UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

BAUSCH HEALTH IRELAND LIMITED,

Patent Owner.

Case IPR2022-00722
U.S. Patent No. 7,041,786

DECLARATION OF KUNWAR SHAILUBHAI

I, Kunwar Shailubhai, under penalty of perjury, declare as follows:

I. INTRODUCTION

1. I am of legal age and otherwise competent to make this declaration.

2. I am the first named inventor on U.S. Patent No. 7,041,786 (Ex. 1001, "the '786 patent"). I have been asked to submit a declaration attesting to how the data disclosed in Table 4 in the specification of the '786 patent and other relevant data related to the peptides disclosed in the '786 patent were generated.

II. EDUCATION AND WORK EXPERIENCE

3. I graduated from the Maharaja Sayajirao University of Baroda with a Ph.D. in Microbiology in 1984 and from the University of Missouri-Saint Louis with an M.B.A. in 2002.

4. I am currently employed by the Pennsylvania Biotechnology Center and Baruch S. Blumberg Institute as a Senior Advisor and Professor.

III. BIOLOGICAL ACTIVITY DATA IN TABLE 4 OF THE '786 PATENT

5. I was involved in synthesizing and testing of guanylate cyclase ("GC-C") receptor agonists that enhance intracellular production of cyclic guanosine monophosphate ("cGMP"), including the peptides of the experimental examples reported in the '786 patent. As such, I have first-hand knowledge of how the peptides reported below were made and tested.

6. I directed the synthesis and testing of the GC-C receptor agonist peptides in order to examine biological activity as disclosed in Table 4 of the '786 patent.

7. Human T84 colon carcinoma cells were obtained from the American Type Culture Collection. (*Id.* at 15:27-29). Cells were grown in a 1:1 mixture of Ham's F-12 medium and Dulbecco's modified Eagle's medium ("DMEM") supplemented with 10% fetal bovine serum, 100 U penicillin/ml, and 100 µg/ml streptomycin. (*Id.* at 15:29-32). The cells were fed fresh medium every third day and split at a confluence of approximately 80%. (*Id.* at 15:32-34).

8. Peptides were custom synthesized by Multiple Peptide Systems, San Diego, California, and by Princeton Biomolecules, Langhorne, Pennsylvania. (*Id.* at 15:36-38). Biological activity of the synthetic peptides was assayed. (*Id.* at 15:38-39). The confluent monolayers of T84 cells in 24-well plates were washed twice with 250 µl of DMEM containing 50 mM HEPES (pH 7.4), pre-incubated at 37°C for 10 minutes with 250 µl DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutylmethylxanthine ("IBMX"), followed by incubation with peptides (0.1 nM to 10 µM) for 30 minutes. (*Id.* at 15:40-46). The medium was aspirated, and the reaction was terminated by the addition of 3% perchloric acid. (*Id.* at 15:46-47). Following centrifugation, and neutralization with 0.1 N NaOH, the

supernatant was used directly for measurements of cGMP using an ELISA kit (Caymen Chemical, Ann Arbor, Michigan). (*Id.* at 15:47-50).

9. As indicated in the following table, the peptides were custom synthesized and purified (>95% purity) using a published procedure (procedure from Klodt, et al., *J. Peptide Res.* 50:222-230 (1997)). (*Id.* at 15:53-54, 18:32). Peptides were evaluated in the T84 cell-based assay for their ability to enhance intracellular levels of cGMP. (*Id.* at 15:55-56). The results of this test are shown in Table 4 below.

TABLE 4

Peptide agonists evaluated for biological activity in the T84 cell bioassay.

SEQ ID NO.*	Compound Code	cGMP Level** (pmol/well)
1	SP301	205
6	SP302	225
7	SP303	195
20	SP304	315
14	SP306	0
4	SP310	0
21	SP316	275

*SEQ ID's for SP301, SP304 and SP316 are the precise amino acid sequences for these analogs as given in the text.
**Intracellular cGMP level observed in T84 cells following treatment with 1 micromolar solution of the respective peptide agonist for 30 minutes. The value observed for SP304 was statistically significant with a $p > 0.5$.

(*Id.* at 16:1-19). I note that the p value below Table 4 contains a typographical error and should say $p < 0.05$. (*Id.* at 16:19).

IV. DATA IN STUDY NUMBER SP-PH-001

10. I directed the preparation and testing of the ability of SP-304 (plecanatide) to stimulate cGMP production in T84 human colon carcinoma cells *in vitro* and evaluated the effects of SP-304, uroguanylin, and other peptides. (Ex. 2027 at TRUL00018209).

11. SP-304, uroguanylin, and two other peptides (SP-302 and SP-303) were tested at concentrations ranging from 10^{-9} M to 10^{-5} M. (*Id.*). Cell culture supernatants were prepared following 30-minute incubation, and cGMP levels were measured using a commercial ELISA assay. (*Id.*).

12. Human colon carcinoma cells T84 (ATCC Number CCL-248), provided by Dr. Lenard Forte, University of Missouri at Columbia, MO, were used in these assays. (Ex. 2027 at TRUL00018210). The cells were cultured in DMEM and Ham's F-12 medium (1:1) containing 5% fetal bovine serum and 60 µg of penicillin plus 100 µg of streptomycin per ml. (*Id.*). Cells were split every 5-6 days by trypsinization. (*Id.*). Frozen stocks of cells were stored in liquid nitrogen. (*Id.*).

13. The following test peptides were synthesized by BACHEM Biosciences, Inc. (King of Prussia, PA) as the trifluoroacetic acid salt form:

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