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

SUPPLEMENTAL 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:

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.