Docket No. 62239-BZA10/JPW/AC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors : Jingyue Ju et al.

Serial No.: 15/380,311 Examiner: Layla D. Berry

Filed : December 15, 2016 Art Unit: 1673

For : MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA

30 Rockefeller Plaza
20th Floor
New York, New York 10112

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF JINGYUE JU, PH.D.

I, Jingyue Ju, Ph.D., declare as follows:

1. I am the first named inventor on the above-identified patent application.

2. I am a Professor of Chemical Engineering and Pharmacology and the Director of the Center for Genome Technology and Biomolecular Engineering at Columbia University in the City of New York ("Columbia").

3. Columbia is the owner (assignee) of rights in the above-identified patent application and has granted a license to the patent application and any patent issued from it to Qiagen.

4. I have been a professor at Columbia since 1999 and my research at Columbia has focused on developing new molecules and methods for DNA sequencing.

5. Prior to 1999, I worked at Incyte Genomics, Inc. and my work there focused on developing and improving DNA sequencing methods for the discovery and sequence identification of genes within the human genome.

Applicant: The Trustees of Columbia University in the City of New York
U.S. Serial No : 16/150,185
Filed: October 2, 2018
Exhibit 1

6. A copy of my curriculum vitae is attached hereto as **Exhibit A**. As indicated therein, I am a named inventor on 39 issued U.S. patents and an author on 96 scientific publications.

7. Based on my extensive experience and expertise in the research and development of DNA sequencing and related technologies, including the design and synthesis of nucleotide analogues and the preparation and use of labeled nucleotide analogues, I am very well familiar with the level of education, knowledge and experience of persons working in these areas.

8. Based on legal advice concerning the meaning of the phrase a "person of ordinary skill in the art" or "POSA", I think I am well qualified to comment on the appropriate definition of a POSA in the field of DNA sequencing and on issues in this field from the perspective of a POSA as of October 6, 2000. In this regard, my opinion is that a POSA would have been a person with a Ph.D. degree in chemistry, chemical biology, or a related discipline and at least two years postdoctoral experience in the area of DNA sequencing, particularly the design and synthesis of nucleotide analogues for use in DNA sequencing.

9. This Declaration sets forth my opinions as to what a POSA's understanding would have been as of October 2000 concerning various issues raised by the Examiner with respect to the single claim pending in the above-identified patent application.

I. Indefiniteness

A. Meaning of "small"

10. I understand that the Examiner has raised a concern that the term "small", which appears in the claim, is indefinite and that a POSA would not have had an understanding of the meaning of the term in the context of the claim because the

specification does not provide a standard for assessing whether a 3'-O capping group R on the sugar of the claimed nucleotide analogue is "small".

11. In my opinion, a POSA reading the application, particularly paragraphs 6-8 of the published version of the application and Fig. 1 of the application including the brief description of Fig. 1 in paragraph 35, would readily have understood that the application indicates that the standard for assessing whether a 3'-O capping group R is "small" is the ability of the group to fit into the active site of the DNA polymerase shown in Fig. 1 of the patent application.

12. The POSA would further have understood that the 3D structure shown in Fig. 1 is the same as Fig. 6 previously published by Pelletier et al. (*Science*, Vol. 264, June 24, 1994, 1891-1903) and referred to in paragraph 6 of the published version of this patent application. A copy of Pelletier et al. is attached hereto as **Exhibit B**.

13. The POSA would also have known the precise coordinates of the polymerase structure based on the publication of Pelletier et al. (see "References and Notes" 101, page 1903) and the distances between the sugar of the nucleotide analogue and the key amino acids located in the active site of the polymerase (see Table 3, page 1897 of Pelletier et al.).

14. With the information in the patent application and the information available in Pelletier et al. and software available in October 2000, such as Chem3D Pro, the POSA could have readily calculated the space available around the 3' position of a deoxyribose of a nucleotide analogue in the active site of the polymerase.

15. I have performed an analysis of the space available within the active site of the polymerase to accommodate a 3'-O capped

dNTP and prepared a written summary of the result of this analysis attached hereto as **Exhibit C.** As explained in greater detail in the attached Analysis, the available space is approximately 3.7Å in diameter. Given this available space, the POSA would have understood that the term "small", in the context of the claimed nucleotide analogue, assessed by the standard provided in the patent application meant a 3'-O capping group with a diameter less than 3.7Å.

16. Using this standard the POSA could have readily determined that the two examples of 3'-O capping groups listed in the application, Allyl and Methoxymethyl, had diameters of 3.0Å and 2.1Å, respectively, and therefore were "small." (see attached Analysis, Exhibit C)

17. Using this standard, the POSA could also have readily determined which of the many known 3'-O capping groups were "small". Thus, the POSA would have determined that Methylthiomethyl and Azidomethyl, with diameters of 2.4Å and 2.1Å, respectively, were "small" while 2-Nitrobenzyl with a diameter of 5Å was not small (see attached Analysis, Exhibit C).

18. In summary, a POSA reading the above-identified application and relying on information publicly known as of October 2000 would have known that the standard for assessing whether any specific 3'-O capping group in a nucleotide analogue was "small" was whether it had a diameter less than 3.7Å so that it could fit into the active site of the polymerase. Therefore, the meaning of "small" would not have been indefinite.

B. Definition of R is clear

19. With the meaning of "small" well defined, the POSA looking at the structure shown in the pending claim and the definition of

R in the claim would have been able to readily know whether any given 3'-O capping group in a nucleotide analogue came within the scope of the claim. In this regard, prior art references as of October 2000, such as Tsien (WO 91/06678, May 16, 1991) and Stemple (WO 00/53805, September 14, 2000), identify numerous, chemically cleavable 3'-O capping groups which could be readily evaluated to determine whether they were "small" and also meet other conditions of the claim such as the structural features "OR is not a methoxy or an ester group" and R "does not contain a ketone group". Thus, the POSA would have understood with reasonable certainty the definition of R in the context of the patent application as a whole.

C. The scope of Y

20. Y is defined as a chemically cleavable, chemical linker and as shown in the structure shown in the pending claim, Y is attached by covalent bonds at one end to the base of a nucleotide analogue at a specific position and at the other end to a detectable fluorescent moiety. A POSA would have been familiar with many such chemical linkers from the prior art as of October 2000 including such linkers described by Tsien and Stemple. Therefore, a POSA would have readily understood the meaning of Y in the context of the pending claim as a whole read in light of the patent application.

D. Other functional characteristics

21. In the context of the pending claim as a whole read in light of the patent application, a POSA would have readily understood the meaning of the functional characteristics recited in the claim with reasonable certainty. To the POSA who had read the patent application, the scope of the structures encompassed by the claimed nucleotide analogue would have been clear and not indefinite.

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