Inter Partes Review of U.S. Patent No. 6,060,596

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

___________

ILLUMINA, INC.
    Petitioner

v.

THE SCRIPPS RESEARCH INSTITUTE
    Patent Owner

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U.S. PATENT NO. 6,060,596

ENCODED COMBINATORIAL CHEMICAL LIBRARIES

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PETITION FOR INTER PARTES REVIEW
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I. INTRODUCTION

Petitioner Illumina, Inc. requests inter partes review of claims 1-6 and 10-17 of U.S. Patent No. 6,060,596 (“the ’596 patent”) (Ex. 1001). The earliest application to which the ’596 patent claims priority is assigned to The Scripps Research Institute at Reel 006172, Frame 0362.

The ’596 patent claims bifunctional molecules of formula A—B—C, where A is a polymer comprising a linear series of chemical units, B is a linker, and C is an identifier oligonucleotide comprising a linear series of unit identifier nucleotide sequences, each of which identifies a corresponding chemical unit in polymer A. The patent also claims libraries of these bifunctional molecules. The specification touts an allegedly improved method of making bifunctional molecules using alternating synthesis, involving repeatedly attaching chemical units of polymer A to corresponding unit identifiers of oligonucleotide C through linker molecule B.

The bifunctional molecules and method of synthesis are illustrated below:
Inter Partes Review of U.S. Patent No. 6,060,596

\[ \text{'596 PATENT} \]

\[ \text{LINKER} \]

\[ \text{BEAD} \]

\[ AA_1 \]

\[ \rightarrow \]

\[ \text{OLIGO}_1 \]

\[ AA_2 \]

\[ \rightarrow \]

\[ \text{OLIGO}_2 \]

\[ AA_2 \]

\[ \rightarrow \]

\[ \text{OLIGO}_1 \]

\[ AA_1 \]

\[ \rightarrow \]

\[ \text{OLIGO}_2 \]

\[ \text{REPEAT} \]

\[ \text{Polymer "A"} \]

\[ \text{Linker "B"} \]

\[ \text{Oligonucleotide "C"} \]

\[ AA_n \]

\[ \cdots \]

\[ AA \]

\[ AA \]

\[ \text{LINKER} \]

\[ \text{OLIGO}_1 \]

\[ \text{OLIGO}_2 \]

\[ \cdots \]

\[ \text{OLIGO}_n \]

\[ \text{BEAD} \]

\[ AA_n = \text{monomer unit (e.g. amino acid) at position n} \]

\[ \text{OLIGO}_n = \text{identifier oligonucleotide unit for monomer unit at position n} \]
Supported by a declaration from Dr. Brian M. Stoltz (Ex. 1007), this Petition demonstrates that claims 1-6 and 10-17 are unpatentable. Prior art not considered by the Office, including U.S. Patent No. 6,143,497 (“Dower”) (Ex. 1008), establishes that the claimed molecules and libraries would have been obvious. The ’596 patent, for example, uses an “identifier oligonucleotide” to identify a linked polymer’s structure, where each unit in the identifier oligonucleotide identifies a corresponding chemical unit in the polymer. But Dower previously described the same strategy: using an “oligonucleotide identifier tag” where each unit within the tag identified a corresponding unit within a linked polymer structure. Dower was not considered during prosecution, is far more relevant than any prior art the Office considered, and renders the claims of the ’596 patent unpatentable. The claims also lack adequate written description in the priority applications and therefore are not entitled to any earlier priority date. Consequently, U.S. Patent No. 5,573,905 (Ex. 1003), which published from Scripps’s earliest priority application and has the same specification as the ’596 patent, anticipates the challenged claims.

II. GROUNDS FOR STANDING

Petitioner does not own the ’596 patent; Petitioner is not barred or estopped from requesting IPR; and this Petition is being filed less than a year after Petitioner
was served with a complaint alleging infringement of the ’596 patent. 37 C.F.R. § 42.104(a).

**III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8**

**A. Real Parties-in-Interest**

Petitioner certifies that Illumina, Inc. is the real party-in-interest and that no other party exercised control or could exercise control over Illumina’s participation in this proceeding, the filing of this Petition, or the conduct of any ensuing trial. 37 C.F.R. § 42.8(b)(1).

**B. Related Matters**

The following judicial proceeding is a related matter: *The Scripps Research Institute v. Illumina, Inc.*, Case No. 3:16-cv-661-JLS-BGS (S.D. Cal., filed March 17, 2016). 37 C.F.R. § 42.8(b)(2).

The ’596 patent (Ex. 1001) was filed March 3, 1998, as USSN 09/033,743 (Ex. 1002). It claims the benefit of priority to U.S. Patent No. 5,723,598 (Ex. 1005) (filed June 18, 1996, as USSN 08/665,511; Ex. 1006) and U.S. Patent No. 5,573,905 (Ex. 1003) (filed March 30, 1992, as USSN 07/860,445; Ex. 1004).

**C. Lead and Back-up Counsel; Consent to Electronic Service**

The signature block below provides lead counsel, back-up counsel, and service information for Petitioner. Petitioner designates William B. Raich (william.raich@finnegan.com) as lead counsel, and Michael J. Flibbert
Petitioner consents to electronic service of all documents.

IV. FEE PAYMENT

The required fees are submitted under 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office may charge them to Deposit Account No. 06-0916.

V. STATEMENT OF PRECISE RELIEF REQUESTED

A. Claims for Which Review Is Requested

Petitioner requests that the Board institute an IPR proceeding and cancel claims 1-6 and 10-17 of the ’596 patent under 35 U.S.C. § 311.

B. Statutory Grounds of Challenge

Petitioner requests that the Board institute trial on the following grounds:

(1) Claims 1-6 and 10-17 are obvious under pre-AIA 35 U.S.C. § 103(a) over Dower (Ex. 1008);
(2) Claims 1-6 and 10-17 are obvious under pre-AIA 35 U.S.C. § 103(a) over Dower in view of Juby et al., Tetrahedron Lett. 32(7):879-82 (1991) (“Juby”) (Ex. 1010) or U.S. Patent No. 5,141,813 (“Nelson”) (Ex. 1011); and


Dower was filed on March 6, 1998, as U.S. Patent Application No. 09/036,599 (Ex. 1030), and issued on November 7, 2000. It claims priority to U.S. Patent Application Nos. 08/484,085, filed June 7, 1995 (Ex. 1014) and 07/762,522, filed September 18, 1991 (“Dower App.”) (Ex. 1009). Dower is therefore a U.S. patent with an effective U.S. filing date before the earliest claimed priority date of the ’596 patent. Dower does not share inventors or assignees with the ’596 patent, making it prior art at least under 35 U.S.C. § 102(e). This petition cites to Dower’s application (Ex. 1009) filed on September 18, 1991, which shares an essentially identical specification with the issued patent. Similarly, the petition cites to the Nelson application (“Nelson App.”) (Ex. 1012) filed on August 28, 1989.

Juby published on February 11, 1991, and is prior art under § 102(b).

does not share inventors or assignees with the ’596 patent. Therefore, Nelson is prior art to the ’596 patent at least under § 102(e).

Dower and Nelson are also prior art under § 102(b) for the reasons detailed in section IX below, namely that the claims of the ’596 patent lack adequate written description support under 35 U.S.C. § 112, first paragraph, in the claimed priority applications. Because the ’596 patent is not entitled to the benefit of these applications, claims 1-6 and 10-17 are anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 5,573,905 (published Nov. 12, 1996).

VI. STATE OF THE ART

In the early 1990s, researchers understood that they needed to screen many molecules to facilitate drug discovery. Ex. 1007 ¶20. One emerging area of chemistry, combinatorial chemistry, was viewed as a promising strategy for synthesizing large numbers of potentially active compounds for screening. Id. But while some polymeric peptides could be synthesized, tracking the identity of screened compounds was challenging. Id. One known tracking technique involved attaching a polymer such as a peptide to an oligonucleotide tag. Id. at ¶21.

A. Preparing Bifunctional Molecules

Bifunctional polymer-oligonucleotide conjugates and methods of preparing them were known before the earliest filing date of the ’596 patent. Ex. 1013 at
Abstract; Ex. 1007 ¶¶22-23. For instance, Juby reported methods of preparing peptide-oligonucleotide conjugates through direct synthesis on a solid support with a multifunctional linker. Ex. 1010 at Fig. 1; Ex. 1007 ¶23. Accordingly, skilled artisans were familiar with methods for synthesizing and conjugating an oligonucleotide to a peptide.

B. Use of Oligonucleotide Tags to Track Molecules

By the early 1990s, oligonucleotides were understood to possess functional advantages that made them effective tagging agents, including ease of synthesis, amplification, and sequencing. Ex. 1007 ¶24. For example, WO1990014441A1, which published on November 11, 1990, discusses using the order of nucleic acids in a tag to provide information about a material that can be easily recovered via PCR amplification. Ex. 1015 at p. 5, ll. 10-14 and p. 7, ll. 20-26; Ex. 1007 ¶24.

One main purpose for tagging polymers with oligonucleotides was to facilitate library screening. Ex. 1007 ¶25; Ex. 1043 at p. 55. Identifying an effective therapeutic agent often required screening many potential molecules. Ex. 1007 ¶25. For instance, skilled artisans might screen a library of small molecules for desirable biochemical properties. Id.

A screening library may contain thousands or even millions of polymers, such as peptides. Id. at ¶26; Ex. 1016 at Abstract. This created a need for synthetic techniques that could produce a large library of peptides, while also
systematically identifying the amino acid sequence of each candidate peptide. Ex. 1016 at Abstract; Ex. 1009 at p. 3, l. 28-30; Ex. 1007 ¶26.

C. Split and Pool Synthesis Facilitated the Rapid Synthesis of Large Numbers of Polymers

By the early 1990s, researchers had not only developed techniques for synthesizing bifunctional molecules, they also recognized the need to efficiently synthesize, screen, and track the identity of many candidate molecules. Ex. 1007 ¶27-28. For example, combinatorial split and pool procedures, such as those described in Dower, permitted the synthesis of large numbers of different oligomers. Ex. 1009 at Fig. 1; see also Ex. 1016 at Abstract, Ex. 1017, and Ex. 1018. Those procedures coupled amino acids stochastically (i.e., randomly) to different beads apportioned into separate reaction vessels, before pooling and splitting, repeating the process until a desired peptide length was reached. Ex. 1007 ¶29.

Both Dower and the ’596 patent discuss the same split and pool method. Ex. 1009 at Fig. 1 and p. 12, l. 32–p. 13, 19; Ex. 1001 at 2:55-63. Figure 1 in Dower (Ex. 1008) illustrates the split and pool synthesis scheme:
FIG. 1.
While split and pool methods provided an easy way to prepare peptide libraries, the resulting peptides still required time-consuming sequencing after screening. Ex. 1007 ¶30; Ex. 1019 at p. 262, ¶3; Ex. 1020 at Table 4.

D. **Dower’s Alternating Parallel Synthesis Technique**

*Dower* overcame the deficiencies associated with identifying peptides in a combinatorial library by synthesizing bifunctional molecules using an alternating parallel synthesis technique: “A general stochastic method for synthesizing random oligomers on particles is disclosed. A further aspect of the invention relates to the use of identification tags on the particles to facilitate identification of the sequence of the monomers in the oligomer.” Ex. 1009 at Abstract; Ex. 1007 ¶¶31-32.

*Dower* describes bifunctional molecules comprising an “oligomer … composed of a sequence of monomers,” a bead and flanking “linker molecule,” and “an oligonucleotide identifier tag” comprising identifier units, each of which identifies a corresponding monomer unit in the oligomer. Ex. 1009 at p. 3, l. 37 – p. 4, l. 3, and p. 4, ll. 20-24; Ex. 1007 ¶33. The oligomer and identifier tag are operatively joined through the linker molecules flanking the bead. Ex. 1009 at p. 4, ll. 20-21; Ex. 1007 ¶33.

*Dower* defines an “oligomer” as a “sequence of monomers, the monomers being any member of the set of molecules which can be joined together to form an oligomer or polymer.” Ex. 1009 at p. 3, l. 37 – p. 4, l. 3. *Dower* states that the
“identifier tag” provides a way “to identify the sequence of monomers in the oligomer.” *Id.* at p. 4, ll. 14-15. An identifier tag may contain nucleotide identifier units, which *Dower* describes as “a natural, high density information storage medium.” *Id.* at p. 20, ll. 4-5; Ex. 1007 ¶34.

To synthesize oligomers linked to corresponding oligonucleotide identifier tags, *Dower* assembles monomer units (such as amino acids) and nucleotide units in alternating steps on a solid support. Ex. 1009 at p. 3, l. 35 – p. 4, l. 12. *Dower* assembles the units in the oligonucleotide identifier tag “base-by-base before, during, or after the corresponding oligomer (e.g., peptide) synthesis step,” or alternatively using a “block-by-block” approach, with each block comprising multiple nucleotides that provide “the monomer-type information.” *Id.* at p. 20, ll. 21-35.

*Dower* discusses techniques for attaching the monomers and identifier units, including directly to a bead, or by attaching them in a linear fashion outward from linker molecules flanking the bead. *Id.* at p. 4, ll. 20-21 and p. 20, l. 21 – p. 21, l. 10; Ex. 1007 ¶35. The linear attachment of units in the oligonucleotide identifier tag “preserv[es] the order of the steps in the linear array of the oligonucleotide chain as it grows in parallel with the oligomer.” Ex. 1009 at p. 20, ll. 25-27. The position of each nucleotide unit relative to the linker records the identity and position of the corresponding monomer. *Id.* at p. 20, ll. 34-35. As a result,
sequencing the oligonucleotide identifier tag identifies the structure of the oligomer. *Id.* at p. 18, ll. 36-39 and p. 20, ll. 7-16; Ex. 1007 ¶36.

For example, *Dower* describes an oligomer having three monomer units attached in the order A-C-B, with corresponding nucleotide identifier tag sequences “attached to one another in the order of the steps: A, A-C, A-C-B.” Ex. 1009 at p. 18, ll. 9-35. When the identifier units are attached in a linear fashion to “one another in the order of the steps,” each monomer unit will have a corresponding nucleotide identifier unit in the oligonucleotide identifier tag providing both monomer position and identity information. *Id.* at p. 18, ll. 29-35; Ex. 1007 ¶37.

The overall number of units in the oligomer and corresponding oligonucleotide identifier tag will depend on the total number of split and pool reaction steps applied during synthesis. *Id.* at ¶38. *Dower* describes examples of about 20 monomer units, or 3 to 8 monomer units. Ex. 1009 at p. 16, l. 10-11.

*Dower* also describes using alternating synthesis to produce a library of bifunctional molecules. *Id.* at p. 12, l. 32–p. 13, l. 19; Ex. 1007 ¶39.

The schematic below illustrates *Dower*’s method and resulting bifunctional molecule:
E. The Prior Art Recognized Benefits of Synthesizing on a Solid Support and Screening in Solution, and Provided the Means to Do So

It was known in the early 1990s that polymers could be generated more efficiently on a solid support, but screened more effectively in solution. Ex. 1007
¶41. For example, U.S. Patent No. 5,504,190 ("Houghten") (Ex. 1021), described the importance of synthesizing polymer library members on a solid support, such as a bead or controlled pore glass, to increase production efficiency and library size. Ex. 1022 at p. 2, ll. 26-30, and p. 3, ll. 6-10 and 29-32. As Houghten is a patent that claims priority back to an application filed on November 19, 1991, this petition cites to Houghten’s application ("Houghten App.") (Ex. 1022).

Houghten also discussed the benefits of releasing the synthesized polymers from the solid support to facilitate solution-phase screening. Id. at p. 9, l. 27 – p. 10, l. 2 and p. 21, ll. 18-23. Those benefits include reducing steric hindrance, avoiding altered binding kinetics, and preserving normal interactions with receptors and other binding sites. Id.; see also Ex. 1023 at p. 63.

Other publications described linkers suitable for attaching an oligonucleotide to a polymer on a solid support that could then be released after synthesis. Ex. 1007 ¶42-46. Juby, for example, discussed methods and linkers for synthesizing peptide-oligonucleotide conjugates on solid supports that could be released after synthesis. Id. at ¶43. Juby linked a peptide to an oligonucleotide through a multifunctional phosphoramidite linker on a Teflon solid support. Ex. 1010 at Summary and p. 879-80. Juby released the Teflon support after attaching the peptide to the oligonucleotide through the linker. Id. at p. 879 (Fig. 1). Another paper discussing the same phosphoramidite linker states that “since the chemistry
for conjugating amine groups is well-established, virtually any reporter molecule can be covalently attached to an oligonucleotide through this linkage.” Ex. 1024 at p. 7179. Notably, the ’596 patent uses this phosphoramidite linker. Ex. 1001 at 25:4-8; Ex. 1007 ¶46.

Nelson likewise described methods and linkers for synthesizing peptide-oligonucleotide conjugates. Ex. 1007 ¶44; Ex. 1012 at Abstract, p. 3, ll. 12-20, and p. 6, ll. 1-9 and 21-27. Nelson discusses solid-phase chemistry, and attaches its linker to oligonucleotides and polymers such as proteins. Ex. 1012 at p. 6, ll. 1-9.

Juby and Nelson both use solid-phase synthesis techniques similar to Dower’s solid-phase synthesis to generate bifunctional molecules. Ex. 1007 ¶45.

VII. SUMMARY OF THE ’596 PATENT

A. Specification and Claims

The ’596 patent claims bifunctional molecules of formula A—B—C, where A is a polymer comprising a linear series of chemical units, B is a linker, and C is an identifier oligonucleotide comprising unit identifier nucleotide sequences, where each unit within identifier C identifies a corresponding chemical unit within polymer A. E.g., Ex. 1001 at 43:1-14. The ’596 patent also claims libraries of these molecules. Id. at 44:4-5.

The ’596 patent lists Sydney Brenner as a co-inventor. Dr. Brenner was a co-recipient of the 2002 Nobel Prize for his work on the nematode worm
Caenorhabditis elegans. Ex. 1025. That work did not relate to the technology at issue here.

The ’596 patent uses unit identifier oligonucleotides to indicate the position and identity of chemical units in an attached polymer, allowing for post hoc deconvolution of the polymer’s structure by sequencing the oligonucleotide. Ex. 1001 at 2:50-63. Similar to Dower, the ’596 patent touts the efficiency of oligonucleotide identifiers to track polymer structures in a library. Id. at 2:35-38 and 3:1-11.

The ’596 patent purports to describe a novel synthesis technique for attaching the chemical units of a polymer in alternating steps with corresponding unit identifier nucleotide sequences. Id. at 2:47-62. But this is the same strategy described in Dower. Ex. 1007 ¶51. As in Dower, the unit identifier nucleotide sequences in the ’596 patent may be added nucleotide-by-nucleotide or block-by-block. Ex. 1001 at 10:52-56. Likewise, the ’596 patent proposes using the prior art’s split and pool method to prepare a combinatorial library “by repetition of this alternating parallel process after pooling and division of the reaction products.” Id. at 10:4-7. The ’596 patent provides limited examples of synthesizing peptide-oligonucleotide conjugates. Id. at 26:16 – 29:2. It also mentions hypothetically preparing many different types of polymers without illustrating any chemical structures. Id. at 4:44-54.
The prophetic examples in the ’596 patent suggest routine peptide synthesis using a known linker. *Id.* at 12:47-67, 13:1-15, and 25:1-8; Ex. 1024 at p. 7180, Compound 1 in Fig. 1; Ex. 1007 ¶52.

The ’596 patent’s description of library generation is both hypothetical and based on the split and pool procedures described by *Dower* and *Houghten*. Ex. 1001 at 28:1-29:6; Ex. 1007 ¶53.

In sum, the ’596 patent describes a bifunctional molecule produced by alternating synthesis, where each unit identifier nucleotide sequence on one side of a linker molecule identifies a chemical unit on the opposite side of the linker. The only examples discussed in the patent are protein-oligonucleotide conjugates, and those structures are prophetic.

**B.  *Dower and Juby Were Not Considered During Prosecution***

The ’596 patent is a division of U.S. Patent No. 5,723,598 (filed June 18, 1996, as USSN 08/665,511), which is in turn a division of U.S. Patent No. 5,573,905 (filed March 30, 1992, as USSN 07/860,445). Neither *Dower* nor *Juby* was cited or considered during prosecution. Ex. 1001 at “References Cited.” *Nelson* was cited but never discussed. *Id.*

**C.  *Level of Ordinary Skill in the Art***

The ’596 patent purports to claim priority through a series of divisionals to an application filed on March 30, 1992. A person of ordinary skill in the art
(“skilled artisan”) in 1992 would have had an advanced degree (typically a Ph.D.) in organic chemistry or biochemistry, and two or more years of practical experience in organic chemical synthesis, including synthesis of linear polymers. Ex. 1007 ¶14.

The perspective of one of ordinary skill in the art is supported in this Petition through the Declaration of Dr. Brian M. Stoltz (Ex. 1007), a tenured Professor of Chemistry at the California Institute of Technology.

D. Claim Construction

Because the ’596 patent expired on Mar. 30, 2012, the Phillips claim-construction standard applies. See In re Rambus Inc. 753 F.3d 1253, 1256 (Fed. Cir. 2014).

Claim 1 states:

1. A bifunctional molecule according to the formula A—B—C,

   wherein A is a polymer comprising a linear series of chemical units represented by the formula \((X_n)_a\),

   wherein X is a single chemical unit in polymer A, B is a linker molecule operatively linked to A and C. [sic] and identifier oligonucleotide C is represented by the formula \((Z_n)_a\),

   wherein a unit identifier nucleotide sequence Z within oligonucleotide C identifies the chemical unit X at position n; and
wherein n is a position identifier for both X in polymer A and Z in oligonucleotide C having the value of 1+i where i is an integer from 0 to 10, such that when n is 1, X or Z is located most proximal to the linker, and a is an integer from 4 to 50.

Ex. 1001 at 43:2-14.

Unless otherwise noted, Petitioner contends that the claim terms of the '596 patent should have their plain and ordinary meaning. Petitioner offers constructions of the following terms, supported by the intrinsic evidence.

1. “linker molecule”

Claim 1 requires a “linker molecule” B to operatively link polymer A and oligonucleotide C. This term should be given its plain meaning of any group of atoms that operatively links polymer A and oligonucleotide C. The linkage need not take any particular form and need not directly link A to C; it performs the function of bringing the polymer and oligonucleotide into proximity so that the identifier units can identify the chemical units. Ex. 1007 ¶56.

Consistent with this interpretation, the specification states that a linker molecule can be “any molecule that performs the function of operatively linking” components A and C, and the specification emphasizes that “the nature of the linkage is not considered an essential feature of this invention.” Ex. 1001 at 8:20-24 and 39-41 (emphasis added).
The specification provides only one example of a bifunctional molecule using one linker. *Id.* at 25:1-17. The example does not indicate any intent to limit the claims to this particular linker. Indeed, Figure 2 in the ’596 patent refers to the linker molecule by the generic term “LINK.” *Ex. 1007 ¶ 57-58.

A skilled artisan would understand “linker molecule” to include any group of atoms that operatively links polymer A and oligonucleotide C. *Id.* at ¶59. For instance, a 1992 biotechnology dictionary defines “molecule” as a “grouping of defined atoms, joined in a particular way,” and claim 1 only adds the requirement that the molecule “operatively” (i.e., functionally) link components A and C. *Ex. 1029 at p. 228.

As such, the linkage in claim 1 need not take any particular form, but simply maintains the polymer and oligonucleotide in proximity so that the oligonucleotide’s units can identify the polymer’s chemical units.

2. **Polymer A comprising “chemical units represented by the formula \((X_n)_a\)” and identifier oligonucleotide C “represented by the formula \((Z_n)_a\)”**

While these terms should not affect the patentability analysis, Petitioner provides the following remarks to assist the Board in understanding the claimed subject matter.

Claim 1 recites a bifunctional molecule according to the formula \(A\rightarrow B\rightarrow C\), wherein “\(A\) is a polymer comprising a linear series of chemical units represented
by the formula \((X_n)_a\), wherein X is a single chemical unit in polymer A.” Ex. 1001 at 43:3-5. Claim 1 further states that oligonucleotide “C is represented by the formula \((Z_n)_a\), wherein a unit identifier nucleotide sequence Z within oligonucleotide C identifies the chemical unit X at position n.” *Id.* at 43:7-10.

- The term “X” refers to an individual chemical unit in polymer “A,” and the term “Z” refers to a corresponding unit identifier sequence in oligonucleotide “C.” Each unit “Z” identifies the corresponding unit “X.”

- The subscript “n” identifies the position of each corresponding “X” and “Z” unit in the bifunctional molecule, with the “X” and “Z” units closest to the linker molecule “B” each assigned position n=1, followed by the next closest units to the linker molecule assigned position n=2, and so on.

- The subscript “a” identifies the total number of “X” units in polymer “A” and the corresponding number of “Z” units in oligonucleotide “C.” Claim 1 requires a minimum of 4 and a maximum of 50 such units.

Claim construction begins with the claim language itself. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). Claim 1 states that the terms “\((X_n)_a\)” and “\((Z_n)_a\)” respectively refer to “chemical units” and “unit identifier nucleotide
sequence[s].” *Id.* at 43:4 and 7-8. Thus, each “X” and “Z” represents an individual chemical unit and its corresponding unit identifier sequence. Ex. 1007 ¶62.

Claim 1 indicates that the subscript “n” serves as “a position *identifier for both X ... and Z.*” Ex. 1001 at 43:10-11 (emphasis added). Claim 1 further states “that when n is 1, X or Z is located most proximal to the linker.” *Id.* at 43:12-14. As such, “n” defines the position of each chemical unit X relative to the linker B and also defines the corresponding position of the associated unit identifier sequence Z. Ex. 1007 ¶¶63-64.

Claim 1 states that “a is an integer from 4 to 50,” indicating that it identifies the total number of “X” units in polymer “A” and the corresponding number of “Z” units in oligonucleotide “C.” Ex. 1001 at 43:13-14; *see also* 5:63-65 and 9:9-11. Thus, claim 1 requires a minimum of four chemical units in polymer A and four unit identifier sequences in oligonucleotide C, and a maximum of 50 such units (a=4-50). This is consistent with dependent claim 11, which states that “a . . . represents the *number of chemical units of X* forming polymer A.” *Id.* at 44:9-11 (emphasis added). Ex. 1007 ¶¶65-66.

The specification supports this interpretation of “a.” It states that the length of the polymer is “defined by a,” which “represents the number of chemical units of X forming polymer A.” Ex. 1001 at 4:39-40 and 9:9-11. The specification
reiterates, when discussing oligonucleotide C, that “a is an integer as described previously to connote the number of chemical unit identifiers in the oligonucleotide.” *Id.* at 5:63-65 (emphasis added). Thus, “a” corresponds to the number of chemical units and unit identifiers in the bifunctional molecule. Ex. 1007 ¶67.

The ’596 patent provides a hypothetical example of a bifunctional molecule having four chemical units and four corresponding unit identifier nucleotide sequences “represented by the formula $X_4X_3X_2X_1$-B-$Z_1Z_2Z_3Z_4$.” Ex. 1001 at 5:66-67 and 6:1. The specification states:

In this example, the sequence of *oligonucleotides* $Z_1, Z_2, Z_3$ and $Z_4$ identifies the structure of *chemical units* $X_1, X_2, X_3$ and $X_4$, respectively. Thus, there is a correspondence in the identifier sequence between a chemical unit $X$ at position $n$ and the unit identifier oligonucleotide $Z$ at position $n$.

*Id.* at 6:2-6 (emphasis added). This example uses four unit identifiers to identify four chemical units (a=4), with the position of each unit consecutively numbered outward from the linker molecule (n running from 1-4). Ex. 1007 ¶68.

The ’596 prosecution history does not support any alternate interpretation of $(X_n)_a$ and $(Z_n)_a$. Indeed, Scripps stated during prosecution of a parent case (USSN 08/665,511, which issued as US 5,723,598) that “a” represented “the length of the polymer,” which could be “from 2 to 50 units” resulting from the repeated
attachment of chemical units and corresponding unit identifiers. Ex. 1026 at p. 22 (emphasis added).\(^1\)

**VIII. CLAIMS 1-6 AND 10-17 ARE OBVIOUS OVER DOWER ALONE OR IN VIEW OF JUBY OR NELSON**

*Dower* describes bifunctional molecules corresponding to formula A—B—C as recited in the ’596 patent and methods of making such molecules using alternating parallel synthesis. *Dower* also discusses libraries of bifunctional molecules. To the extent Scripps argues that *Dower* does not describe a linker molecule as claimed (despite expressly describing a “linker molecule” flanking a bead joining the oligonucleotide to the oligomer), it would have been obvious to one of ordinary skill in the art to use such a linker. For instance, the skilled artisan would have looked to the linkers of *Juby* (Ex. 1010) or *Nelson* (Ex. 1011) and would have been motivated to combine either of those references with *Dower* with a reasonable expectation of success. Thus, claims 1-6 and 10-17 are obvious over *Dower* alone or in view of *Juby* or *Nelson*.

\(^1\) The phrase “2 to 50” appears to be a typographical error, as the specification only mentions a range of “4 to 50” units.
A. *Dower Alone Renders the Claims of the ’596 Patent Obvious*

1. *Dower uses alternating parallel synthesis to produce bifunctional molecules*

*Dower* describes the same alternating parallel synthesis discussed in the ’596 patent to attach monomer units, such as amino acids, to oligonucleotide identifier units. Ex. 1009 at p. 20, ll. 19-36, and p. 21-22, bridging paragraph. Each added amino acid is followed by a corresponding oligonucleotide unit. *Id.* The resulting molecule comprises an oligonucleotide sequence where the units identify the monomers in the oligomer with a one-to-one correspondence. *Id.* at p. 12, ll. 21-24; Ex. 1007 ¶71.

*Dower’s* synthetic methods produce bifunctional molecules corresponding to those recited in claim 1, containing an “oligomer … composed of a sequence of monomers,” a bead and a flanking “linker molecule,” and “an oligonucleotide identifier tag” for the oligomer, with a one-to-one correspondence between each monomer in the oligomer and a nucleotide unit in the oligonucleotide tag. Ex. 1009 at p. 3, l. 37 – p. 4, l. 1, and p. 4, ll. 13-21 and 29-31. The oligomer and oligonucleotide tag are operatively linked through the linker molecules flanking the bead. *Id.* at p. 4, ll. 20-21, p. 11, ll. 20-23, and p. 12, ll. 25-29; Ex. 1007 ¶73.

Although *Dower* does not characterize its bifunctional molecules using the same “A—B—C” formula recited in the claims of the ’596 patent (e.g., (Xₙ)ₐ and (Zₙ)ₐ), this difference in nomenclature is irrelevant because *Dower’s* bifunctional
molecules meet the structural and functional requirements of the claims. Ex. 1007 ¶72.

2. Each chemical unit in Dower’s bifunctional molecule is identified by a corresponding oligonucleotide identifier unit

Each oligonucleotide identifier tag unit in Dower (what the ’596 patent refers to as a unit identifier nucleotide sequence “Z”) identifies a monomer (what the ’596 patent refers to as chemical unit “X”) at the corresponding position in the oligomer. Ex. 1009 at p. 18, ll. 29-39 and p. 20, ll. 24-27 and 33-35; Ex. 1007 ¶74. Dower indicates that after each monomer unit (such as an amino acid) is attached to the growing oligomer, a corresponding identifier unit is added to the growing oligonucleotide tag. Ex. 1009 at p. 13, l. 13-19.

Dower adds units in an oligonucleotide tag in a “block-by-block” fashion, where each block carrying “monomer-type information” is added after attaching each monomer unit of the oligomer. Id. at p. 20, ll. 31-35. Thus, each unit in the oligonucleotide tag identifies a corresponding monomer in the oligomer by “preserving the order of the steps in the linear array of the oligonucleotide chain as it grows in parallel with the oligomer.” Id. at p. 20, ll. 25-27; Ex. 1007 ¶75.

In an example, Dower describes an oligomer having three monomer units attached in the order A-C-B, with each corresponding nucleotide identifier tag sequence “attached to one another in the order of the steps: A, A-C, A-C-B.” Ex. 1009 at p. 18, ll. 9-35. This method builds up the oligomer and its corresponding
identifier oligonucleotide tag sequence so that the monomer unit closest to the 
linker (i.e., n=1) corresponds to the closest identifier tag unit (again, n=1), with 
iterative steps (n = 2, 3, etc.) each adding a new monomer and corresponding 
identifier tag. \textit{Id.} at p. 18, ll. 29-39 and p. 20, ll. 24-27 and 33-35; Ex. 1007 ¶76.

\textit{Dower} contemplates repeating the alternating synthesis steps “one to about 
20 times,” meaning a total of 1-20 units (i.e., a = 1-20), and thus provides species 
falling within the 4-50 unit range specified by claim 1. Ex. 1009 at p. 13, ll. 18-19; 
Ex. 1007 ¶77. Moreover, \textit{Dower} discusses exemplary oligomers with about 20 
monomer units, preferably 3 to 8 units. Ex. 1009 at p. 16, l. 10-11.

3. \textit{Dower describes a “linker molecule”}

\textit{Dower} discusses attaching the oligomer and oligonucleotide tag through a 
“linker molecule.” Ex. 1009 at p. 4, ll. 20-21. The ’596 patent notes that a “linker 
molecule … can be any molecule that performs the function of operatively linking 
the chemical moiety to the identifier oligonucleotide” because “the nature of the 
linkage is not considered an essential feature.” Ex. 1001 at 8:20-24 and 39-41.

Either the “linker molecule[s]” flanking the bead in \textit{Dower}, or the 
combination of bead and flanking linkers, qualifies as linker molecule “B” in the 
’596 patent. Ex. 1007 ¶80.

\textit{Dower}’s “linker molecule” meets this claim limitation because the claims 
require only that linker molecule B is “operatively linked” to components A and C
(Ex. 1001 at 43:5-6) rather than being directly linked. Ex. 1007 ¶80. As stated in 
*Dower*, “the solid supports may-be [sic] joined to the oligomers and the identifier 
tags by means of a linker molecule.” Ex. 1009 at p. 4, ll. 20-21. Regardless of the 
presence of the bead, *Dower*’s “linker molecule” operatively links polymer A and 
identifier oligonucleotide C. Indeed, the ’596 patent expressly contemplates 
bifunctional molecules synthesized on solid supports that can either be removed or 
*left attached* after synthesis. Ex. 1001 at 14:48-55. Scripps itself has also 
previously asserted that linker molecules joined to a solid support satisfy the claim 
requirements. Ex. 1046 at p. 5.

Alternatively, *Dower*’s combination of a bead and flanking linker molecules 
qualifies as linker molecule “B” in the ’596 patent. The presence of the bead does 
not interfere with the functional operative linkage of the polymer and 
oligonucleotide identifier. Ex. 1007 ¶81. *Dower* discusses the use of solid 
supports as small as “1 nm.” Ex. 1009 at p. 14, l. 1. This is much smaller than 
many chemical or biological molecules, including proteins, and its combination 
with the flanking linker molecules does not prevent the operative linkage of the 
polymer and oligonucleotide identifier. Ex. 1007 ¶81; Ex. 1031 at p. 5, Fig. 1-5.

*Dower* describes two ways of generating bifunctional molecules. Ex. 1007 
¶82. In one method, *Dower* attaches each individual oligonucleotide tag directly to 
the bead. Ex. 1009 at pp. 20-21, bridging paragraph. Alternatively, both the
oligomer and oligonucleotide identifier tag grow outward from linkers flanking the bead. *Id.* at p. 20, ll. 21-36; Ex. 1007 ¶82.

In sum, *Dower* describes bifunctional molecules falling within the scope of claim 1. Ex. 1007 ¶¶78 and 82. Sections VIII.B-F below discuss the motivation to use alternate linkers and expectation of success. Section VIII.H below includes an element-by-element claim chart.

4. *Dower describes the subject matter of the remaining claims of the ’596 patent*

The elements of remaining claims 2-6 and 10-17 are disclosed in *Dower*, as detailed in the chart below.

For example, *Dower* describes adding 3’ and 5’ PCR primer sites to the oligonucleotide identifier tag. Ex. 1009 at p. 4, ll. 23-26 and p. 20, ll. 7-9; *see also id.* at p. 24, ll. 3-5 and p. 25, ll. 1-3. *Dower* therefore provides an oligonucleotide identifier tag as in claims 6 and 17 of the ’596 patent: P1-(Z_n)_a-P2, where P1 and P2 are PCR primer sites adapted to amplify the identifier oligonucleotide. Ex. 1007 ¶83.

*Dower* generates a “synthetic oligomer library that incorporates identifier tags.” Ex. 1009 at p. 12, l. 32–p. 13, l. 19. *Dower* uses a variation of the split and pool method to repeatedly attach peptides and oligonucleotide identifier tags, generating a synthetic library of tagged polymers. Ex. 1007 ¶84. The bifunctional
molecules generated in *Dower* satisfy the requirement of claim 10, where a library is any “plurality of species of bifunctional molecules.” Ex. 1001 at 44:4-5.

*Dower* discusses a “typical” library having each bifunctional molecule present in a molar equivalent of 1.0. Specifically, *Dower* provides an example building a library in which “equal numbers” of solid supports in each reaction vessel are linked to oligomers and identifier tags. This would yield an equal number of each species in the library, such that each species of bifunctional molecule is present in a molar equivalent of 1.0. Ex. 1009 at p. 12, ll. 1-24; Ex. 1007 ¶85. Due to variability in synthesis efficiency, the ratio may fluctuate somewhat. Ex. 1007 ¶85. But because *Dower* uses the same alternating parallel synthetic strategy as the ’596 patent, *Dower* at a minimum necessarily produces molar ratios falling within the range specified in claim 16 of the ’596 patent. *Id.*

**B. Motivation to Remove the Bead from *Dower*’s Bifunctional Molecules**

*Dower* synthesizes oligomers linked to oligonucleotide tags through linker molecules on beads. The ’596 patent notes that a linker molecule can be any molecule that performs the function of operatively linking the chemical moiety to the identifier oligonucleotide and that “the nature of the linkage is not considered an essential feature of this invention.” Ex. 1001 at 8:20-24, 8:39-41. Given these statements, and because the linker in *Dower* operatively links the oligomer and identifier tag, it would have been obvious from *Dower* alone to construct a
bifunctional molecule having a structure corresponding to formula A—B—C as claimed in the ’596 patent. Ex. 1007 ¶86.

But even if the Board determines that the bifunctional molecules claimed in the ’596 patent cannot include a bead, the claimed subject matter would still have been obvious. The skilled artisan would have modified Dower to use an alternative cleavable linker so that the solid support could be released after synthesis. Id. at ¶87. As explained in more detail in subsections E and F below, a skilled artisan would have used a cleavable linker to obtain the known benefits of removing the solid support to facilitate subsequent solution-phase screening, and would have done so with a reasonable expectation of success. Id.

Juby and Nelson provide examples of suitable cleavable linkers. They address the same objective as Dower—attaching a peptide to an oligonucleotide using compatible solid-phase chemistry. Id. at ¶88. Because all three references address similar objectives using similar chemistries, the skilled artisan would have been aware of them and would have been motivated to combine the references to obtain the benefits discussed below. Id. Moreover, the skilled artisan would have reasonably expected success from such a combination because Juby and Nelson had already used their linkers to successfully conjugate polymers to oligonucleotides. Id. at ¶89.
C. *Juby Describes a Linker for Attaching an Oligonucleotide to a Polymer on a Releasable Solid Support*

*Juby* described a multifunctional phosphoramidite linker cleavably attached to a solid support that was capable of operably linking an oligonucleotide to a peptide. Ex. 1010 at p. 880. This is the same phosphoramidite linker exemplified in the ’596 patent and in other prior art. Ex. 1001 at 25:4-8; Ex. 1007 ¶90; Ex. 1024 at p. 7180, Compound 1 in Fig. 1. The linker is also compatible with *Dower’s* solid-phase synthesis methods. Ex. 1010 at p. 880; Ex. 1007 ¶¶90-91.

*Juby* used the linker in solid-phase synthesis on a Teflon support to produce peptide-oligonucleotide conjugates. Ex. 1010 at Figure 1, reproduced below; Ex. 1007 ¶¶92-93. The solid support was subsequently cleaved to release the oligonucleotide-peptide conjugate. Ex. 1010 at p. 880-81.

![Chemical structure diagram](image)

*Juby’s* solid-phase synthesis of peptide-oligonucleotide conjugates used standard chemical reactions and reagents readily accessible to one of ordinary skill. Ex. 1007 ¶94; Ex. 1010 at p. 880. Indeed, *Juby* provided “a facile synthesis starting directly with commercially available reagents.” *Id.* at p. 882.
Juby therefore described a releasable linker suitable for the solid-phase synthesis of a peptide operatively linked to an oligonucleotide. Ex. 1007 ¶93. Accordingly, a skilled artisan could readily envision using Dower’s alternating parallel synthesis with Juby’s compatible linker to produce the claimed bifunctional molecule. Id. at ¶95.

D. Nelson Describes Multifunctional Linkers for Attaching an Oligonucleotide to a Polymer

Nelson describes multifunctional linkers for use in solid-phase oligonucleotide synthesis. Ex. 1012 at Abstract. The linkers contain a protected hydroxide group suitable for solid-phase oligonucleotide synthesis, a protected amine group suitable for attaching a protein or other reporter molecule, and an attachment position for the solid support. Id. at p. 3, ll. 15-20 and p. 5, ll. 1-9; Ex. 1007 ¶96.

Nelson states that its multifunctional linkers can link oligonucleotides to polymers such as proteins. Ex. 1012 at p. 6, ll. 1-9. Nelson discusses a multifunctional linker attached to a solid support through a cleavable arm that “is stable to all the conditions of solid phase oligonucleotide synthesis.” Id. at p. 3, l. 25–p. 4, l. 17. Nelson states that the linker “is fully adaptable to commercial DNA synthesizers and is as easy as synthesizing normal oligonucleotides.” Id. at p. 8, ll. 13-14.
Nelson’s multifunctional linkers are compatible with Dower’s solid-phase synthesis chemistry. Ex. 1007 ¶97.

Nelson attached an oligonucleotide to a multifunctional linker on a solid support and cleaved the oligonucleotide-linker from the solid support. Ex. 1012 at p. 12, ll. 9-19. Nelson then attached a biotinylated peptide to the oligonucleotide-linker. Id. at p. 12, ll. 20-23; Ex. 1007 ¶¶98-100. Nelson’s biotinylated peptide is a polypeptide because the ’596 patent states that the alphabet of possible amino acid residues can include “any molecule that satisfies the basic chemistry defining an amino acid.” Ex. 1001 at 14:57-67 (emphasis added); Ex. 1007 ¶¶101.

While Nelson cleaved the linker from the solid support before attaching the peptide, a skilled artisan would have understood that Nelson’s linker and chemistry were compatible with the reverse order of steps: attaching the peptide before cleavage from the solid support. Ex. 1007 ¶102. A person of ordinary skill would understand that chemistry was available to attach a polymer to Nelson’s linker in the solid phase before cleaving from the solid support, including the chemistry used in Dower. Id. at ¶103.

As such, a skilled artisan could readily envision using Dower’s alternating parallel synthesis with the compatible multifunctional linkers in Nelson to produce the claimed bifunctional molecule. Id. at ¶104.
The schematic below shows the obvious combination of *Dower* with *Juby* or *Nelson*. 
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\[ \text{DOWER} + \text{JUBY / NELSON} \]

\[ \text{BEAD} \rightarrow \text{LINKER} \rightarrow \text{BEAD} \rightarrow \text{AA} \rightarrow \text{OLIGO}_1 \rightarrow \text{BEAD} \rightarrow \text{AA} \rightarrow \text{LINKER} \rightarrow \text{OLIGO}_1 \rightarrow \text{BEAD} \rightarrow \text{AA} \rightarrow \text{OLIGO}_2 \rightarrow \text{BEAD} \rightarrow \text{AA} \rightarrow \text{LINKER} \rightarrow \text{OLIGO}_1 \rightarrow \text{OLIGO}_2 \rightarrow \text{BEAD} \rightarrow \text{AA} \rightarrow \text{REPEAT} \rightarrow \text{CLEAVE} \]

\[ \text{AA} \rightarrow \text{AA} \rightarrow \text{LINKER} \rightarrow \text{OLIGO}_1 \rightarrow \text{OLIGO}_2 \rightarrow \text{OLIGO}_n \rightarrow \text{BEAD} \rightarrow \text{AA} \rightarrow \text{AA} \rightarrow \text{AA} \rightarrow \text{LINKER} \rightarrow \text{OLIGO}_2 \rightarrow \text{OLIGO}_3 \rightarrow \text{OLIGO}_n \rightarrow \]

\[ \text{AA}_n = \text{monomer unit (e.g. amino acid) at position n} \]

\[ \text{OLIGO}_n = \text{identifier oligonucleotide unit for monomer unit at position n} \]
E. Motivation to Combine Dower with Juby or Nelson

*Dower* prepared bifunctional molecules on a solid support. Ex. 1009 at p. 12, ll. 21-29 and p. 12, l. 32–p. 13, l. 12. One of ordinary skill would have sought to obtain the benefits of solid-phase synthesis followed by solution-phase screening, and therefore would have been motivated to use *Dower*’s methods on a solid support that could be released after synthesis. Ex. 1007 ¶105.

The skilled artisan seeking to obtain these benefits would first consider other art disclosing solid-phase preparation of bifunctional molecules. *Id.* *Juby* and *Nelson* report effective multifunctional linkers attached to solid supports that could be released after synthesis, and chemistry for attaching oligonucleotides to polymers. *Juby* describes a multifunctional linker for the solid-phase synthesis of peptide-oligonucleotide conjugates on a bead. *Id.* at ¶90; Ex. 1010 at p. 880. *Nelson* also describes linkers for solid-phase synthesis and attaches an oligonucleotide to a biotinylated peptide. Ex. 1012 at p. 5, ll. 19-25, p. 12, Example 2, and p. 16, Sequence 1; Ex. 1007 ¶99.

Thus, all three references relate to highly similar chemical pathways with the same purpose of forming peptide-oligonucleotide conjugates on solid supports. One of ordinary skill therefore would have looked to the linkers of *Juby* and *Nelson* and considered them compatible with *Dower*’s alternating synthesis.

1. **Known benefits of solid-phase synthesis and solution-phase screening**

   Known benefits of solid-phase synthesis followed by solution-phase screening would have provided strong motivation for the skilled artisan to modify Dower to incorporate a cleavable linker from Juby or Nelson. Juby and Nelson report effective synthesis for similar peptide-oligonucleotide conjugates. Thus, one of ordinary skill seeking to produce a bifunctional molecule on a solid support that could be released after synthesis would combine Dower’s alternating synthesis with the linkers in Juby and Nelson to prepare bifunctional molecules as claimed. Ex. 1007 ¶109.

   Existing methods for preparing peptides and oligonucleotides generally used a solid support, as in Dower, Juby, and Nelson, to eliminate laborious purification procedures. Id. at ¶110; Ex. 1032 at Abstract. Houghten, for example, emphasized the importance of synthesizing polymer library members on a solid support to increase production efficiency and library size. Ex. 1022 at p. 2, ll. 26-30, and p. 3, ll. 6-10 and 29-32.
While solid-phase synthesis is advantageous for preparing oligonucleotide-polymer conjugates, solution-phase reagents are better suited to many biological screening methods. Ex. 1007 ¶¶111-112. Solid support-bound peptides have “limited application,” and therefore should be “cleaved directly into a medium compatible with their final use.” Ex. 1033 p. 6660, col. 1, ¶¶1-2. Solid supports can interfere with binding to a biological target due to steric hindrance or other chemical interactions. Ex. 1007 ¶111. The solid support may result in candidate sequences (e.g., a peptide in an oligonucleotide-peptide conjugate) having limited access to a biological target, potentially hindering their detection in a screen. Id. Certain assays therefore require solution-phase probes. Ex. 1034 at Abstract.

*Houghten* discusses the limited applicability of solid-phase linked peptides in screening assays. Those peptides did not “interact in a ‘normal’ manner with acceptor sites, analogous to natural interaction processes.” Ex. 1022 at p. 9, l. 27–p. 10, l. 2; Ex. 1007 ¶112. Also, the binding rate kinetics of solid-phase immobilized biological molecules can differ from those of the corresponding solution-phase molecules. Ex. 1023 at p. 63; Ex. 1007 ¶112.

Thus, the prior art expressly identified benefits of synthesizing molecules on a solid support but screening them in solution. A skilled artisan would have recognized these known benefits, and would have been motivated to consider using
Dower’s alternating synthesis with the cleavable linkers of Juby or Nelson. Ex. 1007 ¶113.

2. The art provided multifunctional linkers for synthesizing on a solid support but screening in solution

The prior art not only discussed the need for rapid synthesis of polymer libraries tagged with identifier oligonucleotides that could be screened in solution, but it also discussed how to achieve these benefits using linkers that could be released from solid supports after synthesis. Id. at ¶114. For example, Houghten used a “selectively severable covalent bond” to synthesize molecules on a solid support, then transfer the peptide to a solution phase by cleaving the covalent bond between the peptide and solid support. Ex. 1022 at p. 21, ll. 18-23.

A skilled artisan would have been motivated to prepare Dower’s bifunctional molecules on a solid support that could be removed before screening. Ex. 1007 ¶115. This artisan would have sought to identify a suitable multifunctional linker that could be cleaved from the solid support without disrupting the polymer-oligonucleotide linkage. Id.

Juby and Nelson provide linkers that offer this very benefit. Id. at ¶116. For instance, Juby links a peptide to an oligonucleotide through a multifunctional linker and then treats the completed peptide-oligonucleotide conjugate with sodium periodate to release the molecule from a Teflon support. Ex. 1010 at p. 881 and Fig. 1. Nelson states that its multifunctional linkers have a “cleavable linking arm”
connecting to a solid support, which “covalently connects to the solid phase (W) through a cleavable linkage, and is stable to all the conditions of solid phase oligonucleotide synthesis.” Ex. 1012 at p. 4, ll. 8-11.

Accordingly, one of ordinary skill would have been motivated to use the cleavable linkers in *Juby* or *Nelson* with the bifunctional molecules of *Dower*. The combination would retain the benefits of *Dower*’s solid-phase synthesis and provide the art-recognized benefits of subsequently releasing the molecules from the solid support before screening. Ex. 1007 ¶117.

While the skilled artisan might have contemplated a limited number of alternatives to using the cleavable linkers of *Juby* or *Nelson* to facilitate solution-phase screening, none provided the combination of synthesis efficiency and subsequent screening flexibility afforded by a cleavable linker. *Id.* at ¶118. For instance, the artisan could hypothetically synthesize bifunctional molecules on beads, maintain each molecule in a separate test tube, and then separately cleave the oligomer and oligonucleotide tag from the bead in each tube, leaving unattached oligomers and tags in solution. *Id.* Those oligomers could be screened in solution, but could not be evaluated for competitive binding. *Id.* Also, millions of test tubes would be required to separate out each member of a large library. These drawbacks would have discouraged the skilled artisan from pursuing such
alternatives and encouraged the skilled artisan to take the route of combining

Dower with Juby or Nelson, as discussed above. Id.

F. The Skilled Artisan Would Have Reasonably Expected Success in Combining Dower’s Method with the Linkers of Juby or Nelson

One of ordinary skill in the early 1990s would have reasonably expected success from incorporating a cleavable linker into Dower’s synthetic methods because Juby and Nelson provide effective linkers for preparing similar conjugates that could be cleaved from solid supports after synthesis. Id. at ¶119.

Juby and Nelson successfully attached peptides to oligonucleotides with their linkers. Id. Juby did so using the same phosphoramidite linker reagent as the ’596 patent. Ex. 1010 at Summary, Fig. 1, and pp. 880-81; Ex. 1007 ¶120. Nelson coupled a biotinylated peptide to an oligonucleotide by forming an amide bond, the same type of bond used in Dower to attach amino acid monomers to the growing peptide oligomer. Ex. 1012 at p. 12, ll. 9-24; Ex. 1007 ¶121.

One of ordinary skill would have understood that these references concern similar conjugation chemistry. Ex. 1007 ¶122. Indeed, during prosecution, Scripps pointed to Nelson and another paper discussing the linker used in Juby (id. at ¶¶90, 108, 120) as “confirm[ing] the operability” of alternating synthesis with linkers for oligonucleotide/peptide conjugates. Ex. 1044 at pp. 11-13.

Thus, the skilled artisan would have had a reasonable expectation of success adding a linker from Juby or Nelson to the synthetic method of Dower because all
three describe related conjugates and compatible chemistries. Ex. 1007 ¶122. A skilled artisan would have synthesized bifunctional molecules that join an oligonucleotide identifier tag to a polymer (such as a peptide) via a cleavable linker attached to a solid support. The skilled artisan would have cleaved the bifunctional molecule off the solid support after synthesis, e.g., to facilitate subsequent biological screening. The resulting molecules, with or without the attached solid support, would correspond to the A—B—C structure claimed in the ’596 patent, as the ’596 patent states that “the nature of the linkage is not considered an essential feature of this invention.” Id.; Ex. 1001 at 8:39-41.

G. Additional Copies of the Oligonucleotide Tag on Dower’s Bead

Scripps may argue that Dower’s beads have multiple attachment sites and thus may incorporate more than one copy of the oligomer or oligonucleotide tag, either directly or through a linker. Ex. 1009 at p. 25, ll. 27-34. But that is irrelevant because the ’596 patent does not exclude other components from the claimed bifunctional molecules. Dower therefore renders the claims obvious. Ex. 1046 at p. 5; Ex. 1007 ¶123.

Moreover, the bifunctional molecules that result from combining Dower and Juby or Nelson would link only a single oligomer to a single oligonucleotide identifier. Ex. 1007 ¶124.
H. Claim Chart

*Dower* alone or in combination with *Juby* or *Nelson* renders obvious certain peptide-oligonucleotide bifunctional molecules, a subgenus encompassed by claims 1-6 and 10-17 of the ’596 patent. The claims as a whole are therefore obvious. *See, e.g.*, *Ex Parte Kubin*, No. 2007-0819 (B.P.A.I. 2007), *aff’d*, 561 F.3d 1351 (Fed. Cir. 2009) (“A single, obvious species within a claimed genus renders the claimed genus unpatentable under § 103.”).

The chart below shows how the skilled artisan would have combined the prior art to arrive at the claims on an element-by-element basis. *See also* Ex. 1007 ¶126.

<table>
<thead>
<tr>
<th>’596 Patent Claims</th>
<th><em>Dower</em> alone, or in view of <em>Juby</em> or <em>Nelson</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A bifunctional molecule according to the formula A—B—C,</td>
<td><em>Dower</em> describes bifunctional molecules and a method of synthesizing them by linking oligomers to identifier tags through linker molecules flanking a bead to produce a structure corresponding to formula A—B—C. Ex. 1009 at Abstract, p. 3, l. 37–p. 4, l. 21, and p. 12, ll. 21-29.</td>
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<tr>
<td>wherein A is a polymer comprising a linear series of chemical units represented by the formula ((X_n)_a), wherein X is a single chemical unit in polymer A, B is a</td>
<td><em>Dower</em>’s oligomer and identifier tag have, respectively, the chemical structure ((X_n)_a) and ((Z_n)_a) because both comprise a series of units that are added in parallel. <em>Id.</em> at p. 12, l. 35–p. 13, l. 16; <em>see also id.</em> at p. 3, l. 36–p. 4, l. 3 and p. 4, ll. 13-20. The tag units can be oligonucleotide units. <em>Id.</em> at p. 4, ll. 22-23. After <em>Dower</em> adds each monomer unit in the oligomer, a corresponding identifier nucleotide unit is added to the</td>
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<td>'596 Patent Claims</td>
<td><strong>Dower alone, or in view of Juby or Nelson</strong></td>
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<tr>
<td>linker molecule operatively linked to A and C. [sic] and identifier oligonucleotide C is represented by the formula $(Z_n)^a$,</td>
<td>oligonucleotide tag. <em>Id.</em> at p. 13, ll. 15-19 and p. 19, ll. 6-9. The oligomer and oligonucleotide tag grow outwards from the linker during synthesis. <em>Id.</em> at p. 20, ll. 24-35. The monomer and identifier added in the first synthesis step would be closest to the linker and have n=1. The total number of units “a” depends on the number of synthesis steps. <em>Id.</em> at p. 16, ll. 7-12 and p. 18, ll. 9-11 and 29-35. For instance, five synthesis steps would add five monomer units to the oligomer and five unit identifiers to the oligonucleotide, and thus a=5.</td>
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<tr>
<td><strong>Dower</strong> describes linker molecules flanking the bead that join the oligomer to the tag. The linkers, or the linkers plus bead, operatively link the oligomer and oligonucleotide tag. <em>Id.</em> at p. 4, ll. 15-21, p. 11, ll. 20-23, and p. 12, ll. 25-29.</td>
<td>If it is determined that the claimed bifunctional molecule cannot include a bead, <em>Juby</em> linked a peptide to an oligonucleotide through a “bifunctional branched modifier” on a solid support. Ex. 1010 at Summary, Fig. 1, and p. 879-880. The branched modifier is a linker that can be cleaved from the solid support. <em>Id.</em> at p. 881 and Fig. 1. <em>Nelson’s</em> linkers may also be used to conjugate oligonucleotides to molecules such as proteins. Ex. 1012 at p. 6, ll. 1-9. <em>Nelson</em> states that the linker can be cleaved from the solid support. <em>Id.</em> at p. 13, ll. 17-19.</td>
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<tr>
<td>wherein a unit identifier nucleotide sequence Z within oligonucleotide C identifies the chemical unit X at</td>
<td><strong>Dower</strong> describes identifier unit “blocks” within the oligonucleotide tag, each of which identifies a corresponding monomer at position n in the oligomer. <strong>Dower</strong> states that the identifier tag can be built in a sequential, step-wide fashion, so that each additional unit (Z) added to the identifier tag (C) corresponds to a new monomer (X) added to the oligomer (A). Ex. 1009 at p. 13, ll. 15-19, p. 18, ll. 9-39 and p. 20, ll. 31-35.</td>
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<tr>
<td>'596 Patent Claims</td>
<td><em>Dower alone, or in view of Juby or Nelson</em></td>
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<td>position n;</td>
<td>As discussed above, <em>Dower</em> describes bifunctional molecules where each unit (Z) in the identifier tag (C) corresponds to a unit (X) in the oligomer (A), so the first unit (Z₁) corresponds to the unit (X₁), and the attachment method “preserv[es] the order of the steps in the linear array of the oligonucleotide chain as it grows in parallel with the oligomer.” <em>Id.</em> at p. 13, ll. 15-19, p. 18, ll. 9-11, and p. 20, ll. 24-35.</td>
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<tr>
<td>and wherein n is a position identifier for both X in polymer A and Z in oligonucleotide C having the value of 1+i where i is an integer from 0 to 10, such that when n is 1, X or Z is located most proximal to the linker,</td>
<td></td>
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<tr>
<td>and a is an integer from 4 to 50.</td>
<td><em>Dower</em> describes embodiments in which “a”—the number of total units in the oligomer (A) and in the identifier tag (C)—is about 20 monomer units, preferably 3 to 8 monomer units, which include species falling between 4 and 50. <em>Id.</em> at p. 16, ll. 10-12 and p. 13, ll. 11-12.</td>
</tr>
<tr>
<td>2. The bifunctional molecule of claim 1 wherein said unit identifier nucleotide sequence Z has a length of from 2 to 8 nucleotides.</td>
<td><em>Dower</em> provides identifier units having 3-10 or more bases, falling within the claimed 2-8 nucleotides per unit range. <em>Id.</em> at p. 20, ll. 31-35.</td>
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<tr>
<td>3. The bifunctional molecule of claim 1 wherein said polymer is an oligosaccharide, polepeptide [sic],</td>
<td><em>Dower</em> states that polymer (A) can comprise, for example, an oligonucleotide or polypeptide. <em>Id.</em> at p. 3, l. 37—p. 4, l. 3.</td>
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<tr>
<td>’596 Patent Claims</td>
<td>Dower alone, or in view of Juby or Nelson</td>
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<td>glycolipid, lipid, proteoglycan, glycopeptide or oligonucleotide.</td>
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<td>4. The bifunctional molecule of claim 1 wherein said polymer A is a polypeptide, X is an amino acid residue in said polypeptide, and unit identifier nucleotide sequence Z is a hexanucleotide sequence that identifies the amino acid residue at position n in polypeptide A.</td>
<td>As stated above for claims 2 and 3, <em>Dower</em> describes a polypeptide in which X is an amino acid residue and each identifier unit may comprises 3 to 10 nucleotides (which would encompass hexanucleotides).</td>
</tr>
<tr>
<td>5. The bifunctional molecule of claim 4 wherein said amino acid residue is selected from the group consisting of natural, modified and non-natural amino acids.</td>
<td><em>Dower</em> discusses the use of natural amino acids in the synthesis of bifunctional molecules. <em>Id.</em> at p. 3, l. 37–p. 4, l. 3, p. 7, ll. 22-23, and p. 8, ll. 6-8.</td>
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<tr>
<td>6. The bifunctional molecule of claim 1</td>
<td><em>Dower</em> uses 3’ and 5’ PCR primer sites according to the formula P1-(Zₙ)ₚ-P2 to facilitate amplifying the identifier oligonucleotide. <em>Id.</em> at p. 4, ll. 23-26; p. 24, ll. 3-7 and p.</td>
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<tr>
<td>'596 Patent Claims</td>
<td>Dower alone, or in view of Juby or Nelson</td>
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<tr>
<td>wherein said identifier oligonucleotide C has a nucleotide sequence according to</td>
<td>26, ll. 26-30.</td>
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<td>the formula P1-((Z_n))_a--P2, where P1 and P2 are nucleotide sequences that</td>
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<td>provide polymerase chain reaction (PCR) primer binding sites adapted to amplify</td>
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<td>the identifier oligonucleotide.</td>
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<td>10. A library comprising a plurality of species of bifunctional molecules</td>
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<td>according to claim 1.</td>
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<td>Dower describes a “synthetic oligomer library that incorporates identifier tags,”</td>
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<td>wherein each species in the library has a different oligomer and corresponding</td>
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<tr>
<td>identifier tag identifying the oligomer sequence.  <em>Id.</em> at p. 12, ll. 21-35.</td>
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<tr>
<td>Dower also describes “a synthetic peptide library having a plurality of different</td>
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<td>members, each member comprising a solid support attached to a different single</td>
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<tr>
<td>peptide sequence and an oligonucleotide identifier tag identifying said peptide</td>
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<td>sequence.”  <em>Id.</em> at p. 21, l. 36–p. 22, l. 2.</td>
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<td>11. The library of claim 10 wherein said plurality of species is defined by the</td>
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<td>formula V(^a), where V represents</td>
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<td>Dower describes the synthesis of libraries of bifunctional molecules using all 20</td>
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<td>amino acids (&quot;V&quot; = 20) at each position “X” in the polymer, where the total</td>
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<td>number of permutations depends on the number of chemical units (i.e., amino acids)</td>
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<td>in the protein. For instance, Dower describes a library of proteins having a</td>
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<td>length of 5 amino acids (&quot;a&quot;=5), resulting in 20(^5) permutations.  <em>Id.</em> at p.</td>
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<td>2, ll. 18–19.</td>
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<td>’596 Patent Claims</td>
<td>Dower alone, or in view of Juby or Nelson</td>
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<tr>
<td>the number of</td>
<td>Dower describes the synthesis of libraries using the 20 different chemical units forming an natural amino acids (V=20). See support for claims 10 alphabet of possible chemical units of X, and a is an exponent and 11. See also id. at p. 21, l. 35—p. 22, l. 19, p. 7, ll. 22-23, and p. 8, ll. 6-8. chemical units of X forming polymer A.</td>
</tr>
<tr>
<td>12. The library of</td>
<td>Dower discusses embodiments in which “a”— the claim 11 wherein X is a natural amino acid and V is 20. number of chemical units in the oligomer (A)—is between 3 and 8. Id. at p. 16, ll. 10-12.</td>
</tr>
<tr>
<td>claim 11 wherein X is a natural amino acid and V is 20.</td>
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<tr>
<td>13. The library of</td>
<td>See support for claim 13.</td>
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<tr>
<td>claim 11 wherein the number of chemical units (a) forming polymer A is from about 3 to about 8.</td>
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<tr>
<td>14. The library of</td>
<td>See support for claim 12 wherein a is 6.</td>
</tr>
<tr>
<td>claim 12 wherein a is 6.</td>
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<tr>
<td>15. The library of</td>
<td>See support for claims 1 and 10.</td>
</tr>
<tr>
<td>claim 12 wherein X is an amino acid and identifier oligonucleotide C is represented by the formula (Zn)a</td>
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<tr>
<td>'596 Patent Claims</td>
<td>Dower alone, or in view of Juby or Nelson</td>
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<tr>
<td>wherein a unit identifier nucleotide sequence Z within oligonucleotide C identifies the chemical unit X at position n: and wherein n is a position identifier for both X in polymer A and Z in oligonucleotide C having the value of 1+i where i is an integer from 0 to 10, such that when n is 1, X or Z is located most proximal to the linker, and a is an integer from 4 to 50 and said unit identifier nucleotide sequence Z has a length from 3 to 6 nucleotides.</td>
<td>Dower discusses a “typical” library having each bifunctional molecule present in a molar equivalent of 1. Dower provides an example building a library in which “equal numbers” of solid supports in each reaction vessel are linked to oligomers and identifier tags, which would yield an equal number of each species in the library such that each species of bifunctional molecule is present in a</td>
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<tr>
<td>16. The library of claim 10 wherein each of said species of bifunctional molecules in said plurality is present</td>
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<tr>
<td>'596 Patent Claims</td>
<td>Dower alone, or in view of Juby or Nelson</td>
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<td>in molar equivalents of from 0.2 to 10.0.</td>
<td>molar equivalent of 1.0. <em>Id.</em> at p. 12, ll. 1-24. Alternatively, at a minimum, <em>Dower</em> inherently describes this limitation. <em>Dower</em> uses the same alternating parallel synthetic strategy as the '596 patent. <em>Dower</em> therefore necessarily produces molar ratios falling within the range specified in claim 16 of the '596 patent. Ex. 1007 ¶85.</td>
</tr>
<tr>
<td>17. The library of claim 11 wherein said identifier oligonucleotide in each of said species of bifunctional molecules has a nucleotide sequence according to the formula P1--(Zₙ)ₐ--P2, where P1 and P2 are nucleotide sequences that provide PCR primer binding sites adapted to amplify the identifier oligonucleotide, and where the nucleotide sequences of P1 and P2 are shared by all bifunctional molecule species in the library.</td>
<td><em>See</em> support for claims 6 and 10.</td>
</tr>
</tbody>
</table>
I. No Secondary Considerations Justify a Conclusion of Non-Obviousness

The ’596 patent provides no evidence of unexpected results or other secondary considerations of nonobviousness. Ex. 1007 ¶125. Nor could any such evidence justify a non-obviousness finding given the strong case of obviousness outlined above. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1372 (Fed. Cir. 2007) (holding secondary considerations insufficient where the record established “a strong case of obviousness”).

IX. DOWER AND NELSON ARE ALSO PRIOR ART UNDER § 102(b) BECAUSE THE CLAIMS LACK WRITTEN DESCRIPTION SUPPORT IN THE PRIORITY APPLICATIONS

The challenged claims lack written description support in the priority applications, U.S. Application No. 08/665,511, filed June 18, 1996, and U.S. Application No. 07/860,445, filed March 30, 1992 (Ex. 1006 and 1004). Thus, the ’596 patent is not entitled to any priority date earlier than the filing date of Application No. 09/033,743 (March 3, 1998) (Ex. 1002), from which the ’596 patent issued. See, e.g., Rackspace US, Inc., v. Personal Web Tech., LLC, Institution Decision, Paper No. 10, IPR 2014-00058 (PTAB Apr. 15, 2014) (IPR

2 Both priority applications share the same specification as the ’596 patent.

Citations to “the priority applications” refer to the application filed on March 30, 1992 (Ex. 1004).
petitioner may assert unpatentability based on an *intervening* reference); *In re NTP, Inc.*, 654 F.3d 1268, 1276-77 (Fed. Cir. 2011).

To gain the benefit of an earlier application under 35 U.S.C. § 120, the earlier application must comply with the written description requirement of § 112 for the claimed subject matter. *Hollmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012). Claims to a genus can meet the written description requirement by providing a representative number of species or common structural features such that the skilled artisan could visualize or recognize the members of the genus. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc). The priority applications fail under either test.

While prior art such as *Dower, Juby*, and *Nelson* describe a peptide linked to an oligonucleotide tag, the claims are not limited to those particular components. Instead, the claims embrace an array of different polymers and unit identifier nucleotide sequences. Ex. 1007 ¶131. Many types of polymers contain a linear series of units, including the seven categories mentioned generically in claim 3 of the ’596 patent. Ex. 1001 at 43:18-20. Yet the priority applications provide no examples or discussion of any polymers other than peptides. Ex. 1007 ¶131.

The claims also cover many different unit identifier nucleotide sequences and identifier schemes, including those using natural nucleotides or non-natural nucleotide analogs. Ex. 1004 at p. 11, ll. 30-35. Yet the priority applications
briefly discuss only one identification scheme providing nucleotide sequences that encode for two amino acids. *Id.* at p. 59, ll. 32-33; Ex. 1007 ¶ 131. The applications provide no guidance on any particular unit identifiers for any other amino acids, let alone the unit identifiers for the chemical units in any other polymer types, the linkages between those polymer types (which could vary), and stereochemical variations within those polymer types. *Id.* Rather, the claims leave it entirely to the skilled artisan to identify a suitable identifier scheme. *Id.*

In the early 1990s, the organic synthesis of many of these potential polymers on a solid support or in solution was still in early development, as was the chemistry to synthesize them in conjunction with unit identifier nucleotide sequences. *Id.* at ¶ 132 and 149. Yet as explained below, the ultimate structure of any given bifunctional molecule is influenced by the chosen synthesis pathway. *Id.* at ¶ 132. Given the limited state of the art, one of ordinary skill would not find the priority applications commensurate with the many permutations claimed in the ’596 patent. *Id.*

**A. The ’596 Patent Claims a Genus of Bifunctional Molecules**

Claim 1 of the ’596 patent encompasses a genus of bifunctional molecules in which *any* polymer A comprising 4 to 50 chemical units is operatively linked through a linker molecule B to *any* identifier oligonucleotide C, so long as each unit identifier in C identifies a corresponding chemical unit in A. *Id.* at ¶ 133.
The priority applications acknowledge that the claimed polymers encompass an array of structurally diverse species. *Id.* at ¶134. Exemplary polymers include “a polypeptide, oligosaccharide, glycolipid, lipid, proteoglycan, glycopeptide, sulfonamide, nucleoprotein, conjugated peptide (i.e., having prosthetic groups), polymer containing enzyme substrates, including transition state analogues, and the like biochemical polymers.” Ex. 1004 at p. 8, ll. 25-31. Indeed, the priority applications indicate that polymer A “can be any monomeric chemical unit that can be coupled and extended in polymeric form.” *Id.* at p. 8, ll. 23-25.

Even within a particular polymer type, a large number of permutations are possible. For example, a polypeptide having just four amino acids (the minimum required by claim 1) could have any of the 20 different natural amino acids at each position, for a total of $20^4$ or 160,000 different permutations. Ex. 1007 ¶135. The number of permutations increases exponentially with longer polypeptides, particularly as the specification contemplates using non-natural amino acids in addition to natural ones. Ex. 1004 at p. 8, l. 33–p. 9, l. 3; Ex. 1007 ¶¶135-36.

None of the dependent claims meaningfully narrow the claimed genus of bifunctional molecules. Claims 2-9 allow for many different categories of polymers varying widely in length. These structurally diverse polymers include a wide variety of bond types, size, and steric features of the component monomers. *Id.* at ¶137. No structures are described for polymer classes other than the minimal
guidance provided for polypeptides. *Id.* Claims 10-17 compound this problem by requiring libraries of such bifunctional molecules.

Even when the polymer is limited to a polypeptide, as in claim 4, it still covers many amino acid sequence options, including non-natural amino acids, as well as many options for identifying those amino acids using different nucleotide identifier strategies. *Id.* at ¶138. The specification states that amino acids broadly include “modified and unusual amino acids,” without identifying where or how to effectuate the modification. Ex. 1004 at p. 10, ll. 10-14. The specification even states that “[p]reviously undescribed amino acids may be developed that can be used in the present invention.” *Id.* at p. 31, ll. 15-16 (emphasis added). It is “axiomatic[]” that the named inventors did not possess materials that were undescribed at the time of filing. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004).

The priority applications contemplate “any polymer backbone modifications that provide increased chemical diversity” in the structure of polymer A, without limitation or guidance on how to select, construct, and incorporate them in a polymer. *Id.* at p. 10, ll. 15-27. Indeed, even for a single category such as amino acids, the priority applications state that “the alphabet of possible amino acid residues can be extended to include *any* molecule that satisfies the basic chemistry defining an amino acid” and “there is no basis to limit the polypeptide backbone
connecting the termini to the conventional amino acid structure.” *Id.* at p. 31, ll. 1-4 and 9-11 (emphasis added). These differences in chemical structure render it impossible to envision all of the polymers encompassed by the claims. *Ex. 1007 ¶139.*

The claims also allow for many different oligonucleotide identifiers, defined only by their identifier function. *Id.* at ¶140. The unit identifier sequences are merely informed by the “complexity of the library, the number of chemical units to be uniquely identified, and other considerations relating to requirements for uniqueness of oligonucleotides such as hybridization and polymerase chain reaction fidelity.” *Ex. 1004* at p. 11, ll. 16-22. The priority applications provide no guidance on how these considerations should affect the identification strategy.

Given the many categories of polymers embraced by the claims, an equally complex oligonucleotide identifier scheme is required, involving many different oligonucleotide identifier units for each type of chemical unit encompassed by the claims. *Ex. 1007 ¶141.* The permutations further expand based on the chosen number of nucleotides in each unit identifier, such as trinucleotides, hexanucleotides, etc. *Id.* The specification states only that each unit identifier may comprise “from about 2 to about 10 nucleotides, although nothing is to preclude a unit identifier from being longer.” *Ex. 1004* at p. 11, ll. 22-24. It further encourages the use of longer unit identifiers to reduce the similarity between
sequences, but provides no other guidance on suitable identifier sequences. *Id.* at p. 12, ll. 26-31.

Notably, neither the claims nor the specification even restricts the unit identifiers to sequences comprising natural nucleotides. *Id.* at p. 11, ll. 30-35; Ex. 1007 ¶142.

**B. Insufficient Examples in the Priority Applications**

The priority applications provide only a few examples limited to a single type of polymer: *peptide*-oligonucleotide conjugates. Ex. 1004 at p. 61, ll. 5-29; Ex. 1007 ¶143. But an “adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.” *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008) (emphasis added). Moreover, species that are “all of the similar type,” as in the ’596 patent, do not “do not qualitatively represent other types of [species] encompassed by the genus.” *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-01 (Fed. Cir. 2014). Here, the claims cover many other types of polymers beyond peptides, such as oligosaccharides and lipids, without providing any examples showing how units in these polymers could be identified using corresponding unit identifier nucleotide sequences.

Moreover, none of the examples (actual or prophetic) of *peptide*-oligonucleotide bifunctional molecules fall within the claims of the ’596 patent.
The constructs described in the examples all have fewer than four amino acids, but the claims require at least four chemical units in polymer A and at least four corresponding unit identifiers in oligonucleotide C. Ex. 1004 at p. 61, ll. 13-16 and 24-27. The priority applications do not even make clear which peptides were actually attached to oligonucleotides because they mix present and past tense verbs. *Id.* at p. 52, l. 19 – p. 61, l. 34; Ex. 1007 ¶144. And no guidance at all is provided on the structure or construction of any other polymer (such as an oligosaccharide or lipid) encompassed by the claims. Ex. 1007 ¶144.

Although the priority applications suggest selecting from a laundry list of known polymers, they provide no further examples or information, and encompass any polymer comprising chemical units that could be identified by corresponding unit identifier nucleotide sequences. Ex. 1004 at p. 8, ll. 25-31. Listing known polymers types is no substitute for a precise description of representative examples of each type of polymer. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) (“a generic statement . . . without more, is not an adequate written description of the genus”).

Likewise, the priority applications provide almost no details of the oligonucleotide sequences or identifier strategies to use for any given polymer type. Ex. 1007 ¶140. Instead, the claims encompass any oligonucleotide having unit identifier sequences that *function* to identify corresponding chemical units in
the attached polymer. *Lilly*, 119 F.3d at 1568 (“A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.”). The priority applications only exemplify two unit identifier nucleotide sequences, all in the context of polypeptide-oligonucleotide molecules. Ex. 1004 at p. 59, ll. 32-33. No examples are provided of unit identifier sequences for any other types of polymers encompassed by the claims. Ex. 1007 ¶143.

The priority applications also provide only a single exemplary linker molecule for linking polypeptides and oligonucleotides. Ex. 1004 at p. 53, ll. 7-11. They do not explain how to link other polymers (like oligosaccharides and lipids) to oligonucleotides. This further compounds the number of unguided permutations embraced by the claims. Ex. 1007 ¶145.

The skilled artisan would not consider these few, limited examples of polypeptide-oligonucleotide conjugates adequate to represent the numerous polymers and oligonucleotide identifier sequences encompassed by the claimed bifunctional molecules. *Id.* at ¶146. Thus, the claims represent a mere “wish” or “research plan” to capture any future development of suitable bifunctional molecules, rather than an adequate written description. *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004); *AbbVie*, 759 F.3d at 1300.
C. No Guidance on Structural Features Common to All Members of the Claimed Genus

Not only do the priority applications fail to provide sufficient representative examples, they also fail to identify any common structural features that would allow the skilled artisan to visualize the members of the claimed genus. The claims of the ’596 patent recite a formula A—B—C, but this formula encompasses open-ended categories of polymers, linkers, and oligonucleotide identifiers. Ex. 1007 ¶147. While the priority applications recite a generic list of known polymer types (Ex. 1004 at p. 8, ll. 25-31), they provide no guidance on how to incorporate polymers other than polypeptides into bifunctional molecules or even what those alternate polymers would look like. Ex. 1007 ¶147.

The polymers encompassed by the claims would include a diverse repertoire of monomers, each with different chemical structures, properties, and steric sizes. Id. However, the priority applications fail to describe any structural features, suitable reagents, or reaction conditions for making polymers other than polypeptides. Nor do the applications otherwise show that those bifunctional molecules could have been synthesized in the early 1990s. Chiron, 363 F.3d at 1255 (no written description support for chimeric antibodies where technology to make such antibodies did not yet exist).

Given the early state of synthetic chemistry for many of the polymers encompassed by the claims, the skilled artisan would struggle to visualize, let
alone synthesize, the structures of many of those polymers, and then further associate those structures with suitable identifier oligonucleotides selected from the tremendous repertoire of potential identifier oligonucleotides encompassed by the claims. Ex. 1007 ¶148. The skilled artisan would need to rely on undisclosed (and at the time, highly limited) knowledge to determine the nature of the polymer, the oligonucleotide identifier strategy, and how to implement compatible chemistries to operatively link the components. *Id.*

Aside from certain polypeptides and oligonucleotides, the art in the early 1990s was at a nascent state for the solid-phase synthesis of many types of polymers. *Id.* at ¶¶148-149; Ex. 1036 at p. 10704, col. 2; Ex. 1037 at p. 6. It was challenging just to synthesize the polymers themselves, without even attempting to add the oligonucleotide-compatible chemistry needed to make the claimed bifunctional molecules. Ex. 1007 ¶149; Ex. 1038 at p. 1399, col. 3. Structures and suitable chemistries for synthesizing polymers such as lipids and oligosaccharides, and then linking them to suitable oligonucleotide identifier units, were not generally available until at least the late 1990s. Ex. 1007 ¶149; Ex. 1039 at p. 162, col. 1.

Not only do the priority applications provide limited guidance on the polymers, they also fail to provide an adequate description of how to select suitable identifier oligonucleotide sequences that identify each polymer type, simply
instructing the skilled artisan to select functional identifier sequences. Ex. 1007 ¶¶ 150 and 157. Claiming all oligonucleotides, however, that “achieve a result without defining what means will do so is not in compliance with the description requirement.” *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

Indeed, even for polypeptides, the priority applications provide only limited examples of sequences identifying two amino acids using two hexanucleotides. Ex. 1007 ¶ 151; Ex. 1004 at p. 59, ll. 32-33. The applications do not describe suitable unit identifier sequences for any of the other 18 natural amino acids or any modified or non-natural amino acids encompassed by the claims. Ex. 1001 at 43:26-28. The claims are not limited to the triplet codon system. Ex. 1004 at p. 13, ll. 4-8.

To visualize just a fraction of the claimed subject matter would thus require considerable ingenuity. Taking oligosaccharide-oligonucleotide bifunctional molecules as an example, Dr. Stoltz explains that the skilled artisan would first have to envision the structure of each of the many different oligosaccharides encompassed by the claims without any detailed guidance from the priority applications. Ex. 1007 ¶ 152. Oligosaccharides are complex molecules having higher order structures, and envisioning their structures would involve at least selecting the desired monosaccharides, the appropriate glycosidic bonds between each monomer, and the stereochemistry of the linked monosaccharides. *Id.* at
¶¶152-53; Ex. 1040 at pp. 228-29. This would have been nearly impossible in the early 1990s. Ex. 1007 ¶154. Even in 1996, or as late as 2001, synthesizing oligosaccharides and determining their structures was “extremely difficult.” Ex. 1041 at p. 1520; Ex. 1042 at p. 1523, col. 1.

Even assuming that the skilled artisan could envision the desired oligosaccharide, one would also need to design an appropriate oligonucleotide identifier system. Ex. 1007 ¶155. This system would need to assign a distinct unit identifier sequence for each type of monosaccharide, as well as provide a way to identify the linkages between monosaccharides and the stereochemistry embedded in the structure of the oligosaccharide. Id. But no guidance is provided in the priority applications, and indeed some of the reaction conditions described in those applications for polymer synthesis are incompatible with certain nucleotides that might be used in the identifier oligonucleotide. Id. at ¶156; Ex. 1004 at p. 57, ll. 28-33; Ex. 1009 at p. 23, ll. 30-31. Moreover, the applications do not describe reaction conditions for any other polymer type besides polypeptides. Ex. 1007 ¶156.

The priority applications thus leave it entirely to the skilled artisan’s imagination how to select suitable nucleotide identifiers compatible with a chosen polymer, requiring unguided decisions for at least the following elements of the identifier oligonucleotide:
a. The length of the unit identifier sequences;

b. The nucleotide bases; and

c. The unit identifier sequences that identify each distinct monosaccharide, as well as their appropriate linkages and stereochemistry that:

   i. are “easily distinguishable” and do not “differ by only a frame shift” (Ex. 1004 at p. 12, ll. 11-18);

   ii. are not prone to sources of misreading such as “mismatch in DNA hybridization” or “transcription errors during a primer extension reaction” (id. at p. 12, ll. 19-25); and

   iii. do not “occur in another unrelated combination by chance or otherwise during the manipulations of a bifunctional library” (id. at p. 12, ll. 2-8). Ex. 1007 ¶157.

Although the priority applications highlight these pitfalls for selecting suitable oligonucleotide identifier units and designing identifier systems, they fail to describe specific solutions, particularly in the context of non-polypeptide polymers. Id. Thus, a person of ordinary skill would have to determine for themselves how to select appropriate identifier oligonucleotide sequences. And each polymer type encompassed by the claims would raise similar technical challenges, which the priority applications fail to address. Id. at ¶158.
The structure of a bifunctional molecule could also be influenced by the reaction conditions, reagents, and protecting group strategies. *Id.* at ¶159. Assembling many of the claimed polymers would require uniquely-tailored chemistries and compatible linker molecules, each of which would influence the resulting structures. *Id.* The priority applications, however, provide no guidance on the chemical units in any of these polymers other than polypeptides, and no information on the structure or synthesis of polymers containing those chemical units. For instance, the applications provide no guidance on the oligosaccharide-oligonucleotide bifunctional molecules discussed above. *Id.* at ¶¶159-161. And even for peptides, the different options for subunits and identifier nucleotides leave open too many synthetic strategies and structural permutations for one of ordinary skill to envision all the resulting bifunctional molecules. *Id.* at ¶159.

The library claims compound these problems, as they potentially encompass millions of bifunctional molecules. Ex. 1004 at p. 18, ll. 7-12; Ex. 1007 ¶162. Since the named inventors did not possess the full scope of a single claimed bifunctional molecule, they certainly did not possess *libraries* of such molecules.

A skilled artisan in the early 1990s would not consider this extremely limited disclosure in the ’596 priority applications sufficient guidance for the claimed genus of bifunctional molecules. *Id.* at ¶163.
The ’596 patent is therefore not entitled to claim benefit to the earlier-filed priority applications. *Dower* and *Nelson* thus serve as prior art under § 102(b).

**X. U.S. PATENT NO. 5,573,905 ANTICIPATES CLAIMS 1-6 AND 10-17**

As the ’596 patent is not entitled to the benefit of any earlier-filed application, claims 1-6 and 10-17 are anticipated under 35 U.S.C. § 102(b) by Scripps’s U.S. Patent No. 5,573,905. The ’905 patent published more than a year before the filing of the application that issued as the ’596 patent.

The ’905 patent shares an essentially identical specification with the ’596 patent. As such, it provides all the elements of a bifunctional molecule having the formula A—B—C, where A is a polymer comprising a linear series of chemical units, B is a linker, and C is an oligonucleotide where each unit in the oligonucleotide identifies a corresponding chemical unit in polymer A. Ex. 1003 at 3:16-20, 4:29-36, and 5:49-58.

The ’905 patent provides an example of a bifunctional molecule represented by the formula “X₄X₃X₂X₁-B-Z₁Z₂Z₃Z₄.” *Id.* at 5:59-63. It states that “the sequence of oligonucleotides Z₁, Z₂, Z₃ and Z₄ identifies the structure of chemical units X₁, X₂, X₃ and X₄, respectively,” resulting in “a correspondence in the identifier sequence between a chemical unit X at position n and the unit identifier oligonucleotide Z at position n.” *Id.* at 5:64-67 and 6:1. This example includes
four chemical units and four unit identifiers, consistent with the requirement in claim 1 of the ’596 patent that “a is an integer from 4 to 50.”

The ’905 patent discusses the synthesis of bifunctional molecules through alternating parallel synthesis. *Id.* at 2:45-60. It provides an example of a polypeptide attached to an oligonucleotide identifier through a phosphoramidite linker joined to a Teflon bead that is cleaved off after synthesis. *Id.* at 24:42 – 27:24.

Dr. Stoltz provides a detailed chart mapping each element of claims 1-6 and 10-17 to the relevant discussion in the ’905 patent. Ex. 1007 ¶¶164-66.

Accordingly, the ’905 patent describes each and every element of the ’596 claims. By describing a species of bifunctional molecule (a peptide-oligonucleotide conjugate) within the scope of every challenged claim, the ’905 patent anticipates the challenged claims under 35 U.S.C. § 102(b). *Eli Lilly & Co. v. Barr Laboratories, Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001).
XI. CONCLUSION

Petitioner respectfully requests that the Board institute an IPR and cancel claims 1-6 and 10-17 of the ’596 patent.

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on August 15, 2016, a copy of the foregoing Petition for Inter Partes review of U.S. Patent No. 6,060,596, along with all exhibits and other supporting documents, was served by FedEx overnight delivery on the correspondence address of record indicated in the Patent Office’s public PAIR system for U.S. Patent No. 6,060,596:

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CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing Petition for *Inter Partes* Review contains 13,934 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

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