

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

10X GENOMICS, INC. and THE BOARD OF)	
TRUSTEES OF THE LELAND STANFORD)	
JUNIOR UNIVERSITY)	
)	
Plaintiffs,)	
)	
v.)	
)	C.A. No. 22-1117 (JHS)
PARSE BIOSCIENCES, INC.,)	
)	HIGHLY CONFIDENTIAL – SUBJECT
Defendant.)	TO PROTECTIVE ORDER

REBUTTAL REPORT OF JOHN QUACKENBUSH, Ph.D.

June 14, 2024

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informed that even if a patent is directed to an abstract idea, an invention concept can be found in the non-conventional and non-generic arrangement of know and conventional pieces.

VI. The Asserted Patents

A. The Brenner Patents

1. Additional Overview of the Brenner Patents

33. I provided an overview of the Brenner Patents in my Opening Report and incorporate those opinions here. I understand that Dr. Mikawa and Dr. Osborne were deposed after my Opening Report was submitted and I have reviewed the transcripts of those depositions as well as Dr. Cooper's characterizations of the Brenner Patents, including in his supplemental report, for example, in the section entitled "General Comments Regarding the Testimony of Drs. Mikawa and Osborne," (Cooper Supplemental Report at Section II.A). I disagree with Dr. Cooper's characterization of the Brenner Patents and with Dr. Cooper's characterization of Dr. Mikawa and Dr. Osborne's testimony. For example, I disagree that Drs. Mikawa and Osborne thought their invention was limited to the reflex method. As identified below, both inventors provided testimony to the contrary, and Dr. Cooper identifies no testimony where either inventor agreed the invention did not include additional related concepts. I also disagree with Dr. Cooper's opinions in Section II.C, as I have been informed it is not required for inventors to actually perform the claimed method (i.e., actually reduce it to practice), in order to claim it, as long as they had a firm and definite idea of the invention and adequately described and enabled it.

34. Professor Sydney Brenner is one of the named inventors of the Brenner Patents and was a pioneer in the fields of genetics and developmental biology. Professor Brenner grew up in a struggling family in South Africa. At a young age, he excelled at school and attended

medical school at the age of 15. His goal of practicing medicine was hindered by his age, so he instead pursued a Ph.D. at Oxford University. There, he met future Nobel Laureates Drs. Francis Crick and James Watson, who discovered the double-helix structure of DNA, and this shaped Professor Brenner's path to pursue genetics research. *See generally* 10X_PARSE_000044344.

35. Professor Brenner has made many contributions to the field of genetics. *See* Osborne Dep. Tr. at 187:4-11 (“[T]here were also other parts of his prior research that people considered were worthy of a Nobel Laureate, including decoding, for example, how cells decode mRNA, understanding all of that.”). For example, he not only helped discover mRNA, but he also established the codon table through his discovery that the genetic code comprises of a series of three base pair codons that code for specific amino acids. 10X_PARSE_000933135; Osborne Dep. Tr. at 187:4-11; Mikawa Dep. Tr. at 150:25-151:12. This discovery, along with some related insights, is now known today as a part of “the central dogma of molecular biology.”

36. In 2002, he received the Nobel Prize in Physiology of Medicine for his work in the discovery of programmed cell death, which is fundamental to understanding how genes regulate tissue and organ development, using the nematode worm *Caenorhabditis elegans* as a model organism. His work also established *C. elegans*, alongside the likes of the standard laboratory mice, as an important model organism and tool for scientific research. *See* 10X_PARSE_000044335; Mikawa Dep. Tr. at 151:13-18.

37. Also in 2002, Professor Brenner and his colleagues sequenced and published the genome of pufferfish *Takifugu rubripes*. This was the second vertebrate genome to be sequenced, the first being the human genome, which was published in 2001.

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38. Professor Brenner was one of the leading minds in molecular biology, including as of 2009, and founded Population Genetics Technology (“PGT”) to commercialize his inventions. Mikawa Dep. Tr. at 157:12-19 (Q: “. . . in 2009 was there anyone in the world who was more skilled in DNA labeling than Dr. Brenner?” A: “I would say Dr. Brenner is the best”); Osborne Dep. Tr. at 24:13-25:21 (“[T]o begin with, it was around the development and commercialization of some patents that Sydney Brenner had put in place. Obviously we continued to add to that IP over time. That was around tagging and pooling genomes”); 10X_PARSE_000933133. PGT did work on molecular counting and may have had the first granted patent on UMIs. Osborne Dep. Tr. at 34:20-36:22 (“I believe we had the first granted patent on a technology called – well it’s now called a UMI”).

39. He brought with him leading figures in the field of sequencing and genomics to make additional breakthroughs, including Sam Eletr. Mikawa Dep. Tr. at 153:16-154:16 (Sam Eletr was involved with pioneering and commercializing Sanger sequencing). One set of problems Professor Brenner sought to overcome were limitations related to next generation sequencing (“NGS”) technology. Mikawa Dep. Tr. at 155:10-156:13; Osborne Dep. Tr. at 24:7-12 (the business of PGT when he joined was “to interrogate multiple genomes through next generation sequencing”); 32:10-19 (“[A]ll of our efforts were based around library preparation for next generation sequencing.”). Professor Brenner was intimately familiar with NGS. Indeed, he was the Founder of Lynx, a company that discovered and developed the foundational sequencing technology used in NGS platforms. His many contributions to UMIs and sequencing helped lead to the inventions described in the Brenner Patents, some of which are now utilized by 10x Genomics as a part of their Chromium platform. Mikawa Dep. Tr. at 161:20-162:6; Osborne Dep. Tr. at 33:3-11 (“I would say that some of the technologies that we

developed can be applied in that arena” of single cell genomics). Dr. Osborne routinely used two tags, a UMI and a sample tag, while at PGT. Osborne Dep. Tr. at 141:9-23; 192:21-195:2.

40. The Brenner Patents describe a method of “moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide,” i.e., the “reflex method.” ’981 Patent at 1:51-56. The Brenner Patents also disclose that in certain embodiments, the method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID).” *Id.* at 1:56-59; Mikawa Dep. Tr. at 53:7-55:2 (testifying that the “main point as summarized in [the] abstract” was “explaining what the reflex is and with, you know, with MID” and that “this is just like a toy without MID”); 85:14-18 (“The invention is a reflex mechanism, and together with MID.”); Osborne Dep. Tr. at 41:17-42:14 (“one of the limitations of the technology that we were developing at the time was that we were using restriction enzymes to fragment genomes... as I described earlier, there were limitations at the time in terms of the number of bases that one was able to sequence on any given fragment...”).

41. This reflex method overcame significant issues with NGS technology at the time, including NGS’s inability to read fragments beyond a particular length, typically up to 400 base pairs. *See id.* at 16:62-17:35; Mikawa Dep. Tr. at 34:3-11 (“in those days the next generation sequence read length is pretty much restricted. You cannot read a long sequencing using in just maybe 300, up to 300, or 400 maybe.”). As part of the reflex method invention, Professor Brenner and the other inventors invented an approach that permitted the user to, after fragmentation of the nucleic acids and sequencing of the fragments, link the sequenced data to the polynucleotide and source of origin, including the cell from which a nucleic acid originated, using a MID with two tags. *See* Mikawa Dep. Tr. at 53:7-55:2 (testifying that “You can use

MID to locate where your DNA is coming from, and the MID tells you where it's coming from... But using this MID you know where these molecules are coming from, so you can exactly tell what this set of the DNA fragment is coming from...”), 165:24-166:15 (“MID... differentiate[s] the source of the materials” in the reflex technology, and the “Source may be a single cell”); Osborne Dep. Tr. at 29:18-30:11 (performed linkage analysis related to haplotyping, which are part of the Brenner Patents); '981 Patent at Fig. 5. As Dr. Mikawa testified, the first time he heard of the concept of tagging polynucleotides with two different tags was at Professor Brenner's house. Mikawa Dep. Tr. at 86:16-23.

42. The specification confirms the MID is inventive and was a key aspect to the reflex method. '981 Patent at Fig. 5; Osborne Dep. Tr. at 50:16-51:4 (“the definition section...provides a mechanism to understand the context of specific words that are used through the rest of the patent application.”), 192:9-14 (testifying the methods of tagging and use of MIDs were applicable to single cell sequencing). Figure 5 contrasts the prior art methods of analysis against the approach of the disclosed inventions, which uses MIDs and the reflex method, for two nucleic acids originating from two different sources, such as two individual cells. *Id.* at 1:38-44; 23:18-32; Mikawa Dep. Tr. at 167:17-169:23, 177:7-14 (describing Figure 5 and stating “you can say DNA 1 and DNA 2 are coming from a single cell 1 and 2”); Osborne Dep. Tr. at 195:3-197:18 (describing Figure 5). On the left side of Figure 5, using prior art methods, the two nucleic acids are fragmented, which is required for NGS and then sequenced. '981 Patent at Fig. 5. While the polymorphisms from the two nucleic acids are identified by this approach, there is no way to identify which polymorphism came from which nucleic acid, and whether a single nucleic acid had 1, 2, or 3 of the polymorphisms identified. '981 Patent at Fig. 5. The inventions solved this linkage issue, as demonstrated by the right-hand side of Figure 5.

By tagging the nucleic acids with a MID and then carrying the MID across each nucleic acid fragment using the reflex method, the sequenced fragments can be linked to the nucleic acid from which it was derived. While Figure 5 is a simplified depiction, persons of skill reviewing Figure 5 in the context of the disclosures would understand that the MID can include a tag that traces the nucleic acids to their cell of origin, and include a second tag to distinguish among the nucleic acids from that same cell. *See id.*; *id.* at 23:18-32; Osborne Dep. Tr. at 48:12-25 (“MID – and I would need to read the definition section of the patent to be sure of what the potential of an MID was in this context.”).

43. Dr. Cooper first asserts that “the specification of the Asserted Brenner Patents describes a method not covered by their claims—a technique called the ‘reflex method’ that relates to the processes for rearranging sequences of interest in a polynucleotide.” Cooper Report ¶52. I agree that the reflex method is one of the inventions disclosed in the Brenner Patents, but it is not the only invention disclosed in the Brenner Patents. Indeed, the “reflex method” relies on the use of a “MID.” Osborne Dep. Tr. at 63:20-64:13 (“what we thought of as the reflex technology, isn’t just necessarily one technology, it’s an umbrella term for multiple technologies...”). For example, Figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, and 12 all depict tagging polynucleotides with a “MID.” The Brenner Patents disclose that “having each nucleic acid tagged with a unique MID allows analysis of the sequence of each nucleic acid using the reflex sequence methods described herein.” ’981 Patent at 15:36-50.

44. The Brenner Patents disclose that in certain embodiments, a “tag or combination of tags associated with a polynucleotide whose identify (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample. In certain embodiments, the MID on a polynucleotide is used to identify the source from which the polynucleotide is derived.” ’981

Patent at 6:33-38. The specification further discloses that a nucleic acid sample “may be a pool of polynucleotides derived from different sources, (e.g., polynucleotides derived from different individuals, different tissues or cells, or polynucleotides isolated at different time points), where the polynucleotides from each different sources are tagged with a unique MID” and that the MID may be “employed to uniquely tag each individual polynucleotide in a sample.” ’981

Patent at 6:38-47. Thus, persons of skill would have understood that the “MIDs” used in the reflex method could incorporate these various features, including (1) a tag that “identif[ies] the source from which the polynucleotide is derived” and (2) a tag that “differentiate[s] polynucleotides in a sample.” ’981 Patent at 6:33-47. As such, the claimed inventions of the asserted Brenner Patents do incorporate an invention that can be used with the “reflex method,” but is a distinct invention disclosed in the Brenner Patents that is separately claimed.

45. Uses of these MIDs are also disclosed. The Brenner Patents disclose that the “[i]dentification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived . . .).” ’981 Patent at 6:47-51. Thus, not only can you track each nucleic acid by tagging each with a unique MID (’981 Patent at 15:36-50), but you can use those unique MIDs to analyze the makeup the polynucleotides at a granular level, including by counting various nucleic acids to determine the number of each present in the original sample. Persons of skill would have understood this is particularly useful in analyzing the makeup of an individual’s genome, including heterogeneity across a sample from a patient, or for analyzing gene expression, where the number of mRNA transcripts in a sample can reveal which genes are being expressed, how much of each gene is getting expressed, and by which individual cells.

46. Dr. Cooper next asserts that the “specification of the Brenner Patents reflects that the tagging method is not the invention but a prior art technique.” Cooper Report ¶53. I disagree with this characterization. The specification states that the use of MIDs for certain uses were known and points to particular disclosures of the use of a MID. ’981 Patent at 6:56-64, 15:20-29. This statement does not relate to the use of two tag sequences for the use of single cell analysis, which is the claimed invention. And as explained by Dr. Mikawa, Figure 5, which is indisputably part of the “invention,” discloses analyzing nucleic acids from different sources, and those sources can be different single cells. *See* Mikawa Dep. Tr. at 166:10-15; 167:17-169:23.

47. As discussed in greater detail below, the applications in the Brenner Patent family preceding the asserted Brenner Patents included limitations requiring the use of the MID, which would be understood to encompass the dual tagging later claimed in the asserted Brenner Patents.

2. Prosecution History of the Brenner Patents

48. The Asserted Brenner Patents are continuations in a family that was extensively examined during prosecution. I have reviewed these file histories and summarize some key interactions that confirm the USPTO thoroughly considered the art and arguments Dr. Cooper presents now for invalidity.

(a) The Patent Office Confirms That the Use of the Claimed Tags Was Not Anticipated or Rendered Obvious by Prior Art Disclosing Molecular Tags

49. During prosecution of App. No. 13/387,343 (“’343 application”)—the first non-provisional application in the ’981 Patent’s family, which, similar to the ’981 Patent, claimed the use of a MID “whose identity can be used to differentiate polynucleotides in the sample”—

Claim 25. The method of claim 1, wherein said plurality of tagged polynucleotides are pooled with tagged polynucleotides from other single cells of said plurality of cells prior to the amplifying of step (c).

305. For the reasons discussed above with claim 1, it is my opinion that Linnarsson in view of McCloskey does not render obvious claim 25 of the '013 Patent.

* * *

306. Taken together, it is my opinion that Linnarsson in view of McCloskey does not render obvious claim 25 of the '013 Patent.

Claim 26. The method of claim 1, wherein said plurality of amplified polynucleotides are pooled with amplified polynucleotides from other single cells of said plurality of cells prior to the sequencing of step (d).

307. Claim 26 of the '013 Patent requires that said plurality of amplified polynucleotides are pooled with amplified polynucleotides from other single cells of said plurality of cells prior to the sequencing of step (d) of claim 1. For the reasons discussed above in claim 1, I disagree with Dr. Cooper's analysis in claim 26.

* * *

308. Taken together, it is my opinion that Linnarsson in view of McCloskey does not render obvious claim 26 of the '013 Patent.

C. The Asserted Claims of the Brenner Patents Are Adequately Described in the Specification

309. Dr. Cooper opines that the Asserted Claims of the Brenner Patents are “invalid under 35 U.S.C. § 112 ¶ 1 for lack of adequate written description of the alleged invention.” Cooper Report ¶474. To support his opinion, Dr. Cooper notes that “[t]he inventions as a whole, as recited in the claims, are not described anywhere in the specification,” the specification lacks any working examples and a POSA” would have been unable to fill any gaps

in the disclosure with general knowledge and skill in the art.” *Id.* I disagree for the reasons I discuss below and generally in my report.

1. Support for Single Cells

310. Dr. Cooper opines that the support for single cells is “a single, indirect passage in the shared specification of the Asserted Brenner Patents.” Cooper Report ¶ 476. Dr. Cooper further opines that Figure 5’s reference to “[identification] of nucleic acids polymorphisms in homologous nucleic acids in a sample (e.g., the same region derived from a chromosomal pair of diploid cell or viral genomes/transcripts) . . . fails to describe a single cell.” *Id.* I disagree.

311. As I have discussed above, the Brenner Patents disclose a number of discrete inventions and the Reflex method is one such invention and analysis of single cell is another one. Dr. Copper limits his reading of the Brenner specification to the Reflex method. Dr. Cooper’s narrow interpretation does not comport with the actual contents of the Brenner specification, which describes many technical details, including both the Reflex method and the claimed inventions, which are related to the innovations of the Reflex method. The Brenner specification states that “the present invention removes the limitations imposed by current sequencing technologies, as well as being useful in a number of other nucleic acid analyses.” ’981 Patent at 1:45-47. This statement in the Background section of the specification supports my opinion that the Brenner specification’s description of MIDs is not limited to the use of MIDs in the Reflex method. Further, while Figure 5 is a simplified depiction, a skilled artisan reviewing Figure 5 in the context of the disclosures in the Brenner specifications would understand that, as it is in the case of analyzing single cells, the MID can include a tag that traces the nucleic acids to their cell of origin, and include a second tag to distinguish among the

nucleic acids from that same cell. Moreover, there is additional support for using the inventions to analyze the nucleic acids from single cells.

- “For example, *a nucleic acid sample may be a pool of polynucleotides derived from different sources*, (e.g., polynucleotides derived from different individuals, *different* tissues or *cells*, or polynucleotides isolated at different times points), *where the polynucleotides from each different source are tagged with a unique MID.*” ’981 Patent at 6:33-7:22;
- “In certain embodiments, the nucleic acid sample being analyzed is derived from a single source (e.g., a single organism, virus, tissue, cell, subject, etc.), *whereas in other embodiments, the nuclei acid sample is a pool of nucleic acids extracted from a plurality of sources* (e.g., a pool of nucleic acids from a plurality of organisms, tissues, *cells*, subjects, etc.), *whereby ‘plurality’ is meant two or more.* ’981 Patent at 14:61-15:6;
- “In certain embodiments, *nucleic acid fragments that are to be pooled with nucleic acid fragments derived from a plurality of sources* (e.g., *a plurality of* organisms, tissues, *cells*, subjects, etc.), whereby “plurality” is meant two or more. *In such embodiments, the nucleic acids derived from each source includes a multiplex identifier (MID) such that the source from which the each tagged nucleic acid fragment was derived can be determined. In such embodiments, each nucleic acid sample source is correlated with a unique MID, where by unique MID is meant that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID.*” ’981 Patent at 15:7-15:35;

- “In certain embodiments, *each individual polynucleotide* (e.g., double-stranded or single-stranded, as appropriate to the methodological details employed) *in a sample to be analyzed is tagged with a unique MID so that the fate of each polynucleotide can be tracked in subsequent processes (where, as noted above, unique MID is meant to indicate that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID)*. For example (and as described below), having each nucleic acid tagged with a unique MID allows analysis of the sequence of each individual nucleic acid using the reflex sequence methods described herein. This allows the linkage of sequence information for large nucleic acid fragments that cannot be sequenced in a single sequencing run.” ’981 Patent at 15:36-15:50;

In my opinion, these disclosures, read in the context of the specification as a whole and the accompanying Figures, each of which use a “MID,” disclose and support analyzing nucleic acids from single cells.

312. Dr. Cooper also opines that there is no description of tagging the polynucleotides of single cells and distinguishing the polynucleotides of one single cell from those of another single cell or from those of the same cell.” Cooper Report ¶478. I disagree. The Brenner specification defines MID as a “tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag sequence) can be used to differentiate polynucleotides in a sample.” ’981 Patent at 6:33-36.

313. Further, in describing the cell-specific barcode, the Brenner specification explains that an MID can be used to “provide[] a correlation between a polynucleotide and its source” where the sample may comprise a pool of polynucleotides sourced from different cells.

Id. at 6:44-45. Indeed, the Brenner specification states that a nucleic acid sample “may be a pool of polynucleotides derived from different sources, (e.g., polynucleotides derived from different individuals, different tissues or cells, or polynucleotides isolated at different times points), where the polynucleotides from each different sources are tagged with a unique MID.”

Id. at 6:38-44.

314. In describing the molecule-specific barcode, the Brenner specification is also clear. It explains that MIDs may be “employed to uniquely tag each individual polynucleotide in a sample.” *Id.* at 6:45-47. Specifically, the specification states, “[i]dentification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived . . .).” *Id.* at 6:47-51.

315. Dr. Cooper also ignored the extent to which the Brenner specification leverages and extends earlier work by Brenner and his colleagues that provides the background and foundation for the claimed invention of analyzing single cells with MIDs and their description in the Brenner specification. The Brenner specification incorporates by reference other Brenner Patents that further describe the use of such tags. For example, in its description of the molecule-specific barcode, the Brenner specification incorporates U.S. Patent No. 7,537,897. ’981 Patent at 6:51-52. That patent, titled “Molecular Counting” describes in detail the function of a molecule-specific barcode. *See, e.g.*, U.S. Patent No. 7,537,897 at 1:64-2:4 (“The invention provides a method of counting molecules in a sample by converting the problem of counting molecules into one of counting sequences of oligonucleotide tags. molecules to be counted in a sample are each labeled with a unique oligonucleotide tag. Such tags are then amplified and

identified. The number of different oligonucleotide tags detected, or counted, is equal to the number of molecules in the sample.”).

316. The Brenner specification also incorporates U.S. Patent No. 7,544, 473 titled “Nucleic Acid Analysis Using Sequence Tokens” and U.S. Patent No. 7,393,665 titled “Methods and Compositions for Tagging and Identifying Polynucleotides” specifically “for their description of nucleic acid tags and their use in identifying polynucleotides.” ’981 Patent at 6:56-63. For example, U.S. Patent No. 7,544,473 provides methods and compositions for “tagging nucleic acid sequence fragments, e.g., a set of nucleic acid sequence fragments from a single genome, with one or more unique members of a collection of oligonucleotide tags, or sequence tokens, which, in turn, can be identified using a variety of readout platforms.” U.S. Patent No. 7,544,473 at 1:57-62. *See also id.* at 1:62-64 (“As a general rule, a given sequence token is used once and only once in any tag sequence.”). U.S. Patent No. 7,393,665 similarly describes methods of employing unique tags to polynucleotides by attaching short tags, or “words,” to successive subsets of a sample. U.S. Patent No. 7,393,665 at Abstract (“Words, or subunits, of oligonucleotide tags index submixtures in successively more complex sets of submixtures (referred to herein as ‘tiers’ of submixtures) that a polynucleotide goes through while successive words are added to a growing tag.”).

317. That the Brenner specification also describes the Reflex method in detail, and provides examples where the Reflex method is performed in conjunction with the use of MIDs does not diminish the fact that MIDs and the process by which they are used for single-cell sequencing analysis is adequately described.

318. As such, it is my opinion that there is adequate written description for analyzing polynucleotides from different single cells in the Brenner Patents.

2. Support for Methods of Tagging with Groups of Cells

319. Dr. Cooper opines that there is no adequate support for “the introduction of cell-identifying tags to a plurality of cell.” Cooper Report ¶ 480. I disagree. As I discuss above, the Brenner Patents also incorporate other patents that describe how to introduce tags.

320. Further, as Dr. Cooper admits elsewhere in his report, a skilled artisan would have known how to introduce tags to a group of cells at the time. Dr. Cooper, however, makes conclusory assertions that several claims lack written description support without considering the knowledge that a POSA would have at the time. As stated earlier, a person of ordinary skill in the art with respect to the asserted patents here would have a Ph. D. in molecular biology, molecular genetics, biochemistry, physics, mechanical engineering, or a related discipline, with two years of academic, research, or industry experience in the field of genomic or transcriptome sequencing, microfluidic technology, or microsystems for chemical and biochemical analysis, and would also be able to consult a specialist for certain specialized knowledge, as is common in the field. I note that Dr. Cooper does not disagree with my definition of a person of skill so I disagree with Dr. Cooper’s conclusions that certain claims lack written description support to the extent they fail to properly account for the knowledge of a person of skill.

321. Further, the Brenner specification and its incorporated references including the provisional application describes generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides comprising (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and (ii) a multiplex identifier (MID) sequence comprising: I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and II. a second tag sequence distinguishing the

sample polynucleotide from other sample polynucleotides derived from the same single cell. For example, the provisional application describes an MID that comprises a sequence to identify the cell of origin: “[i]n certain embodiments, nucleic acid fragments that are to be pooled with nucleic acid fragments derived from a plurality of sources (e.g., a plurality of organisms, tissues, cells, subjects, etc.), where by ‘plurality’ is meant two or more. In such embodiments, the nucleic acids derived from each source includes a multiplex identifier (MID) such that the source from which the each tagged nucleic acid fragment was derived can be determined. In such embodiments, each nucleic acid sample source is correlated with a unique MID, where by unique MID is meant that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID.” Provisional at 19 (emphasis added).

322. The provisional further clarifies that the MID can comprise a sequence that identifies the polynucleotide of origin: “[i]n certain embodiments; each individual polynucleotide (e.g., double-stranded or single-stranded, as appropriate to the methodological details employed) in a sample to be analyzed is tagged with a unique MID so that the fate of each polynucleotide can be tracked in downstream processes (where, as noted above, unique MID is meant to indicate that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID).” Provisional at 20 (emphasis added).

323. The provisional also clarifies that the MID can comprise two tags and be used to uniquely tag and track each individual polynucleotide. Provisional at 8 (stating “[i]n certain embodiments; the MID on a nucleic acid is used to identify the source from which a nucleic acid is derived. For example, a nucleic acid sample may be a group of nucleic acids pooled from

different sources, (e.g.; nucleic acids derived from different individuals, different tissues or cells, or nucleic acids isolated at different times points), where the nucleic acids from each different source is tagged with a unique MID. Identification of the MID on a nucleic acid thus allows one to determine from which source the nucleic acid is derived. In other Words, the MID provides a correlation between a nucleic acid and its source. In certain embodiments, MIDs are employed to uniquely tag each individual nucleic acid in a sample.”).

324. Additionally, Dr. Cooper’s opinions are contradictory. Elsewhere he opines that this limitation is rendered obvious by Linnarsson, which discloses tagging a plurality of cells with cell-specific tags. Cooper Report ¶¶200-206. While I disagree with Dr. Cooper’s opinions as it relates to obviousness for the reasons discussed in Section X.B, this disclosure in Linnarsson confirms that POSA knew how to tag a group of cells with a different cell-specific tag. Dr. Cooper does not address Linnarsson, or explain why that approach would not have been within the knowledge of a POSA.

325. As such, it is my opinion that there is adequate written description support of how to introduce a plurality of tags to a group of cells such that the tags can then be used to distinguish the single-cell origin of a polynucleotide.

3. Support for Ligation

326. Dr. Cooper opines that “the specification does not provide any explanation as to how ligation would be used to add a tag to either track the cellular origin or distinguish between polynucleotides.” Cooper Report ¶ 482. I disagree.

327. The provisional application which is incorporated to the Brenner Patents describes how to add tag by ligation. “The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer

technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label”.

328. I again note that Dr. Cooper’s opinions are contradictory, as elsewhere he opines that ligation was a conventional technique within the knowledge of a POSA. Cooper Report ¶¶238. While I disagree with his opinions on obviousness as it relates to the claims that require ligation for the reasons discussed in Sections X.A-B, I generally agree that POSA knew how to add tags via ligation and, in the correct workflow, that this could be a successful approach.

329. As such, it is my opinion that there is adequate written description support to add a tag by ligation to either track the cellular origin or distinguish between polynucleotides.

4. Support for Two Tag Sequences

330. Dr. Cooper opines that “the specification fails to disclose any methods of tagging polynucleotides with two tag sequences within different single cells.” Cooper Report ¶484. Dr. Cooper also opines that “the specification lacks any adequate disclosure of such a second tag” distinguishing between molecules. *Id.* ¶489. I disagree.

331. As I describe above, a skilled artisan reviewing the Figures, including Figure 5, in the context of the disclosures in the Brenner specifications would understand that, as it is in the case of analyzing single cells, the MID can include a tag that traces the nucleic acids to their cell of origin, and include a second tag to distinguish among the nucleic acids from that same cell. Indeed, I note that the definition of “MID” in the Brenner specifications expressly contemplates a “combination of tags” and identifies a tag that identifies the source of origin, including a cell, and a tag that distinguishes among polynucleotides in the sample. As such, there is adequate written description support in the Brenner Patents for two tag sequences.

332. Further, as I describe above, the Brenner specification also incorporates various Brenner patents including the '473 Patent and the '665 Patent. These patents, in general, disclose the use of unique tags to identify the origins of a sample polynucleotide and to distinguish it from other polynucleotides from the same cell. Because the method of adding tags is a routine and conventional method, a skilled artisan would have known how to use different first tag sequences for different single cells.

333. Dr. Cooper opines that “[t]here is one reference in the Definitions section of the specification wherein a MID is defined that references the use of a second tag. Beyond that one reference the specification is silent as to the design of second tags, the use of them, methods for their attachment, or their function (*e.g.*, distinguishing between molecules).” Cooper Report ¶ 491. I disagree that there is only one other reference to a tag that performs the function of the second tag sequence for the reasons discussed above, including because there are multiple disclosures of using a tag to differentiate between the polynucleotides in a sample. *E.g.*, '981 Patent at 15:36-15:50; 22:48-67.

334. I again note that Dr. Cooper's opinions are contradictory, as elsewhere he opines that tagging polynucleotides was within the knowledge of a POSA and that both a cell tag and a UMI were separately known. Cooper Report ¶¶ 200-206, 221-228. While I disagree with his opinions on obviousness as it relates to the claims for the reasons discussed in Sections X.A-B, I generally agree that POSA knew how to tag polynucleotides and POSA would have understood that the inventors were in possession of this invention.

335. As such, it is my opinion that there is adequate written description support for methods of distinguishing polynucleotide molecules using a first and second tag sequence.

5. Support for Counting Nucleic Acids with Two Tags

336. Dr. Cooper opines that “there is no disclosure of counting methods accomplished through a dual tagging scheme as recited in the claims.” Cooper Report ¶ 496. I disagree.

337. Dr. Cooper opines that the Brenner specification does not adequately describe a method of “counting nucleic acids in a sample” because the specification states, [a]ny convenient method for tagging and/or counting individual nucleic acid molecules with unique tags may be employed.” Cooper Report ¶ 495; ’981 Patent at 22:36-47 (incorporating by reference U.S. Patent No. 7,537,897). As that statement itself illustrates, counting nucleic acid molecules was known and could be achieved by “[a]ny convenient method.” For example, the ’897 Patent describes that “[d]igital measurements of polynucleotides have been made, wherein measured amounts are correlated with integral numbers of countable events, e.g. numbers of sequence tags.” ’897 Patent at 1:42-45; *see also* ’897 Patent (“In one form of the invention, oligonucleotide tags are counted by successively sorting them into separate subsets based on the identity of the subunits at different positions within the tags . . .”). ’897 Patent at 2:43-46. Dr. Cooper’s assertion that there is no disclosure of counting methods for a dual tagging scheme does not change my opinion. A POSA at the time of the invention would have known how to count nucleic acid molecules and would understand that the inventors possessed a method of doing so through a dual tagging scheme as recited in the claims.

338. I again note that Dr. Cooper’s opinions are contradictory, as elsewhere he opines that counting tagged polynucleotides was within the knowledge of a POSA and was rendered obvious by various references. Cooper Report ¶¶ 298-301. While I disagree with his opinions on obviousness as it relates to the claims for the reasons discussed in Sections X.A-B, I generally agree that POSA knew how to count and, with the disclosures of the Brenner Patents

teaching how to use dual tagging for single cell analysis, would have been capable of counting these tagged polynucleotides and would have understood the inventors were in possession of this invention.

339. As such, it is my opinion that there is adequate written description support to count nucleic acids with two tags.

6. Support for “a method for multiplexed analysis . . . performing combinatorial tagging”

340. Dr. Cooper opines that “the patent fails to describe any methods for a multiplexed analysis of polynucleotides through a combinatorial tagging approach.” Cooper Report ¶ 502. Dr. Cooper further opines that the patent “does not even describe what such multiplexed analysis is, particularly in the context of single cell analysis.” Cooper Report ¶ 503. I disagree.

341. As an initial matter, contrary to Dr. Cooper’s assertion, “multiplex” is not a novel term for a POSA. A skilled artisan would understand it to mean “analysis of many cells at the same time” and such multiplex analysis at a single cell level became possible with the use of cell-specific tags without losing information at the single cell level. The Brenner Patents further disclose that polynucleotides can be tagged “by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension.” *Id.* at 7:15–22. In addition, as I discuss above, tagging was a routine and conventional method used at the time of the effective filing of the Brenner Patents so that a skilled artisan would have known how to do a multiplex analysis with two different tags through a combinatorial tagging approach where one tag is attached by ligation and the other one is by primer extension.

342. As such, it is my opinion that there is adequate written description support for “a method for multiplexed analysis ... performing combinatorial tagging.”

7. Support for Claimed Ratios of Sample Polynucleotides to Second Tag Sequences

343. Dr. Cooper opines that “the Brenner Patents do not describe methods with [a number of different second tag sequences that is larger than the number of sample polynucleotides] and do not describe how to obtain these ratios of tagging.” Cooper Report ¶ 505. I disagree.

344. As an initial matter, I am not a lawyer, but I have been informed that one can consider cited references to determine what a skilled artisan would understand from the patent disclosures. As I understand it, Brenner et al. has been cited for the proposition that one needs to include a number of distinct MIDS many times greater than the actual number of molecules to be analyzed. It has been explained to me that a skilled artisan would be able to consult this reference to understand the claimed ratios of sample polynucleotides to second tag sequences.

345. Dr. Cooper admits that Brenner et al., Proc. Natl. Acad. Sci USA 2000 97(4): 1665-70 discloses how to achieve the majority of individual nucleic acid molecules being labeled with a unique tag by including many times greater number of MIDs than the actual number of molecules to be analyzed. Further, a skilled artisan would know that to achieve majority of sample polynucleotides to be labeled with a unique tag, one needs to include an excess number of tags to ensure that majority of sample polynucleotides would be labeled.

346. As such, it is my opinion that there is adequate written description support for claimed ratios of sample polynucleotides to second tag sequences.

8. Support for “wherein said plurality of cells is provided in a plurality of wells”

347. Dr. Cooper opines that “the specification, however, does not describe providing a plurality of cells in a plurality of wells.” Cooper Report ¶ 510. I disagree.

348. Dr. Cooper ignores the knowledge of a skilled artisan at the time. A skilled artisan would know that in order to do single cell analysis, one approach to tagging the cells would be to have a plurality of cells in a plurality of wells.

349. I again note that Dr. Cooper’s opinions are contradictory, as elsewhere he opines that having a plurality of cells in a plurality of wells was rendered obvious by various references. Cooper Report ¶¶368-70. While I disagree with his opinions on obviousness as it relates to the claims for the reasons discussed in Sections X.A-B, I generally agree that POSA knew how separate cells into a plurality of wells, and would have understood the inventors were in possession of this invention.

350. As such, it is my opinion that there is adequate written description support for a plurality of cells in a plurality of wells.

9. Support for Disclosure of Claimed Invention as Integrated Whole

351. Dr. Cooper opines that “the Asserted Claims are invalid because the specification does not contain any one embodiment or disclosure that describes all of the claimed inventions as an integrated whole.” Cooper Report ¶ 511. I disagree.

352. To the extent, one needs to disclose an embodiment that describes all of the claimed inventions as an integrated whole, Dr. Cooper ignores Figure 5 and the knowledge of a skilled artisan at the effective filing date. As I describe above, while Figure 5 is a simplified depiction, a skilled artisan reviewing Figure 5 in the context of the disclosures in the Brenner

specifications would understand that, as it is in the case of analyzing single cells, the MID can include a tag that traces the nucleic acids to their cell of origin, and include a second tag to distinguish among the nucleic acids from that same cell. When combining the disclosure of Figure 5 with the knowledge of a skilled artisan and the use of routine and conventional method like ligation, a POSA would have understood that the inventors possessed what they claimed.

353. As such, it is my opinion that there is adequate written description support for the claimed inventions of the Brenner Patents as integrated whole.

10. Responses to Dr. Cooper's Supplemental Report

354. I have reviewed the written description section of Dr. Cooper's Supplemental Report. Cooper Supp. Report at ¶¶ 27-33. The cited testimonies from Drs. Mikawa and Osborne do not change my conclusions. As I discuss above, Dr. Cooper's reliance on the inventor testimony does not change the fact that there is adequate written description support for single cell analysis in the Brenner Patents.

D. The Asserted Claims of the Brenner Patent Are Enabled; Persons of Skill Could Practice the Asserted Claims of the Brenner Patents Without Undue Experimentation

355. Dr. Cooper opines that "the claimed methods, in my opinion, are not disclosed in the specification and so the specification does not enable the full scope of the claims." Cooper Report ¶ 517. To support his opinion, Dr. Cooper notes that "the Brenner Patents do not include any working examples demonstrating how the claimed inventions would work." *Id.* Dr. Cooper concluded that "to the extent a [POSA] could not perform the claimed method based on the ordinary skill in the art, the Brenner Patents do not contain any disclosures that would

supplement the skill in the art and enable the methods claimed.” *Id.* I disagree for the reasons I discuss below and generally in my report.

356. Dr. Cooper has analyzed several factors to determine if a POSA could make and use the invention without having to do undue experimentation, and that whether undue experimentation is required is a conclusion reached by weighing several factors, including:

- the quantity of experimentation necessary;
- the amount of direction or guidance presented;
- the presence or absence of working examples;
- the nature of the invention;
- the state of the prior art;
- the relative skill of those in the art;
- the predictability or unpredictability of the art; and
- the breadth of the claims.

357. Below are my responses to Dr. Cooper’s statements related to these factors in the order he presented them in his report.

1. Nature of Invention

358. Dr. Cooper opines that the Brenner specification describes the Reflex method, the figures of the Brenner Patents are all directed to the ‘reflex method,’ and the examples “are directed to methods and applications for the ‘reflex method.’” Cooper Report ¶ 520. According to Dr. Cooper, because the claims pertain to methods of analysis by dual tagging polynucleotides, the Brenner Patents cannot be enabling. Cooper Report ¶ 522. As I discuss above, the Reflex method is a way by which a POSA can attach an MID (comprising one or more tags) to a polynucleotide of interest. This method is described in detail in the Brenner Patents. This provides support for the claimed inventions.

359. Further, as I discuss above, it was impossible to perform the single cell analysis claimed by the Brenner Patents without the use of MIDs. As such, it is irrelevant whether the

Brenner Patents do not provide any “new” guidance for tagging. Without the inventive use of MIDs disclosed and enabled in the Brenner Patents, there would not be an invention.

360. It is my opinion that a skilled artisan would be able to practice the full scope of the claims without undue experimentation related to the novel use of MIDs for the claimed single cell analysis.

2. Working Examples

361. Dr. Cooper opines that “while the Asserted Claims relate to methods of analysis and/or counting nucleic acids in single cells though dual tagging of polynucleotides, none of the examples discloses a working example of the claimed dual tagging approach.” Cooper Report ¶ 523. I disagree.

362. As I discuss above, while Figure 5 is a simplified depiction, a skilled artisan reviewing Figure 5 in the context of the disclosures in the Brenner specifications would understand that, as it is in the case of analyzing single cells, the MID can include a tag that traces the nucleic acids to their cell of origin, and include a second tag to distinguish among the nucleic acids from that same cell. As such, a skilled artisan would know how to practice the claimed invention after reviewing Figure 5.

363. It is my opinion that a skilled artisan would be able to practice the claimed invention of the novel use of MIDs without undue experimentation after reviewing Figure 5.

3. Quantity of Experimentation

364. Dr. Cooper opines that “the specification includes virtually no disclosure guiding a [POSA] in how to perform the claimed methods.” Cooper Report ¶ 526. According Dr. Cooper, there is no description involving “using single cells, the use of two tag sequences that identify the single cell origin of the sample and distinguishes different molecules originating

from the same cell, counting nucleic acids after dual tagging, how to perform multiplexed analysis with combinatorial tagging, how to ensure that polynucleotides are randomly associated with tags, the use of wells in the practicing the claimed invention, and how to ensure that a plurality of tags comprises at least 200,000 different second tag sequences.” *Id.* at 527. I disagree for the reasons I discuss in Section X.C. Indeed, the same paragraphs that I noted above as describing the claimed inventions also enable those inventions, for the same reasons. I therefore incorporate as though fully set forth herein my above analysis concerning the written description support of the Asserted Claims.

365. For instance, the provisional further clarifies that “in certain embodiments, nucleic acid fragments that are to be pooled with nucleic acid fragments derived from a plurality of sources (e.g., a plurality of organisms, tissues, cells, subjects, etc.), where by ‘plurality’ is meant two or more. In such embodiments, the nucleic acids derived from each source includes a multiplex identifier (MID) such that the source from which the each tagged nucleic acid fragment was derived can be determined.” Provisional at 19. As is clear in this disclosure, Brenner does not just in passing say that in principle the source of the polynucleotides may be a cell. Brenner states that in fact the source *is* a cell, and that the MID is used to determine which cell [source] the polynucleotide came from. Furthermore, Brenner specifies that the tagged sample is pooled from two or more sources, including two or more cells, which again recognizes tagging at a single-cell level.

366. Further, a skilled artisan reviewing the Figures, including Figure 5, in the context of the disclosures in the Brenner specifications would understand that, as it is in the case of analyzing single cells, the MID can include a tag that traces the nucleic acids to their cell of origin, and include a second tag to distinguish among the nucleic acids from that same cell.

Indeed, I note that the definition of “MID” in the Brenner specifications expressly contemplates a “combination of tags” and identifies a tag that identifies the source of origin, including a cell, and a tag that distinguishes among polynucleotides in the sample. The Brenner Patents further disclose that polynucleotides can be tagged “by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension,” enabling a skilled artisan how to add tags to a polynucleotide sample to perform multiplexed analysis with combinatorial tagging.

367. In addition, as of 2009, counting nucleic acid molecules was known and could be achieved by “[a]ny convenient method.” Scientists also knew how to isolate single cells and did so routinely by employing wells.

368. It is my opinion that a skilled artisan would not engage in a large amount of experimentation to successfully perform any of the claimed methods.

4. Guidance in the Specification

369. Dr. Cooper opines that “there is little guidance in the specification regarding how to practice the claimed dual tagging methods.” Cooper Report ¶ 531. To support his opinion, Dr. Cooper notes that “the specification does not provide a single embodiment that discloses any of the claimed inventions as a whole,” “the specification does not disclose any methods as to achieving a particular ratio of unique second tag sequences,” “the specification fails to disclose analysis of nucleic acids from single cells,” “the specification also provides no guidance as to counting dual-tagged nucleic acids,” and “the specification also fails to provide a skilled artisan on how to randomly associate tags with sample nucleotides, the use of wells . . . , and the use of at least 200,000 different second tag sequences.” *Id.* ¶¶ 532-536. As I discuss above, I disagree. Section X.C.

370. After reviewing the Brenner specification, figures, the incorporated prior art references combined with the general knowledge of the field at the time, a skilled artisan would know how to perform the claimed methods of analysis of single cells with dual tagging without a trial-and-error process. As I understand it, a certain amount of experimentation is permissible and in light of the disclosures, a skilled artisan would not have to engage in burdensome trial-and-error process to practice the claimed inventions of the Brenner Patents.

371. It is my opinion that a skilled artisan would not have to engage in an extensive trial-and-error process that amounts to undue experimentation to practice the claimed inventions of the Brenner Patents.

5. State of the Art

372. Dr. Cooper opines that “the state of the art would have required undue experimentation in light of the specification.” Cooper Report ¶ 538. Dr. Cooper further notes that “to the extent the specification provides any guidance on the claimed dual tagging methods, it is through broad references to prior art techniques.” I disagree.

373. As I discuss above, the claimed invention is the novel use of MIDs to analyze single cells. Once the Brenner Patents disclose the novel use of MIDs along with other disclosures in the patent combined with the general knowledge, a skilled artisan would be able to find ways to use dual tags for single cell analysis without any undue experimentation.

374. Dr. Cooper’s opinion is also contradictory. Dr. Cooper opines that “prior to 2009, methods involving single cells, how to tag the polynucleotides of single cells, and how to distinguish polynucleotides within a cell were still new and developing.” Cooper Report ¶539. Yet, elsewhere, Dr. Cooper opines that each of these features were known and render the claimed inventions obvious. Cooper Report ¶¶159-162.

375. It is my opinion that it would not have taken a skilled artisan undue experimentation to practice the claimed invention after reviewing disclosures in the Brenner specification related to MIDs.

6. Relative Skill of Those in the Art

376. Dr. Cooper opines that “given the wide variety of techniques and methods available and familiar to a [POSA], the lack of guidance in the specification,” a POSA would have had to engage in undue experimentation. Cooper Report ¶ 542. I disagree.

377. As Dr. Cooper admits elsewhere in his report, the claimed inventions of the Brenner Patents all relate to the novel use of MIDs combined with prior art references. As such, a skilled artisan would not engage in undue experimentation.

378. It is my opinion that a skilled artisan would not have to engage in undue experimentation after reviewing the disclosures of the Brenner specification combined with the general knowledge of the art as of 2009.

7. Predictability of the Art

379. Dr. Cooper opines that “particularly around 2009, single cell experimentation would have been unpredictable.” Cooper Report ¶ 543. I disagree.

380. As Dr. Cooper admits elsewhere in his report, the application of prior art methods to the novel use of MIDs would not have required a skilled artisan to engage in undue experimentation to determine a particular methodology to practice the claims.

381. It is my opinion that a skilled artisan would not have to engage in undue experimentation to practice the claimed inventions after combining the general knowledge in the field, the prior art references and the disclosure of the novel use of MIDs in single cell analysis.

8. Breadth of the Claims

382. Dr. Cooper opines that “the Asserted Claims of the Brenner Patents are broad and . . . the specification does not instruct a [POSA] how to practice the claimed dual tagging method without undue experimentation. Cooper Report ¶ 546. I disagree.

383. While the claims may be broad, the Brenner specification discloses enough guidance on the novel use of MIDs in single cell analysis for a skilled person to practice the claimed inventions after combining that guidance with the general knowledge of the field and the disclosures of the cited prior art references.

384. It is my opinion that a skilled artisan would not have to engage in undue experimentation to practice the claimed inventions of the Brenner Patents.

9. Responses to Dr. Cooper’s Supplemental Report

385. I have reviewed the enablement section of Dr. Cooper’s Supplemental Report. Cooper Supp. Report at ¶¶ 36-40. The cited testimonies from Drs. Mikawa and Osborne do not change my conclusions. As I discuss above, Dr. Cooper’s reliance on the inventor testimony does not change the fact that the Brenner specification discloses enough guidance on the novel use of MIDs in single cell analysis for a skilled artisan to practice the claimed inventions when that person combined the general knowledge of the field and the disclosures of the cited prior art references.

E. The Asserted Claims of the Brenner Patents Are Definite

386. Dr. Cooper has opines that the asserted claims of the Brenner Patents are indefinite. Cooper Report ¶¶ 550-555. Dr. Cooper identifies four areas of indefiniteness: the Reflex method, the use of single cells, the use of a first and second tag sequence, and the claim element “a method for multiplexed analysis . . . performing combinatorial tagging.” I disagree.

HIGHLY CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

As an initial matter, Dr. Cooper's opinion does not identify or explain why POSA would have been unable to determine the scope of the claims with reasonable certainty with respect to any term, which I have been informed is the relevant question for indefiniteness. Instead, Dr. Cooper's opinions seem to be directed to written description.

387. Dr. Cooper has opined that the claims fail to particularly point and distinctly claim the reflex method. Cooper Report ¶ 550. As I discuss above, the Brenner Patents disclose multiple inventions, one of which is the reflex method, and another of which is methods and compositions for tagging polynucleotides with two distinct tags. This second invention is what the claims of the asserted Brenner Patents are directed to. The first tag allows the user to identify the polynucleotide's cell of origin and the second tag allows the user to identify the polynucleotide's molecular origin. In fact, as Dr. Cooper himself admits that "the claims are directed to single cell analysis of polynucleotides." *Id.* ¶ 551. As such, that the Brenner specification also describes the Reflex method in detail and provides examples where the Reflex method is performed in conjunction with MIDs does not mean that the Asserted Claims of the Brenner Patents need to be directed to the Reflex method to be definite.

388. Dr. Cooper has also opined that the claims recite single cell analysis of polynucleotides and this subject matter is outside the scope of what the "inventors actually considered their invention." Cooper Report ¶ 551. As I stated above, the Brenner Patents disclose multiple discrete inventions, one of which is single cell analysis. The Brenner Patents' specification discloses the use of MIDs outside the Reflex method. '981 Patent at 1:45-47. Dr. Cooper also disregards the knowledge of a POSA would have at the time. I note that, according to the standards I have been provided, Dr. Cooper's opinions are not relevant to indefiniteness as they do not go to whether a person of skill could understand the boundaries of a claim with

reasonable certainty. Nevertheless, a POSA would have known how to partition the polynucleotides from single cells from a sample using then-available technologies as well as how to prepare the cells for single cell analysis, introduce the tags, and pool and amplify the tagged molecules. Indeed, Dr. Cooper argues that each of these features was known in the art, and renders the claims obvious. While I disagree that the claims are obvious, I note that Dr. Cooper's opinions are contradictory and support that, with the disclosure of the Brenner Patents in hand, POSAs would have been more than capable of practicing the claimed invention. As such, a POSA would have known how to perform single cell analysis of polynucleotides using the disclosed usage of MIDs.

389. Dr. Cooper has opined that a skilled artisan would have been unable to ascertain the scope of the invention as it relates to the first and second tag sequences. Cooper Report ¶ 552. Again, Dr. Cooper has opined that the Brenner Patents are directed to the Reflex method. As I explained above and Dr. Cooper agrees, the claims are directed to single cell analysis using a first tag capable of identifying the single cell origin of a sample polynucleotide and a second tag sequence distinguishing sample polynucleotide from the same single cell. A POSA would know how to generate these tags, use the tags, or count the tagged molecules as I explained above. As such, a POSA would have known how to utilize these tags in single cell analysis.

390. Lastly, Dr. Cooper has opined that a skilled person would not be informed as the scope of invention's limitation based on 'multiplexed analysis' and 'combinatorial tagging.' Cooper Report ¶ 553. As I explained above, with the use of MIDs disclosed and claimed in the Brenner Patents, a skilled artisan would have known the invention's limitations. As I understand that a patent does not need to have working examples for each embodiment. Further, a POSA would know how to attach one MID by ligation and a second by primer

extension. As such, a POSA would have known how to perform multiplexed single cell analysis of polynucleotides using the disclosed unique usage of MIDs in the Brenner Patents.

391. In sum, it is my opinion that the Asserted Claims of the Brenner Patents are definite.

F. The Asserted Claims of the Brenner Patents Do Not Claim a Law of Nature, Abstract Idea, or Natural Phenomena

1. The Asserted Claims of the Brenner Patents Are Directed to Patentable Subject Matter

392. Dr. Cooper opines that “the Asserted Claims are directed to patent illegible subject matter.” Cooper Report ¶ 556. He further opines that “the Asserted Claims of the Brenner Patents are directed to the abstract idea of tagging and labelling DNA molecules.” *Id.* ¶ 557. I disagree.

393. As I discussed in my opening report, the Brenner Patents are foundational to the single cell analysis field. The Asserted Claims of the Brenner Patents are directed to unconventional and improved methods of “analyzing nucleic acids from single cells using methods that include using tagged polynucleotides containing multiplex identifier sequences.” ’981 Patent, Abstract. This is accomplished by the use of two distinct tags. The first tag allows the user to identify the polynucleotide’s cell of origin and the second tag allows the user to identify the polynucleotide’s molecular origin, allowing the user to accurately determine the number of times a particular gene is expressed regardless of whether the cell’s molecular are fragmented, amplified, or otherwise altered. By adding two different tags to polynucleotides, the user can track the cell of origin of a polynucleotide as well as the level of expression of that polynucleotide in that cell. In contrast, prior art methods utilized fragmenting and tagging polynucleotides, and sequencing those tagged fragments to create a “population library” from

inventiveness of the method—“ [REDACTED] Krane Report

¶470: [REDACTED] In contrast, prior art methods of epigenetic analysis were extremely complex, required large sample inputs, and were time consuming. *See* '995 Patent at Background. This is further confirmed by Dr. Buenrostro's award of the MacArthur Genius Grant from his ATAC-seq invention. Opening Report, ¶589.

598. The testimony of the inventors confirms the unexpected and vast improvement of the ATAC-seq inventions over the prior art methods. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

599. For the reasons discussed in my Opening Report and the reasons discussed above, it is my opinion that the objective indicia confirm my opinion that the Asserted Claims of the Giresi Patents are not obvious.

XIII. Supplementation

600. I reserve the right to consider additional materials and to amend or supplement my opinions in light of additional information that may come to my attention, including any Court rulings and/or new arguments raised by Parse directly or through its experts or any critique of my report or opinions advanced by or on behalf of Parse.

601. If I am called to testify, I may explain principles and terminology referred to in this report as well as documents referenced or cited herein. I reserve the right to utilize visual

aids, animations, demonstrative exhibits, trial exhibits, and other such testimonial aids in support of my testimony to illustrate the bases for my opinions.

HIGHLY CONFIDENTIAL – ATTORNEYS’ EYES ONLY

I declare under penalty of perjury that the foregoing is true and correct.

Dated: June 14, 2024.

A handwritten signature in black ink, appearing to read 'J. Quackenbush', is positioned above a horizontal line.

JOHN QUACKENBUSH, Ph.D.