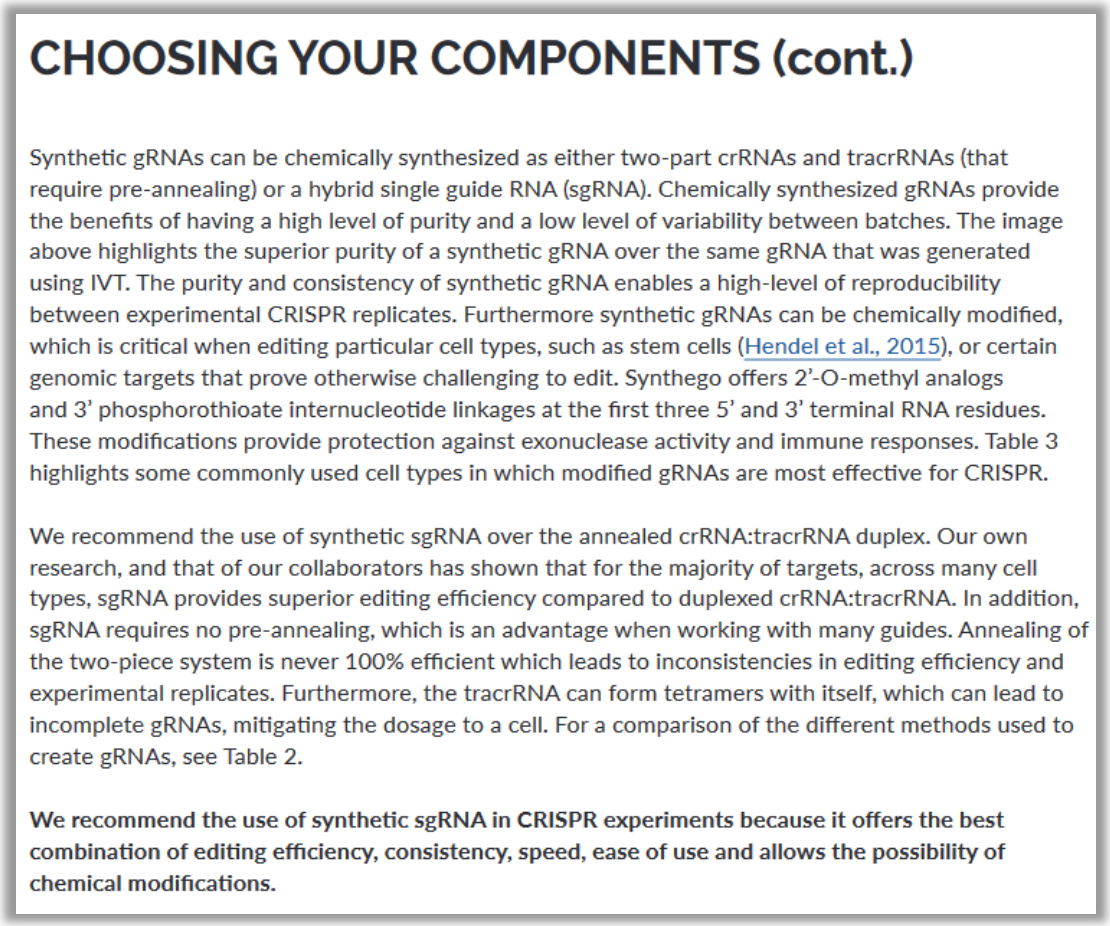


See Biolegio, Products-Services, CRISPR RNA Synthesis, Overview.

89. Biolegio's website offers various materials which instruct how to engage in infringing use of the '001 Patent, including at least claim 1, including advertisements, instruction manuals, guides, posters, and a video prepared, authored, and/or co-authored by Synthego, including but not limited to: (1) a Synthego and Biolegio Whitepaper, titled "Transforming Life Science: CRISPR-Cas9," which provides instructions, recommendations and guides for infringing "applications" of synthetic chemically modified RNA sequences, such as use of such sequences with 2′-O-methyl modifications at the first three 5′ and 3′ terminal RNA residues, as shown below:



(see Biolegio, Products-Services, CRISPR RNA Synthesis, Downloads and Links, Whitepaper, "Transforming Life Science: CRISPR-CAS9"); (2) a Synthego-authored "guide," titled "How to Perform Successful CRISPR Experiments, a Step-by-Step Guide," which provides instructions, recommendations and guides for the infringing use of chemically modified synthetic gRNAs, such as 2′-O-methyl modifications at the first three 5′ and 3′ terminal RNA residues, as shown below:



CHOOSING YOUR COMPONENTS (cont.)

Synthetic gRNAs can be chemically synthesized as either two-part crRNAs and tracrRNAs (that require pre-annealing) or a hybrid single guide RNA (sgRNA). Chemically synthesized gRNAs provide the benefits of having a high level of purity and a low level of variability between batches. The image above highlights the superior purity of a synthetic gRNA over the same gRNA that was generated using IVT. The purity and consistency of synthetic gRNA enables a high-level of reproducibility between experimental CRISPR replicates. Furthermore synthetic gRNAs can be chemically modified, which is critical when editing particular cell types, such as stem cells (Hendel et al., 2015), or certain genomic targets that prove otherwise challenging to edit. Synthego offers 2'-O-methyl analogs and 3' phosphorothioate internucleotide linkages at the first three 5' and 3' terminal RNA residues. These modifications provide protection against exonuclease activity and immune responses. Table 3 highlights some commonly used cell types in which modified gRNAs are most effective for CRISPR.

We recommend the use of synthetic sgRNA over the annealed crRNA:tracrRNA duplex. Our own research, and that of our collaborators has shown that for the majority of targets, across many cell types, sgRNA provides superior editing efficiency compared to duplexed crRNA:tracrRNA. In addition, sgRNA requires no pre-annealing, which is an advantage when working with many guides. Annealing of the two-piece system is never 100% efficient which leads to inconsistencies in editing efficiency and experimental replicates. Furthermore, the tracrRNA can form tetramers with itself, which can lead to incomplete gRNAs, mitigating the dosage to a cell. For a comparison of the different methods used to create gRNAs, see Table 2.

We recommend the use of synthetic sgRNA in CRISPR experiments because it offers the best combination of editing efficiency, consistency, speed, ease of use and allows the possibility of chemical modifications.

(*see* Biolegio, Products-Services, CRISPR RNA Synthesis, Downloads and Links, Guide: "How to Perform Successful CRISPR Experiments"); and (3) a Synthego-authored "poster" titled "Use of Synthetic sgRNAs for Improved CRISPR Editing in Various Cell Types," which provides instructions, recommendations and guides for the infringing use of chemically modified synthetic gRNAs, including use of such gRNAs with 2′-O-methyl modifications at the first three 5′ and 3′ terminal RNA residues, as shown below:

Chemically modified synthetic sgRNA enables efficient CRISPR-Cas9 editing in K562 cells

K562 cells were electroporated using 4D-Nucleofector (Lonza) with *S.aureus* Cas9 or *S.pyogenes* Cas9 expression plasmids along with CRISPRevolution synthetic RNA (Synthego). Guide RNAs were supplied as either: unmodified sgRNA; modified-sgRNA; modified annealed crRNA:tracrRNA (Synthego). Modified sgRNA and crRNA:tracrRNA were chemically synthesized to contain 2'-O-methyl analogs and 3' phosphorothioate nucleotide interlinkages in the terminal three nucleotides at both 5' and 3' ends of the RNA molecule. All guide RNAs targeted the *CCR5* gene. Average editing efficiency was determined four days post-electroporation by cell lysis, PCR and GeneArt cleavage detection (Thermo).

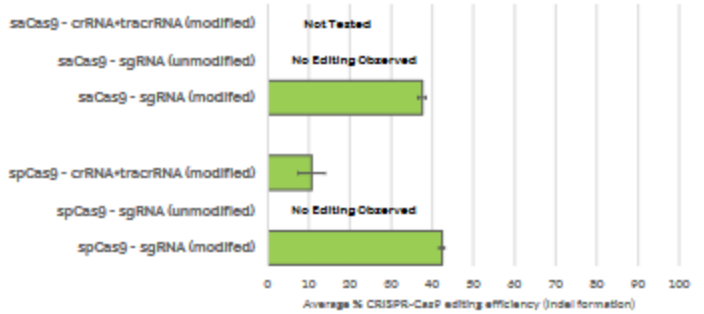


Figure 5. Chemically modified synthetic sgRNA enables reproducible CRISPR-Cas9 DNA editing in K562 cells with both *S.aureus* Cas9 (saC9) or *S.pyogenes* Cas9 (spC9) nucleases, with superior editing efficiency to a 2-part annealed synthetic crRNA:tracrRNA.

Improved editing of CD34+ hematopoietic stem cells using chemically modified synthetic sgRNA

Primary human CD34+ hematopoietic stem cells were electroporated using a 10µl Neon tip (Thermo) with *S.pyogenes* mRNA Cas9 (Trilink) and CRISPRevolution modified synthetic sgRNA (Synthego) or modified annealed crRNA:tracrRNA (IDT). Modified sgRNA were chemically synthesized to contain 2'-O-methyl analogs and 3' phosphorothioate nucleotide interlinkages in the terminal three nucleotides at both 5' and 3' ends of the RNA molecule. Modified crRNA:tracrRNA contained proprietary chemical modifications. The sgRNA targeted the *TCRα* gene in order to knockdown CD3 expression. Editing efficiency was determined seven days post-electroporation by staining with anti-human CD3 (BioLegend) and analysis by flow cytometry, with a mock-treated sample as a control input.

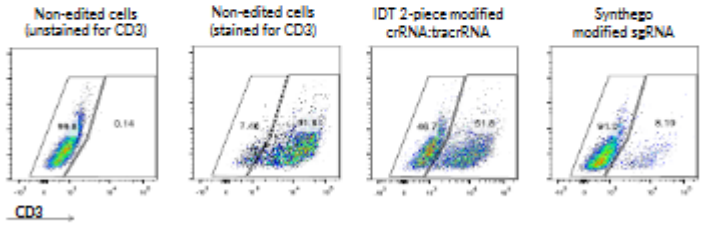


Figure 7. FACS analysis of CD34+ hematopoietic stems cells electroporated with modified synthetic sgRNA or modified crRNA:tracrRNA targeting *TCRα*. Knockdown of *TCRα* yields a CD3-negative phenotype, as seen in 46.7% of modified cr:tracrRNA-transformed cells and 91.0% of modified sgRNA-transformed cells.

(*see* Biolegio, Products-Services, CRISPR RNA Synthesis, Downloads and Links, Poster: "Use of synthetic gRNA for improved CRISPR genome editing").

90. Synthego has had actual knowledge of the '001 Patent at least as of June 24, 2021. Despite this knowledge of the '001 Patent, Synthego has continued to engage in activities to actively induce the infringement of others, including advertising infringing products and/or instructing how to engage in an infringing use of the '001 Accused Products, as depicted in the aforementioned examples. Thus, on information and belief, Synthego (1) had actual knowledge of the patent; (2) knowingly induced international customers and/or those of its global distributors to infringe the patent; and (3) had specific intent to induce the patent infringement.

91. Synthego's infringement of the '001 Patent has been and continues to be deliberate and willful, and this is therefore an exceptional case warranting an award of enhanced damages and attorneys' fees and costs pursuant to 35 U.S.C. §§ 284-285.

92. On information and belief, Synthego will continue to infringe the '001 Patent unless enjoined by this Court.

93. As a result of Synthego's infringement of the '001 Patent, Agilent has suffered monetary damages, and seeks recovery, in an amount to be proven at trial, adequate to compensate for Synthego's infringement, but in no event less than a reasonable royalty with interest and costs. Synthego's infringement of Agilent's rights under the '001 Patent will continue to damage Agilent, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

PRAYER FOR RELIEF

WHEREFORE, Agilent prays for judgment and seeks relief against Synthego as follows:

A. For judgment that Synthego has infringed and/or continues to infringe one or more claims of the Asserted Patents, directly, and/or indirectly by way of inducement;

B. For a preliminary and permanent injunction against Synthego, enjoining it from infringement and inducement of infringement of the Asserted Patents;

C. For judgment awarding Agilent damages adequate to compensate it for Synthego's infringement of the Asserted Patents, including all pre-judgment and post-judgment interest;

D. For judgment that Synthego has willfully infringed and continues to willfully infringe one or more claims of the Asserted Patents;

F. For judgment awarding enhanced damages pursuant to 35 U.S.C. § 284;

G. For judgment imposing a mandatory future royalty payable on each and every product or service sold by Synthego in the future that is found to infringe the Asserted Patents and on all future products and services which are not colorably different from products found to infringe;

H. For judgment awarding attorneys' fees pursuant to 35 U.S.C. § 285 or otherwise permitted by law;

I. For judgment awarding costs of suit; and

J. For judgment awarding Agilent such other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Agilent hereby demands a trial by jury of this action.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

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October 6, 2021