

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.
Petitioner

v.

SPRUCE BIOSCIENCES, INC.
Patent Owner

U.S. Patent 12,115,166

DECLARATION OF MAYA LODISH, M.D.

**IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF U.S.
PATENT NO. 12,115,166**

I, Maya Lodish, M.D., of San Francisco, California, declare that:

I. QUALIFICATIONS AND BACKGROUND INFORMATION

1. My curriculum vitae is attached hereto as Appendix A.

2. I earned a B.A. degree in Biochemistry and Molecular Biology at Dartmouth College in 1998. I then earned an M.D. from Yale University School of Medicine in 2003. I also hold a Masters in Health Science from Duke University, which I earned in 2013. After receiving my M.D., I completed my internship and residency in pediatrics at John Hopkins Hospital in Baltimore, Maryland from 2003 to 2006. I then completed a fellowship in pediatric endocrinology at the National Institutes of Health in Bethesda, Maryland from 2006 to 2009.

3. I am currently a Professor of Clinical Pediatrics and hold the Selma Kaplan Distinguished Professorship in Pediatric Endocrinology/Diabetes at the University of California, San Francisco (UCSF), a position I have held since 2018. Since 2019, I have also served as the Chief of the Division of Endocrinology at UCSF. Prior to these positions, I served as a Deputy Program Director, Staff Clinician, Program Director, and Associate Research Physician at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), positions I held from 2009 to 2018.

4. As part of my position at UCSF, I teach medical students, residents, and fellows in formal courses, including foundational courses/lectures on the

thyroid; lectures on disorders of the adrenal glands, pituitary glands, and hypothalamus; lectures on diabetes; as well as lead small groups of students on a variety of topics. I lecture to students, residents, nursing students, and pediatric endocrinology fellows, as well adult endocrinology and reproductive endocrinology fellows. I also helped to draft the curriculum content guidelines for the American Board of Pediatrics subspecialty content in Pediatric Endocrinology. I have had the privilege of serving as a mentor to over 40 students, fellows in training, and junior faculty members, many of whom have had first author publications and gone on to successful academic careers.

5. I am and have been certified by the American Board of Pediatrics since 2006, as well as the American Board of Pediatrics Sub-board of Pediatric Endocrinology since 2009. I am currently licensed to practice medicine in California. I have also held licenses to practice medicine in Maryland and Virginia.

6. In addition to teaching, I attend in the pediatric endocrinology clinic and on the inpatient pediatric endocrinology consult service (with medical students, residents, and fellows). I collaborate with the UCSF hereditary cancer clinic for management of children with a predisposition to endocrine tumors. I also collaborate with the division of pediatric oncology, to provide endocrine care to survivors of childhood cancer and to neuro-oncology patients.

7. In my career, I have been invited by numerous universities and institutions around the world to present lectures on pediatric endocrinology. I have authored or co-authored over 140 scientific articles, 8 book chapters, and 3 books.

8. At UCSF, I am the principal clinical investigator for studies of novel therapeutics in pediatric endocrinology, including four active protocols. These include a phase II study of the use of osilodrostat in children with Cushing's disease, a phase III study of a once-yearly GnRH agonist in children with precocious puberty, a phase IV study of long-acting growth hormone in children with short stature, and a randomized comparative study between liquid and tablet formulations of levothyroxine in neonates and infants with congenital hypothyroidism. I previously served as a co-investigator on an efficacy and safety study of palovarotene for the treatment of fibrodysplasia ossificans progressive.

9. During my time at the NIH, I was the primary investigator of a study evaluating mifepristone in children with refractory Cushing's disease, as well as primary investigator of a study evaluating the safety and efficacy of pegvisomant in children with growth hormone excess. I was also a co-investigator on a clinical trial studying the use of vandetanib to treat children and adolescents with medullary thyroid cancer.

10. I have been a Principal Investigator in numerous clinical trials. I helped to design the Phase III clinical trial design of crinicerfont in pediatric CAH

patients and went on to serve as a Principal Investigator. I am an author of the New England Journal of Medicine article reporting the result of that study. *See* EX1053. I continue to serve as primary investigator in the open label extension of this trial.

11. I currently serve as a reviewer for various medical journals including the *Journal of the American Medical Association, Lancet, Thyroid, Endocrine, Endocrinology, Diabetes and Metabolism Case Reports, the Journal of Pediatrics, Molecular and Cellular Endocrinology*, and others. I have previously served on the editorial board of the *Journal of Clinical Endocrinology & Metabolism*.

12. I am a member of the Endocrine Society and the Pediatric Endocrine Society, where I have served on various committees and subcommittees.

II. COMPENSATION

13. I am being compensated at my customary rate of \$550 per hour for my work in this matter. My compensation is in no way based on the outcome of this matter and has not influenced my views in this matter.

III. MATERIALS CONSIDERED

14. In writing this Declaration, I have relied on my background, education, and experience as physician, both in treating patient with endocrine disorders, including CAH, and studying the treatment of such disorders in clinical trials. I have also considered, in whole or in part, the following documents in forming my opinion in this matter.

Exhibit No.	Exhibit Description
1001	U.S. Patent No. 12,115,166 to Alexis Howerton, et al. (“the ’166 patent”).
1002	U.S. Prosecution History of the ’166 Patent. Part 1, 1-624 Part 2, 625-1248 Part 3, 1249-1872 Part 4, 1873-2182 Part 5, 2183-2495 Part 6, 2496-2119
1005	Final Written Decision, Paper 64, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (PTAB Nov. 27, 2024).
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. (“Grigoriadis”).
1007	Final Written Decision, Paper 62, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (PTAB Nov. 26, 2024).
1008	Turcu et al., “Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 101(3):1174-80 (March 2016) (“Turcu 2016”).
1009	Auchus et al., “Crinicerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metab.</i> 1-12 (2021) (“Auchus 2021”).
1013	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133-60 (2010) (“Speiser 2010”).
1014	Turcu A.F. & Auchus R.J., “The Next 150 Years of Congenital Adrenal Hyperplasia,” <i>J. Steroid. Biochem. Mol. Biol.</i> , 153:63-71 (Sept. 2015) (“Turcu & Auchus 2015”).
1015	El Maouche et al., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 390:2194-10 (2017) (“El Maouche 2017”).
1016	Merke D.P. & Bornstein S.R., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> , 365:2125-36 (2005) (“Merke & Bornstein 2005”).

Exhibit No.	Exhibit Description
1017	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 103(11):4043-88 (2018) (“Speiser 2018”).
1018	Fahmy et al., “Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use,” <i>Curr. Mol. Pharmacol.</i> , 10(4): 270-281 (2017) (“Fahmy 2017”).
1019	Griebel et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A), a Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. II. Characterization in Rodent Models of Stress-Related Disorders,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):333-45 (2002) (“Griebel 2002”).
1020	Gully et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):322-32 (2002) (“Gully 2002”).
1021	Merke D.P. & Cutler G.B., “New Ideas for Medical Treatment of Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metab. Clin. North. Am.</i> , 30(1):121-35 (2001) (“Merke & Cutler 2001”).
1022	Merke et al., “Future Directions in the Study and Management of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency,” <i>Ann. Intern. Med.</i> , 136:320-34 (2002) (“Merke 2002”).
1024	Merke D.P. & Auchus R.J., “Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” <i>N. Engl. J. Med.</i> 383(13):1248-61 (2020) (“Merke & Auchus 2020”).
1025	Turcu A.F. & Auchus R.J., “Novel Treatment Strategies in Congenital Adrenal Hyperplasia,” <i>Curr. Opin. Endocrinol. Diabetes Obes.</i> , 23(3):225-32 (June 2016) (“Turcu & Auchus 2016”).
1026	Webb E.A. & Krone N., “Current and Novel Approaches to Children and Young People with Congenital Adrenal

Exhibit No.	Exhibit Description
	Hyperplasia and Adrenal Insufficiency,” <i>Best Pract. Res. Clin. Endocrinol. Metab.</i> , 29:449-68 (2015) (“Webb & Krone 2015”).
1027	“Neurocrine Biosciences to Present New Data Analyses for Crinecerfont in Adults with Classical Congenital Adrenal Hyperplasia at ENDO 2021,” Neurocrine Biosciences (March 20, 2021) (“Neurocrine March 20, 2021, Press Release”).
1029	Williams, “Corticotropin-Releasing Factor 1 Receptor Antagonists: A Patent Review,” <i>Expert Opin. Ther. Pat.</i> , 23(8):1057-68 (2013) (“Williams 2013”).
1030	Zorrilla E.P. & Koob G.F., “Progress in Corticotropin-Releasing Factor-1 Antagonist Development,” <i>Drug Discovery Today</i> , 15(9/10):371-83 (2010) (“Zorrilla & Koob 2010”).
1031	Kehne J.H. & Cain C.K., “Therapeutic Utility of Non-Peptidic CRF1 Receptor Antagonists in Anxiety, Depression, and Stress-Related Disorders: Evidence from Animal Models,” <i>Pharmacol. Ther.</i> , 128(3):460-87 (2010). (“Kehne & Cain 2010”).
1032	Deore et al., “The Stages of Drug Discovery and Development Process,” <i>Asian J. Pharm. R. & D.</i> , 7(6):62-67 (2019) (“Deore”).
1033	National Center for Biotechnology Information (2025), PubChem Compound Summary for CID 5282340, Crinecerfont. Retrieved February 4, 2025, from https://pubchem.ncbi.nlm.nih.gov/compound/Crinecerfont .
1035	U.S. Provisional Application Serial No. 62/545,406.
1039	Sarafoglou et al., “Interpretation of Steroid Biomarkers in 21-Hydroxylase Deficiency and Their Use in Disease Management,” <i>J. Clin. Endocrinol. Metabol.</i> 108:2154-75 (March 2023) (“Sarafoglou 2023”).
1041	Sarafoglou et al., “Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies,” <i>J. Clin. Endocrinol. Metabol.</i> 106(11):e4666-79 (2021) (“Sarafoglou 2021”).
1044	“Spruce Biosciences Announces Topline Results from CAHmelia-203 in Adult Classic CAH and CAHptain-205 in Pediatric Classic CAH,” Spruce Biosciences (March 13, 2024) (“Spruce March 13, 2024, Press Release”).
1045	“Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and

Exhibit No.	Exhibit Description
	Pediatric CAH,” Spruce Biosciences (December 10, 2024) (“Spruce December 10, 2024, Press Release”).
1046	Turcu A.F. & Auchus R.J, “Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metabol. Clin. N. Am.</i> , 44:275-96 (2015) (“Turcu & Auchus 2015a”).
1047	Mallappa A. & Merke D.P., “Management challenges and therapeutic advances in congenital adrenal hyperplasia,” <i>Nature Reviews Endocrinol.</i> , 18:337-52 (June 2022) (“Mallappa & Merke”).
1048	Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metabol.</i> , 107(3):801-12 (2022) (“Auchus 2022”).
1049	Claahsen-van der Grinten et al., “Congenital Adrenal Hyperplasia—Current Insights in Pathophysiology, Diagnostics, and Management,” <i>Endocrine Reviews</i> , 43(1):91-159 (2022) (“Claahsen-van der Grinten”).
1052	Auchus et al., “Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia,” <i>N. Engl. J. Med.</i> , 391(6):504-14 (June 2024) (“Auchus 2024”).
1053	Sarafoglou et al., “Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia,” <i>N. Engl. J. Med.</i> , 391(6):493-503 (June 2024) (“Sarafoglou et al. 2024”).
1058	“Neurocrine Biosciences Announces FDA Approval of CRENESSITY™ (crinecerfont), a First-in-Class Treatment for Children and Adults With Classic Congenital Adrenal Hyperplasia,” Neurocrine Biosciences (Dec. 13, 2024) (“Dec. 13, 2024, Neurocrine Press Release”).
1059	National Center for Biotechnology Information (2025), PubChem Compound Summary for CID 134694266, Tildacerfont. Retrieved February 4, 2025, from https://pubchem.ncbi.nlm.nih.gov/compound/134694266 .
1065	Sertkaya et al., “Key cost drivers of pharmaceutical trials in the United States,” <i>Clin. Trials</i> , 13(2):117-26 (2016).
1066	Spierling S.R. & Zorrilla E.P., “Don’t stress about CRF: Assessing the translational failures of CRF ₁ antagonists,” <i>Psychopharmacology (Berl.)</i> , 234(9-10):1467-81 (May 2017).

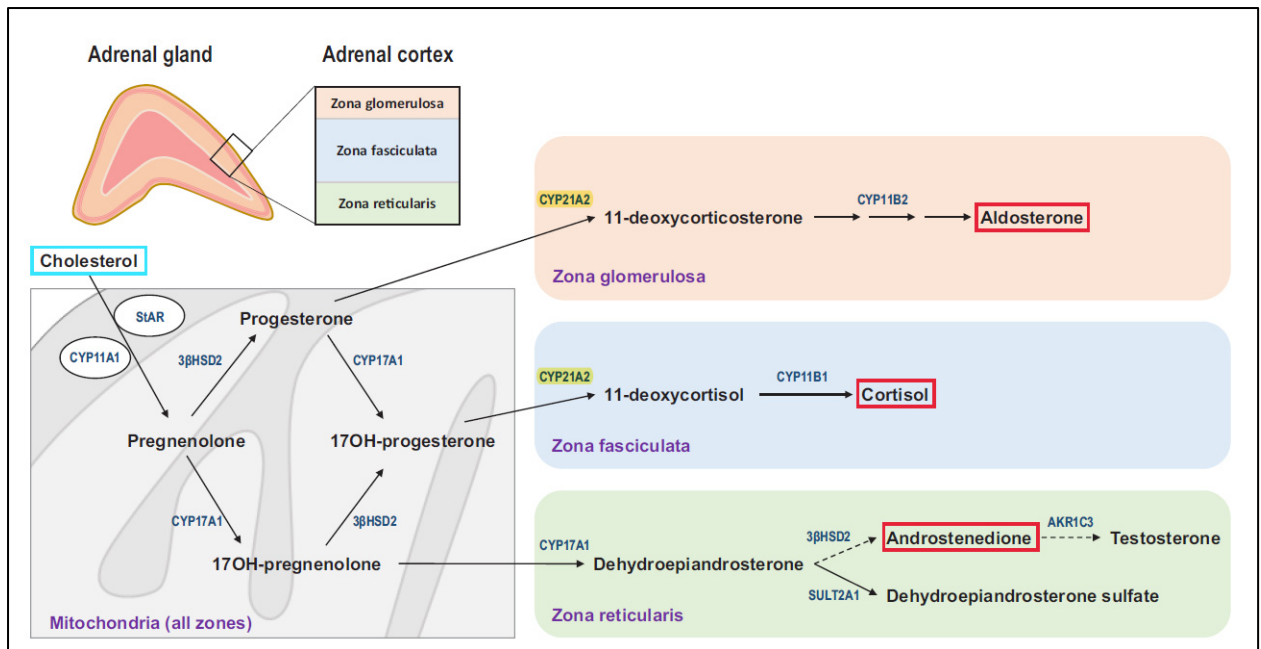
IV. TECHNOLOGY BACKGROUND

A. Congenital Adrenal Hyperplasia

15. Congenital adrenal hyperplasia (CAH) refers to a group of inherited autosomal recessive disorders affecting cortisol biosynthesis. EX1049, 93; EX1053, 2155. Reduced cortisol production disrupts the dynamic equilibrium of the negative feedback inhibition of both hypothalamic corticotropin-releasing factor (CRF) and pituitary corticotropin, which results in hyperplasia of the adrenal cortex. EX1046, 278; EX1053, 494. Approximately 90% to 99% of all CAH cases are caused by 21-hydroxylase deficiency (21OHD) due to mutations to the *CYP21A2* gene. EX1049, 93. CAH and 21OHD are often used interchangeably. EX1049, 93. CAH is conventionally separated into “classic” and “non-classic” forms, based on the severity of enzyme deficiency. EX1049, 93-94; EX1048, 802. However, current thinking views the different allelic variants of *CYP21A2* and their clinical manifestations as a continuum rather than two separate entities. EX1049, 93-94; EX1006, ¶ [0004]. Classic CAH occurs in roughly 1-in-10,000 to 1-in-20,000 persons. EX1024, 1248. Non-classic CAH occurs in roughly 1-in-200 to 1-in-1,000 persons. *Id.* The underlying mechanism for the classic and non-classic forms of 21OHD are the same. Less common forms of CAH, include a mutation of the 11 β -hydroxylase gene *CYP11B1*. EX1006, ¶ [0004]; EX1015, 2195; EX1046, 279.

16. In normal adrenocortical steroid production, all steroids produced in the adrenal cortex are derived from cholesterol. EX1039, 2155. There, cholesterol is enzymatically converted into various adrenocortical steroids, including aldosterone, cortisol, and androstenedione. EX1015, 2196-97. Aldosterone is the main mineralocorticoid steroid hormone produced by the adrenal gland, and it plays a central role in the homeostatic regulation of blood pressure, plasma sodium (Na^+) and potassium (K^+) levels. Cortisol is a glucocorticoid steroid hormone, which plays an important role in regulating blood sugar, immune responses, bone formation, and in the metabolism of fat, protein, and carbohydrates. Androstenedione is a common precursor in the biosynthesis of androgen and estrogen sex hormones.

17. The diagram below, taken from Sarafoglou (2023), depicts a simplified pathway of normal adrenocortical steroid production. In individuals without CAH, this pathway produces the appropriate amount of androgens, mineralocorticoids, and glucocorticoids necessary for normal growth and function. Further, in individuals without CAH, intermediates in this pathway do not significantly accumulate and the production of theoretical side products is minimal. EX1039, 2155.

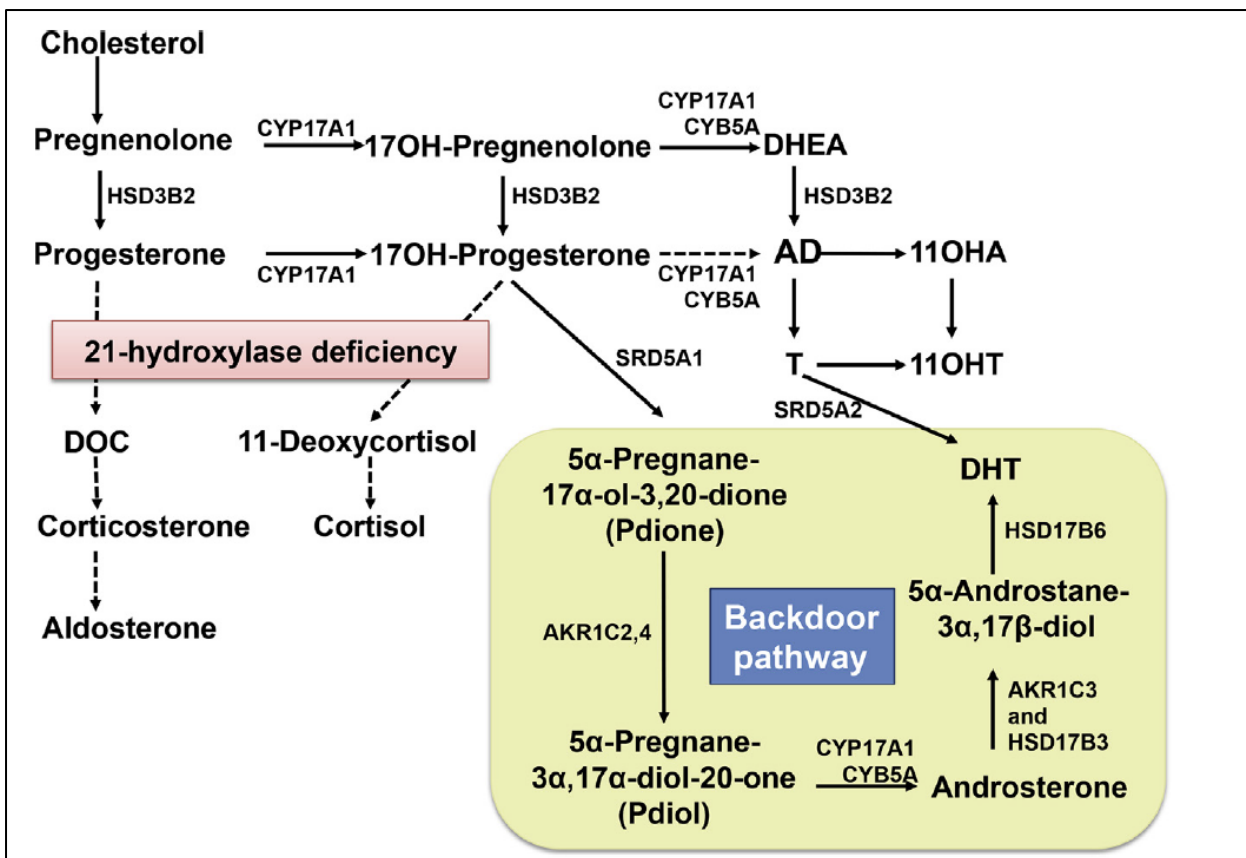


Adapted from EX1039, 2157, Fig. 3. Cholesterol (blue box) is enzymatically converted into various steroids, including aldosterone, cortisol, and androstenedione (red boxes). The protein encoded by the *CYP21A2* gene (yellow highlighting) is involved in the conversion of progesterone into aldosterone and 17-OHP to cortisol.

18. In persons with the most common type of CAH due to 21-hydroxylase deficiency, the protein encoded by *CYP21A2* cannot properly function and fails to convert progesterone into the precursor molecule for aldosterone and likewise fails to convert 17-OH-progesterone (17-OHP) into the precursor molecule for cortisol. EX1046, 280. As a result, insufficient amounts of cortisol are produced along this pathway and 17-OHP begins to accumulate both from overproduction due to ACTH signaling, as well as its inability to be broken down further due to enzymatic deficiency. EX1039, 2155. The reduction of cortisol in turn reduces the negative feedback on the hypothalamic-pituitary-adrenal axis and leads to excess adrenal androgen production, especially 17-OHP. EX1049, 94. The

accumulation of precursor steroids are then shifted to nonaffected androgen pathways or “backdoor pathway,” specifically through CYP17A1, resulting in the overproduction of androstenedione, which are then converted to the sex hormones testosterone and dihydroxytestosterone. EX1046, 280-81; EX1039, 2157.

19. The diagram below, adapted from Turcu & Auchus (2015a), shows the “backdoor pathway” in patients with 21OHD. The red box labeled “21-hydroxylase deficiency” disrupts the downstream conversion of 17-OHP and progesterone into cortisol and aldosterone, respectively. Instead, excess 17-OHP is converted downstream to androstenedione (“A4”, depicted as “AD” in the diagram below) and alternative paths (green box) leading to the overproduction of sex hormones.



Adapted from EX1046, 280, Fig. 2

20. Treatment of patients with classic CAH aims to reset the multiple hormonal imbalances by replacing deficient hormones (cortisol and aldosterone) and controlling adrenal androgen over-production triggered by the accumulation of precursor steroids and their metabolism by alternative androgenic pathways. EX1047, 338. Glucocorticoid replacement is the current standard of care for adults with CAH and has been the standard of care for many decades. EX1047, 338; EX1026, 456-59; EX1001, 11:27-31. But there is no single standard treatment regimen for all CAH patients—the steroid treatments used, and the dosing of those treatments, necessarily vary with a patient’s age, symptoms, severity of CAH, and

response to hormone replacement therapy. For example, hydrocortisone is the steroid predominately in children with CAH given its short half-life and lessened growth suppression. EX1047, 338-39. For adult patients with CAH, either hydrocortisone or longer acting glucocorticoids are used. EX1047, 339; EX1017, 4056; EX1013, 4140, 4147. Mineralocorticoid replacement is also recommended in patients unable to help maintain normal blood volume to maintain blood pressure and electrolyte balance. EX1047, 339; EX1001, 11:38-41; EX1017, 4056-57; EX1013, 4147-48.

21. Glucocorticoid treatment regimens must ensure that sufficient cortisol is available to support normal human physiology. EX1001, 11:42-45. However, the short to intermediate impact of glucocorticoid is often insufficient to reduce the early morning surge in adrenocorticotropin (ACTH), which is the principal driver of downstream androgen overproduction. EX1014, 8; EX1006, ¶ [0066]. The release of ACTH from the pituitary gland follows normal circadian patterns. ACTH is typically released between 1:00 and 2:00 a.m. in most patients, although the exact timing can vary by individual sleep schedules. EX1006, ¶ [0066]. The typical release of ACTH in the early morning hours leads to elevated ACTH levels throughout the morning in CAH patients. In attempts to counteract the excessive androgen production that follows due to inappropriately high ACTH, physicians often prescribe supraphysiological (*i.e.*, larger) glucocorticoid doses. EX1014, 8.

However, this increased exposure to glucocorticoids may lead to debilitating side effects including increased cardiovascular disease risk, glucose intolerance, and bone density loss in CAH patients. EX1014, 8; EX1001, 12:4-7. Elevated cortisol levels resulting from excessive glucocorticoid dosing can also lead to Cushing's syndrome. EX1006, ¶ [0045].

22. Beyond the problems associated with overexposure to glucocorticoids, insufficient cortisol levels in CAH patients can lead to the development of adrenal insufficiency. EX1001, 11:46-47. Failure to reduce the ACTH levels in CAH patients can result in problems associated with the overproduction of androgens, including abnormal puberty, abnormal linear growth, excessive hair growth, virilization, and infertility. EX1016, 2130-32. Balancing the risks between excessive cortisol or excessive androgens in CAH patients is difficult for physicians and patients alike.

B. The Use of CRF1 Receptor Antagonists to Treat CAH

23. Corticotropin-release hormone (CRH), interchangeably referred to as corticotropin-releasing factor (CRF), is a polypeptide hormone secreted by the hypothalamus that increases ACTH secretion by the pituitary gland. EX1049, 102. In turn, CRF may act directly on adrenocortical cells to increase cortisol secretion and expression of *CYP21A2*. EX1049, 102. CRF receptors include two main subtypes, CRF1 and CRF2. EX1018, 270. It has been understood in the field

since at least 2002 that CRF is the main regulator of the release of ACTH from the pituitary gland. EX1019, 333; EX1020, 322.

24. CRF1 receptor antagonists specifically bind to CRF1, thus blocking the ability of the agonist to bind to the receptor, therefore directly reducing ACTH secretion. There are large variety of CRF1 receptor antagonists with different structural properties and different binding affinities for the receptor. In patients with CAH this could in turn decrease the downstream production of androgens and reduce symptoms of hyperandrogenism, while also potentially allowing for the administration of glucocorticoids at physiological doses. EX1048, 802. This normalization of androgen production coupled with lower doses of glucocorticoids has the potential to reduce some of the treatment-associated side effects discussed above.

25. Scientific thought on CRF1 receptor antagonists as a treatment for CAH is well documented. The use of CRF1 receptor antagonists as a potential treatment for CAH has been discussed in the field since the early 2000s. For example, in a 2001 article entitled “New Ideas for Medical Treatment of Congenital Adrenal Hyperplasia,” Drs. Deborah Merke and Gordon Cutler proposed the use of CRF1 receptor antagonists to treat CAH and eliminate the need to rely solely on glucocorticoid negative feedback to prevent excessive adrenal androgen production. EX1021, 130-31. Then, in a 2002 article published in the

Annals of Internal Medicine, Drs. Merke and Bornstein noted that a CRF1 receptor antagonist, in combination with glucocorticoid and mineralocorticoid therapy, could potentially obviate the need for treatments such as antiandrogen-aromatase inhibitors or removal of a patient's adrenal glands. EX1022, 331. These observations were published again in *Lancet* in 2005. EX1016, 2132.

26. Then in 2016, Turcu et al. published the results of a Phase I clinical study evaluating the safety and efficacy of a CRF1 receptor antagonist developed by Neurocrine Biosciences, NBI-77860, in adult patients with 21-hydroxylase enzyme deficiency CAH. EX1008. Turcu and colleagues found that administration of 300 mg and 600 mg doses of NBI-77860 resulted in meaningful reductions in ACTH and 17-OHP in 6 of 8 patients. EX1008, 1179-80. The clinical report also detailed that the administration of 300 mg and 600 mg doses of NBI-77860 reduced androstenedione levels in 6 of 8 patients. EX1008, Table 3. Compared to placebo, administration of 300 mg and 600 mg NBI-77860 reduced androstenedione in the 6:00 to 10:00 a.m. timeframe (referred to as the “morning window” to note the time of peak ACTH elevation in CAH patients) in 6 of 8 patients, including one patient who achieved 57.9% reduction in androstenedione levels after a 600 mg dose and another patient who achieved a 27.9% reduction in androstenedione levels after a 300 mg dose. EX1008, Table 3.

27. Subsequently, several CAH review articles also cited the Turcu 2016 study as showing that a CRF1 receptor antagonist lowered ACTH and 17-OHP concentrations in patients with 21-hydroxylase deficiency CAH. EX1015, 2205; EX1014, 8; EX1025, 6; EX1049, 123.

28. In January 2015, Neurocrine Biosciences filed PCT Patent Application No. PCT/U2015/012315, entitled CRF1 Receptor Antagonists for the Treatment of Congenital Adrenal Hyperplasia. EX1006. The application published on January 26, 2017, as Publication No. US 2017/0020877. EX1006. US 2017/0020877 to Grigoriadis (“Grigoriadis”) discloses that “CRF₁ receptor antagonists have the potential to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen production while using lower, more physiologic doses of hydrocortisone, and thus reducing treatment-associated side effects.” EX1006, Abstract, ¶¶ [0006], [0040]. Grigoriadis discloses a number of specific CRF1 receptor antagonists as useful for the treatment of CAH based on their dissociation half-life, including SSR-125543 [4-(2-chloro-4-methoxy-5-methylphenyl)-N-(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine]. EX1006, ¶¶ [0051], [0054], [0077]-[0083]. SSR-125543 is also known as crinecerfont. *See* EX1033. Crinecerfont was developed by Neurocrine Biosciences for the treatment of CAH (EX1027, 2) and is now FDA approved, as of December 13, 2024. EX1058.

29. Neurocrine has studied crinecerfont as a treatment for CAH. On October 15, 2021, Neurocrine published the results of a Phase II clinical study evaluating crinecerfont for the treatment of CAH. EX1009. The Phase II study was an open-label, multiple-dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in adult subjects with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. *Id.*, 2-4. The study reported that the administration of crinecerfont to CAH patients resulted in reduction of ACTH, 17-OHP and A4 levels, compared to those patients' baseline hormone levels. *Id.*, 3-11, Tables 2-3, Figs. 2-4.

30. Neurocrine also studied crinecerfont for the treatment of CAH in adult and pediatric Phase III clinical studies. EX1052; EX1053. The Phase III studies were multi-dose studies to evaluate the efficacy, safety, and tolerability of crinecerfont versus placebo administered for 28 weeks in pediatric subjects, and 24 weeks in adult subjects with classic CAH due to 21-hydroxylase deficiency. EX1052; 1053. The adult Phase III study found the use of crinecerfont resulted in a greater decrease from baseline in the mean daily glucocorticoid dose, including a reduction to the physiologic range, than placebo following evaluation of adrenal androgen levels. EX1052, Abstract. The pediatric study found crinecerfont was superior to placebo in reducing elevated A4 levels in pediatric participants with CAH and was also associated with a decrease in the glucocorticoid dose from

supraphysiologic to physiologic levels while A4 control was maintained. EX1053, Abstract. Both of these Phase III studies were published in the New England Journal of Medicine. Crinicerfont was approved by the FDA on December 13, 2024, as an adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic CAH. EX1058.

31. Spruce Biosciences, Inc. (“Spruce”) has studied tildacerfont as a potential treatment for CAH. In March 2024, Spruce announced results from a Phase IIb clinical study evaluating tildacerfont for the treatment of CAH. EX1044. Tildacerfont did not meet its primary efficacy endpoint in this study. *Id.* On December 10, 2024, Spruce announced results from a second Phase IIb clinical study evaluating the safety and efficacy of tildacerfont in reducing supraphysiologic glucocorticoid usage in 100 adults with classic CAH. EX1045. Tildacerfont also did not meet its primary efficacy endpoint in the Phase IIb study. *Id.*

V. THE '166 PATENT

32. I have reviewed the '166 patent and its prosecution history. The '166 patent issued on October 15, 2024. Spruce is listed as assignee on the front page of the '166 patent. The '166 patent claims priority to provisional application no. 62/545,406, filed on August 14, 2017. EX1001.

33. The technology described in the '166 patent relates to relates to the use of a single CRF1 receptor antagonist, Compound 1, to treat CAH. Compound 1 is defined in the '166 patent as 3-(4-Chloro-2-(morpholin-4-yl)(thiazol5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine (or alternatively 4-(4-chloro-5-(2,5 dimethyl-7-pentan-3-yl) pyrazolo[1,5-a] pyrimidin-3-yl) thiazol-2-yl) morpholine). EX1001, 1:40-44, 14:40-67. I understand that this compound is also known as tildacerfont. *See* EX1059.

34. All the disclosure in the '166 patent relates to the use of Compound 1 (tildacerfont) to treat CAH. For example, the Summary of the Invention section states, “[t]he present invention provides novel pharmaceutical compositions comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).” EX1001, 1:40-44. When discussing methods of treating CAH that further comprise administering a glucocorticoid, the specification states “[i]n some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.” *Id.*, 7:50-54; *see also id.*, 32:22-29.

35. The '166 patent specification also defines stability as the stability of Compound 1. EX1001, 25:22-28 (“Stable as used herein refers to pharmaceutical

compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1.”). All of the stability data in the ’166 patent relates to pharmaceutical compositions containing Compound 1 as the active ingredient. EX1001, 34:57-36:57 (Example 2).

36. All of the Examples in the ’166 patent relate to Compound 1 (tildacerfont). EX1001, 33:35-47:49. The only clinical data reported in the ’166 patent specification is from Phase I and Phase II studies evaluating Compound 1. *Id.*, Tables 5-8, 44:43-67. As discussed in further detail below, in my opinion, the ’166 patent discloses the use of only tildacerfont for the treatment of CAH.

37. I understand from counsel for Neurocrine that the claims of the ’166 patent define the scope of the legal rights of the patent. Specifically, claim 1, the only independent claim, recites a method for treating CAH as follows:

1. A method for treating congenital adrenal hyperplasia (CAH) in a human, comprising:

administering to said human a therapeutically-effective amount of a CRF₁ receptor antagonist or a pharmaceutically acceptable salt thereof,

wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and

administering to said human a second dose of a glucocorticoid, wherein said second dose of

glucocorticoid is reduced compared to said first dose of glucocorticoid,

wherein an androstenedione (A4) level in said human is reduced from baseline, or

wherein an adrenocorticotrophic hormone (ACTH) level in said human is reduced from baseline, or

wherein a 17-hydroxyprogesterone (17-OHP) level in said human is reduced from baseline,

wherein said CRF₁ receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day, and wherein said CRF₁ receptor antagonist is stable for storage for a minimum of six months.

EX1001, 48:63-49:19.

38. Claim 11 is the only claim that limits the CRF₁ receptor antagonist to Compound 1 (tildacerfont). *Id.*, 50:3-22. I understand that all of the other claims of the '166 patent are not limited to Compound 1 and encompass administering a therapeutically-effective amount of any CRF₁ receptor antagonist. *Id.*, 48:63-50:48.

VI. THE '166 PATENT PROSECUTION HISTORY

39. The application that led to the '166 patent was filed on April 26, 2023, as U.S. Patent Application No. 18/307,718 (“the '718 application”). *See* EX1002. I understand from counsel that the '718 application claimed priority to provisional Patent Application No. 62/545,406 (“the '406 provisional”), which was filed on August 14, 2017. The claims of the '406 provisional were limited to the

administration of Compound 1 (tildacerfont) or a pharmaceutically acceptable salt or solvate thereof. EX1035, 52-61.

40. During prosecution, the Examiner issued only one Office Action, making a non-final rejection of the pending claims as obvious over Neurocrine's published patent Application No. 2017/0020877 ("Grigoriadis"; EX1006) in combination with other prior-art references. EX1002, 2476. I understand that the Examiner did not issue any claim rejections based on lack of written description or lack of enablement. *See id.* The '166 patent issued on October 15, 2024, which was prior to the Board's Final Written Decisions finding the '908 and '201 patent claims unpatentable for lack of written description. EX1001; EX1005; EX1007.

VII. PATENT OFFICE CHALLENGES TO THE RELATED '908 AND '201 PATENTS

41. I understand that Neurocrine has previously challenged two other Spruce patents, U.S. Patent No. 10,849,908 (the "'908 patent") and U.S. Patent No. 11,007,201 (the "'201 patent") in Post-Grant Review ("PGR") proceedings before the Patent Office's Patent Trials and Appeals Board ("the Board"). I have reviewed the declarations of Dr. Robert Carey and Dr. Gordon Cutler, submitted on behalf of Neurocrine in those proceedings.

42. I understand that in the prior PGR proceedings, Neurocrine contended that the '908 and '201 patent claims were unpatentable for lack of written description, and that the challenged claims were unpatentable as anticipated and/or

obvious in view of Neurocrine's prior work. I have reviewed the Board's Final Written Decisions in the prior PGR proceedings and understand that the Board found all claims of the '908 and '201 patents unpatentable for lack of written description. EX1005, 42-59; EX1007, 40-57. I understand that because the Board found all of the '908 and '201 patent claims unpatentable for lack of written description, it did not decide Neurocrine's anticipation and obviousness arguments. EX1005, 59; EX1007, 57.

VIII. LEVEL OF KNOWLEDGE OF ONE OF ORDINARY SKILL IN THE ART PERTAINING TO THE '166 PATENT

43. I understand that Dr. Carey previously opined regarding the knowledge of a person of ordinary skill in the art ("POSA") of two Spruce patents in the same family as the '166 patent, the '908 and '201 patents. Dr. Carey opined that a hypothetical POSA would have a medical degree or a Ph.D. in a field related to endocrinology, and would have knowledge of hormone regulation and disorders, and knowledge of the treatment regimens employed to treat such disorders. The hypothetical POSA would also have at least three years of experience conducting research concerning endocrine disorders, including CAH and other adrenal disorders. In my opinion, a POSA in the field of the '166 patent may have also worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also consulted with others on the team having specialized skills to solve a problem, including analytical chemistry and pharmaceutical formulation.

Based on my review of the '166 patent specification, the patent prosecution history, the prior art, and my experience and general knowledge, I believe this definition of a POSA is applicable to the '166 patent.

IX. INTERPRETATION OF THE '166 CLAIMS AT ISSUE

44. I have been informed by counsel for Neurocrine that for purposes of my analysis, the terms appearing in the '166 patent claims should be interpreted according their ordinary and customary meaning as understood by a POSA in view of the patent's disclosure and prosecution history. In that regard, I understand that the best indicator of claim meaning is its usage in the context of the patent specification as understood by a POSA.

45. I understand that the words of the claims should be given their plain meaning unless that meaning is inconsistent with the patent specification or the patent's history of examination before the Patent Office. I also understand that the words of the claims should be interpreted as they would have been interpreted by a POSA as of the effective filing date of the claimed invention.

46. The term "baseline" appears in '166 patent independent claim 1, and in dependent claims 2-9. EX1001, 48:63-49:46. I understand from counsel that in the prior PGR proceedings addressing the '908 and '201 patents, the Board construed the term "baseline" as meaning "a series of samples taken from an untreated patient with CAH, prior to treatment at intervals that are time-matched to

the sampling intervals to be taken from the patient treated with either a CRF1 receptor antagonist or placebo.” EX1005, 25-26; EX1007, 24-25. The Board determined that no claim construction was necessary to resolve the written description issue in the prior PGRs. EX1005; EX1007

X. LEGAL STANDARDS

47. I am not an attorney, and I will offer no opinion on the law. I am, however, informed by Counsel and understand several principles concerning patentability that I have used in arriving at my opinions.

48. I understand from Counsel that the earliest effective filing date of the '166 patent is August 14, 2017, the date the first provisional patent application in this patent family was filed.

A. Written Description

49. I understand that the specification must contain a “written description” of the claimed invention that allows a POSA to recognize that the inventor invented what is claimed. I understand that the test for written description is whether the disclosure in the specification reasonably conveys to a POSA that the inventor had possession of the full scope of the claimed invention as of the filing date. I understand that the written description requirement is applied in the context of the state of knowledge in the art at the time the patent application was filed.

50. The level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. I understand that factors used to evaluate the sufficiency of a disclosure include: 1) the existing knowledge in the particular field; 2) the extent and content of the prior art; 3) the maturity of the science or technology; and 4) the predictability of the claimed method or invention.

51. I understand that when a claim recites a genus of compounds using functional language to define a claimed result, the specification must disclose either a representative number of compounds falling within the scope of the genus that achieve the claimed result, or structural features common to the members of the family that achieve the claimed result, so that a POSA can visualize or recognize the members of the family.

B. Enablement

52. I understand that the specification must “enable” a POSA to make and use the full scope of the claimed invention. I understand that an enabling disclosure is one which provides sufficient detail to allow a POSA to make and use the claimed invention without “undue experimentation.”

53. I understand that the following factors may be considered in deciding whether a POSA would have to engage in undue experimentation to make an use

the invention: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

54. I understand that none of the above factors is alone dispositive. Rather, whether the degree of experimentation required is undue may involve weighing these factors in the context of the claimed invention and the state of the art at the time of the original application to determine whether a POSA would need to engage in undue experimentation to make and use the full scope of the claimed invention.

55. I understand that the specification must enable a POSA to make and use the entire scope of the claimed invention, but it need not describe every single embodiment with particularity. For example, when a patent claims an entire class of compounds by their function rather than physical characteristics or chemical properties such as structure, the patent must provide some “general quality” of the class that gives those compounds that function.

XI. OPINIONS REGARDING WRITTEN DESCRIPTION OF THE '166 PATENT

56. In my opinion, the Challenged Claims lack written description support. Independent claim 1 of the '166 patent recites, among other things, “[a]

method for treating congenital adrenal hyperplasia (CAH) in a human, comprising: administering to said human a therapeutically-effective amount of a CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof.” EX1001, 48:63-49:19.

Claim 1 is not limited to a particular CRF1 receptor, and thus I understand claim 1 encompasses a genus of CRF1 receptor antagonists that have the function of reducing glucocorticoid dosing, and reducing an A4, ACTH, or 17-OHP level from baseline, and that are stable for storage for a minimum of six months. I understand that dependent claims 2-10 and 12-21 also encompass a genus of CRF1 receptor antagonists that perform the recited functions.¹ EX1001, 49:20-50:2, 50:23-48.

A. The only CRF1 receptor antagonist disclosed in the '166 patent specification is tildacerfont.

57. Although the '166 patent claims encompass an entire class of CRF1 receptor antagonists, the patent itself describes a single compound, Compound 1 (tildacerfont). Throughout the '166 patent specification, the description of the invention points only to tildacerfont and to no other CRF1 receptor antagonists. *See, e.g.*, EX1001, Abstract, 1:32-40, 4:45-5:2, 8:37-40, 8:63-67, 9:19-22, 9:46-49, 35:62-41:41, 41:43-43:53. For example, the Summary of the Invention section states: “The present invention provides novel pharmaceutical compositions

¹ Claim 11, which depends from claim 1, claims a specific CRF1 receptor antagonist, namely Compound 1, which is tildacerfont. I understand that Neurocrine is not challenging the patentability of claim 11.

comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine [i.e., tildacerfont] and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).” EX1001, 1:32-36 (emphasis added). The specification provides structural information for tildacerfont (Compound 1), but no other compounds. *See, e.g., id.*, 1:40-45. All the examples, including the reported clinical data, in the ’166 patent describe only tildacerfont. *Id.*, 33:35-47:37, Tables 5-8. In my opinion, there is no disclosure of any other CRF1 receptor antagonist or any other compound besides tildacerfont for the treatment of CAH in the ’166 patent. I am aware that the Board came to the same conclusion when evaluating the ’908 and ’201 patents, which have the same specification as the ’166 patent. *See* EX1005, 43-44; EX1007, 41-43.

58. Spruce’s clinical research article titled “Tildacerfont in Adults with Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies” (EX1041) describes tildacerfont as being a “second-generation CRF1 antagonist” having “unique structural features” compared to other CRF1 receptor antagonists. EX1041, 4667. The ’166 patent does not describe what these “unique structural features” are, nor does it teach a POSA how to identify other CRF1 receptor antagonists that might share these features.

59. The '166 patent specification also does not describe any structural features common to the CRF1 receptor antagonists that could be administered to treat CAH and achieve the claimed reductions in glucocorticoid dosing, and in reducing A4, ACTH, or 17-OHP levels from baseline, and that are stable for storage for a minimum of six months. The only disclosure in the '166 patent in the specification is of tildacerfont (i.e., Compound 1). Further, I am not aware of anything in the '166 patent specification that discloses a structure to function relationship that could indicate a class or genus of CRF1 receptor antagonists would have the potential to be therapeutically effective, as claimed.

B. At the time of the '166 patent filing, the prior art did not describe common structural features of therapeutically effective CRF1 receptor antagonists.

60. CRF1 receptor antagonists are compounds that interfere with or inhibit CRF1 receptors. Compounds that interfere with or inhibit CRF1 receptors are defined functionally and are not defined by a particular structure or structures.

61. As of August 17, 2017, the effective filing date, some CRF1 receptor antagonists had already been characterized, and that characterization showed that CRF1 receptor antagonist compounds have a wide variety of structural features. *See, e.g.*, EX1018; EX1029. Two such references are the Williams article (EX1029) and the Fahmy article (EX1018).

62. In my opinion, the Williams article (EX1029) illustrates that there are no common structural features that identify a class of therapeutically effective CRF1 receptor antagonists. Williams describes that a “typical” CRF1 receptor antagonist consist of a “core” nitrogen heterocycle with an aryl substituent adjacent to the core nitrogen atom and a branched alkyl group attached at the opposite end of the core. EX1029, 2. Williams describes a number of classes and sub-classes of CRF1 receptor antagonists, the most prevalent of which Williams designates as “Type 1” as depicted in Figure 2. EX1029, 2, Fig. 2. Because of the additional unspecified alkyl and other variations in Fig. 2 of Williams, the “Type 1” subclass comprises a large and indeterminate number of unique structures.

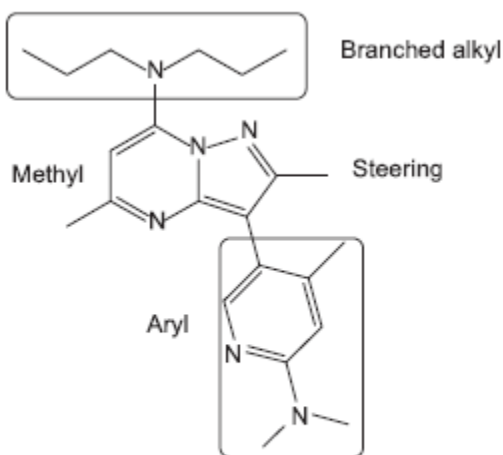


Figure 2. Regions of CRF₁ antagonist SAR.

EX1029, Fig. 2.

63. Williams discloses that CRF1 antagonists in the “Type 1” subclass “have been associated with less than optimal physicochemical properties and it was

assumed that these were a major contributor to CRF1 antagonist struggles in the clinic.” EX1029, 2. Williams goes on to describe a number of optimization efforts that were aimed at improving the physicochemical properties of CRF1 antagonists, including 1) restricting the conformational freedom of the branched alkyl side chain; 2) increasing polarity by introducing aromatic heterocycles in the aryl region and 3) reducing the number of carbon atoms in the core region. *Id.*, 2-4. In my opinion, Williams teaches that the “Type 1” CRF1 receptor antagonists are not therapeutically effective.

64. The Williams article contains no mention of CAH and does not describe any particular CRF1 receptor antagonist as useful to treat CAH. Williams also does not disclose that the administration of any particular CRF1 receptor antagonist can achieve reduced glucocorticoid dosing in a patient, or reduce A4, ACTH, or 17-OHP levels in a patient. On the contrary, Williams discloses that the majority of clinical studies examining the utility of CRF1 receptor antagonists studied stress-related conditions such as anxiety, depression, substance abuse, post-traumatic stress disorder, and stress-induced relapse in craving responses to food, nicotine, and alcohol. EX1029, 1-2.

65. Williams also states that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.” EX1029, 9. In my opinion, this statement, and Williams’ disclosure as a

whole, would teach a POSA that CRF1 receptor antagonists were not therapeutically effective for any particular indication, and not therapeutically effective for the treatment of CAH.

66. Williams also reports on additional subclasses of CRF1 receptor antagonists that have a variety of structural features. For example, Williams describes a number of “first-generation CRF1 antagonists” identified in Figure 1, several of which do not fall within the “Type 1” subclass illustrated in Figure 2:

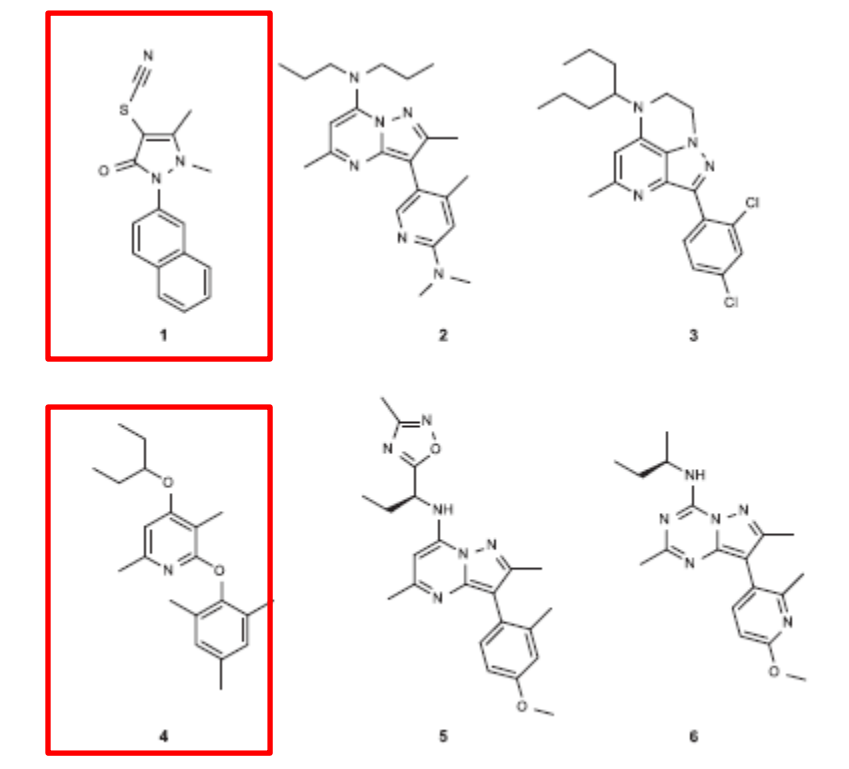


Figure 1. First-generation CRF₁ antagonists.

EX1029, Fig. 1 (red boxes showing CRF1 receptor antagonists that do not fall within Figure 2 structure).

67. As another example of the diversity of structure inherent in known CRF1 receptor antagonists, Williams also reports monocyclic CRF1 receptor antagonists, which have a monocyclic heterocycle instead of the “core” nitrogen heterocycle Williams describes as characteristic a “typical” CRF1 receptor antagonist. EX1029, 4-5, Fig. 6. Williams also notes “another unique structural class of CRF1 antagonists that do not appear to overlap in similar chemical space with the traditional compounds,” which he refers to as atypical CRF1 antagonists. *Id.*, 7, Fig. 11.

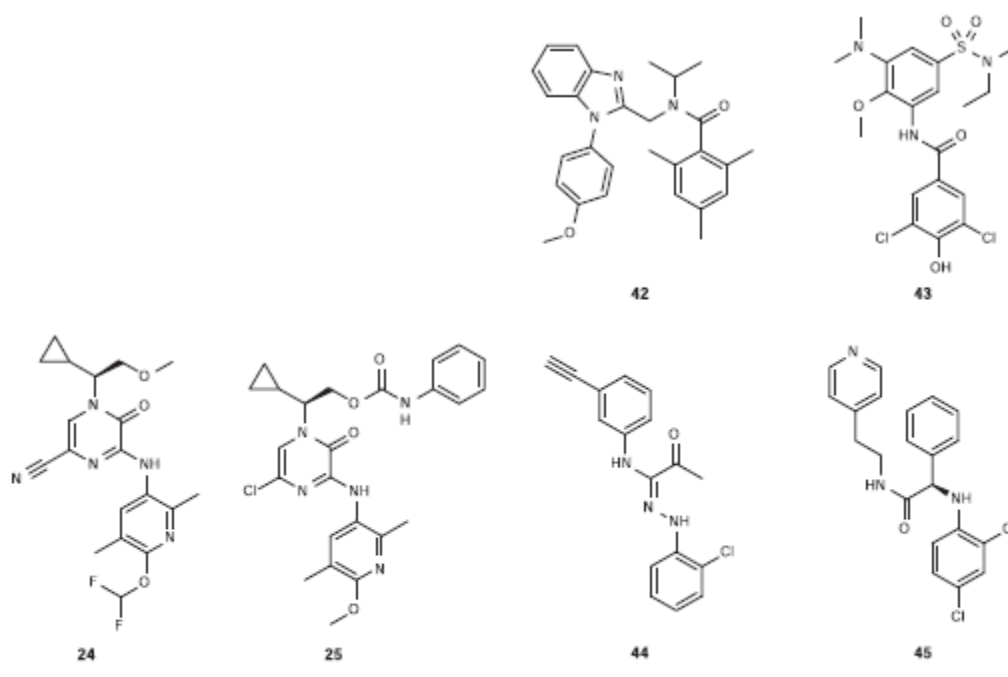


Figure 6. Type I monocyclic CRF₁ antagonists.

Figure 11. Atypical CRF₁ antagonists.

EX1029, Figs. 6, 11. In my opinion, the Williams article reflects that CRF1 receptor antagonists have a wide variety of structural features, and that at the time

of the patent filing a POSA would not know based on structural features which, if any, CRF1 receptor antagonists would be useful to treat CAH.

68. Fahmy (EX1018) also illustrates that CRF1 receptor antagonists can have a wide variety of structural features. Fahmy et al. discloses a broad structure described as a “basic CRF1 receptor antagonist pharmacophore” with a generalized description in which the authors state “CRF1 receptor antagonists are typically built of three moieties: a hydrophobic moiety up, a proton accepting moiety in the middle, and an aromatic moiety down.” EX1018, 3, Fig. 1.

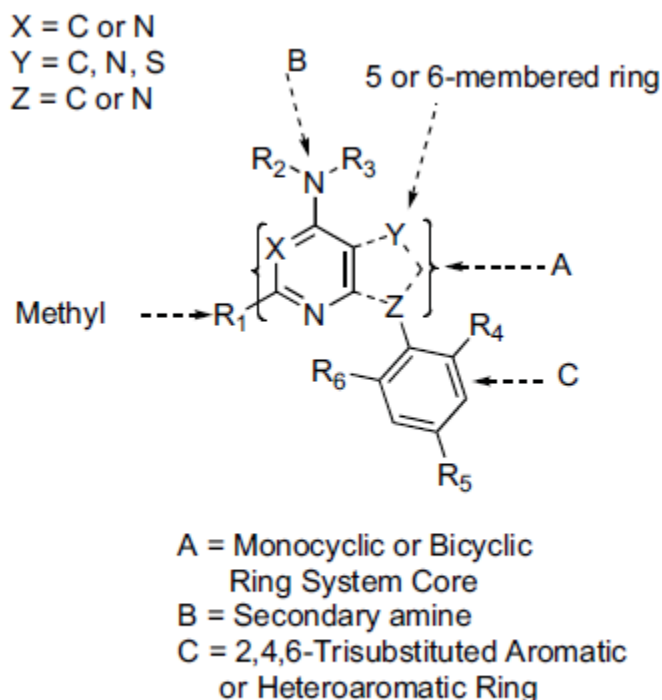
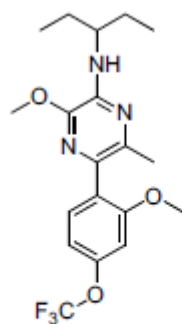


Fig. (1). Pharmacophore structure of CRF1 antagonists.

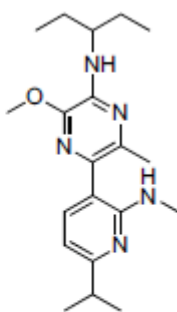
EX1018, 3. This general description, which comprises a large and indeterminate number of unique chemical structures, does not provide any information on what

structural features of CRF1 receptor antagonists would be important for identifying a therapeutically effective CAH treatment.

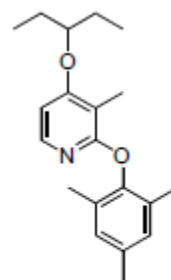
69. Fahmy also identifies other CRF1 receptor antagonist structures that do not fall within the broad, general structure disclosed in Figure 1. For example, Fahmy teaches that CRF1 receptor antagonists can be classified according to the number of rings in the heterocyclic core ring system, as monocyclic, bicyclic, or tricyclic CRF1 receptor antagonists. EX1018, 3-7. Fahmy categorizes monocyclic CRF1 receptor antagonists further into pyrazine, pyridine, pyrimidine, and thiazole subclasses. *Id.*, 3-5, Figs. 2-5.



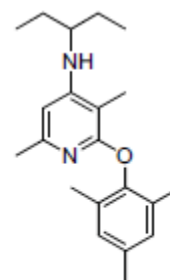
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CP-316311



CP-376395

Fig. (2). Structures of pyrazine CRF antagonists.

Fig. (3). Structures of pyridine CRF antagonists.

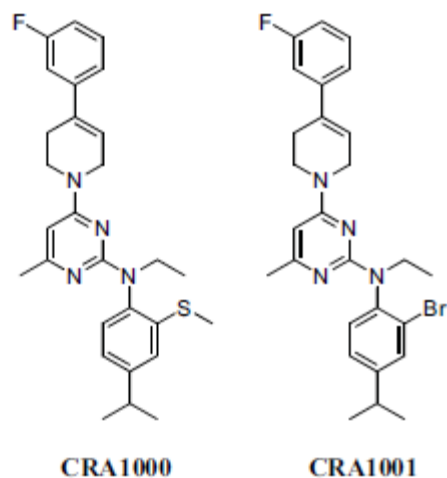


Fig. (4). Structures of pyrimidine CRF antagonists.

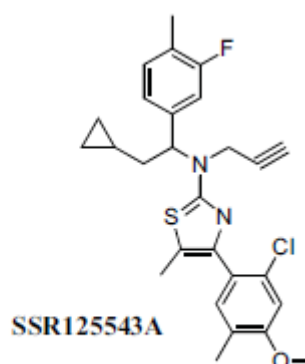


Fig. (5). Structures of thiazole CRF antagonist.

EX1018, Figs. 2-5.

70. Fahmy similarly describes subclasses of bicyclic CRF1 receptor antagonists: pyrrolo[2,3-d]pyrimidines; pyrazolo[1,5- α]1,3,5-triazines; pyrazolo[1,5- α]pyrimidines; and imidazo[1,2-b]pyridazines. EX1018, 5-7; Figs. 6-10.

71. Fahmy also describes subclasses of tricyclic CRF1 receptor antagonists: triazaacenaphthylenes; and tetraazaacenaphthylenes. EX1018, 7-8, Figs. 11-12.

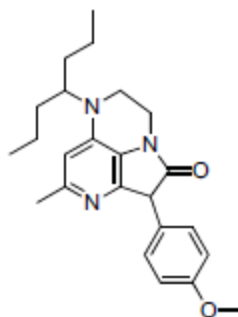
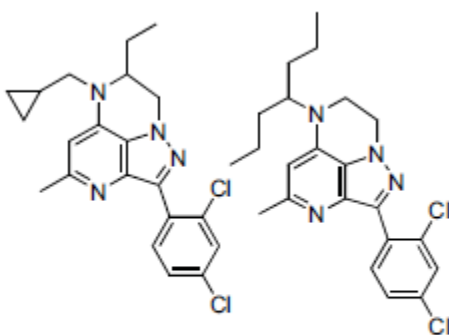


Fig. (11). Structure of Triazaacenaphthylenes CRF antagonists.



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Fig. (12). Structure of Tetrazaacenaphthylenes CRF antagonists.

EX1018, Figs. 11-12.

72. In my opinion, Fahmy does not identify structural features of CRF1 receptor antagonists that would tell a POSA that a certain CRF1 receptor antagonists would be useful for the treatment of CAH. The only mention of CAH in Fahmy is that a single CRF1 receptor antagonist, verucerfont, was under investigation by Neurocrine as a possible treatment for CAH. EX1018, 7. In my opinion, this disclosure would not tell a POSA whether verucerfont, or any other CRF1 receptor antagonist, would be effective to treat CAH, including whether it

could reduce glucocorticoid dosing, or reduce A4, ACTH, or 17-OHP levels in a patient.

C. Additional references demonstrate that whether CRF1 receptor antagonists could be clinically useful was unpredictable.

73. There is a high level of unpredictability in the field as to whether any CRF1 receptor antagonist will be therapeutically effective in a human for any indication, much less therapeutically effective to treat CAH. As described above, the Williams article reviewed the study of CRF1 receptor antagonists as of 2013 and concluded that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.”

EX1029, 9. Williams also reports on several clinical studies in which CRF1 receptor antagonists failed to demonstrate utility in treating depression and anxiety disorder. *Id.*, 2. A 2010 article by Zorrilla et al. noted that while one CRF1 receptor antagonist, R121919, demonstrated efficacy in reducing depression symptoms (but was discontinued for safety reasons), two other CRF1 receptor antagonists failed to show efficacy in treating depression. EX1030, 377-78. Further, a 2010 review article by Kehne et al. also noted that several CRF1 receptor antagonists had failed to demonstrate efficacy in treating depression disorders. EX1031, 24-25. Additionally, an article by Spierling and Zorrilla likewise summarized clinical trial outcomes of small-molecule CRF1 antagonists

studied for various indications and noted that several of the studied CRF1 receptor antagonists lacked efficacy. EX1066, Table 1. These results regarding efficacy of CRF1 receptor antagonists demonstrate that a POSA would not understand nor assume that a genus of CRF1 receptor antagonists would be therapeutically effective to treat CAH, or any other indication.

74. Aside from purely structural differences, Neurocrine's own work published in Grigoriadis (EX1006) provides evidence for why a POSA would expect differences in therapeutic effectiveness among different CRF1 receptor antagonists based on receptor affinity of the antagonist. Grigoriadis shows a 980-fold difference in the kinetically determined CRF1 receptor affinities for 13 different CRF1 receptor antagonists. EX1006, ¶[0078]. Crinecerfont showed the highest receptor affinity, and based on this property, Neurocrine chose crinecerfont to take forward into future development. The half-lives of CRF1 receptor dissociation for the 13 CRF1 receptor antagonists also greatly differed (by 165-fold, from 2.6 min for NBI 27914 to 430 min for crinecerfont). EX1006 ¶¶ [0080]-[0083]. These differences in receptor affinity may produce differences in effectiveness. Unlike Grigoriadis, the '166 patent does not teach the receptor affinity of tildacerfont, nor provide any comparisons between the receptor affinity of tildacerfont with other CRF1 receptor antagonists, which could indicate a potential relationship between structure and function.

75. In summary, the prior art taught that CRF1 receptor antagonists could display a considerable variety of structures, and that most were not shown to be therapeutically effective for their studied indication. Whether any particular CRF1 receptor antagonist would be effective to treat CAH was, and is, unpredictable. The '166 patent claims the use of an entire class of CRF1 receptor antagonists to treat CAH that can achieve the claimed reduction in glucocorticoid dosing, and reductions in A4, ACTH, or 17-OHP from baseline. However, the only CRF1 receptor antagonist disclosed in the '166 patent is tildacerfont, and Spruce has indicated tildacerfont has “unique structural properties.” EX1041, 4667. The '166 patent also does not disclose any information about the relationship between CRF1 receptor antagonist structure and its function as a potential treatment for CAH. For these reasons, in my opinion the limited disclosure of the '166 patent is not commensurate with claiming the use of an entire class of CRF1 receptor antagonists to treat CAH in claims 1-10 and 12-21.

XII. OPINIONS REGARDING ENABLEMENT OF THE '166 PATENT

76. It is my opinion that the '166 patent does not adequately enable the class of CRF1 receptor antagonists or pharmaceutically acceptable salts thereof recited in claims 1-10 and 12-21. Specifically, in view of the breadth of the claims, the nature of the invention, the nascent state of the art, the level of one of ordinary skill, the unpredictability in the art, the lack of direction provided in the

'166 patent, the existence of no working examples other than those related to tildacerfont, and the quantity of experimentation needed to make or use the full scope of the claimed CRF1 receptor antagonists, it is my opinion that a POSA would have to perform undue experimentation to practice the invention as broadly as claimed.

77. As discussed above, claim 1 recites a broad genus of CRF1 receptor antagonists that treat CAH in a human by reducing glucocorticoid dosing and A4, ACTH, or 17-OHP levels from baseline. Thus, the claim defines the broad genus only by its function. The claim does not limit the genus by any quality common to all members of the genus, such as size, structure, chemical nature, drug absorption, metabolism, or receptor binding affinity. None of the other claims that Neurocrine challenges in this proceeding, i.e., claims 2-10 and 12-21, narrow the claimed genus of CRF1 receptor antagonists. Specifically, none of these claims recite a quality common to the claimed class of CRF1 receptor antagonists.

78. It is my opinion that claim 1 encompasses every CRF1 receptor antagonist having the recited functions, and thus, encompass an unknowable number of putative CRF1 receptor antagonists. The putative CRF1 receptor antagonists could include, for example, both large molecules (e.g., peptides) and small molecules (e.g., chemical compounds). For example, Zorrilla (EX1030) states that CRF1 receptor antagonists include peptide CRF1 antagonists,

antagonists with signal transduction selectivity and non-peptide CRF1 antagonists that act via the extracellular domains of the CRF1 receptor. EX1030, 371. Given the unknowable number of putative CRF1 receptor antagonists, it would take a POSA years of iterative, trial-and-error experimentation to make and use all potential CRF1 receptor antagonists falling within the scope of the claim.

79. It is my opinion that the '166 patent does not provide a POSA with adequate direction or guidance as to which CRF1 receptor antagonists within the claimed genus of CRF1 receptor antagonists could treat CAH in a human by reducing glucocorticoid dosing and reducing an A4, ACTH, or 17-OHP level from baseline. The '166 patent discloses only one example of a CRF1 receptor antagonist that purportedly treats CAH: Compound 1 (tildacerfont). The '166 patent discloses the structure of tildacerfont but does not describe any quality or features common to the members of the claimed genus, such as size, structure, or chemical nature. The '166 patent does not explain what features of tildacerfont make it particularly suitable for treating CAH. The '166 patent also does not teach a POSA a means for distinguishing functional from non-functional members of the claimed genus, nor does it teach a means for predicting which CRF1 receptor antagonists will function as claimed. Thus, the only way a POSA can practice the full scope of the claims is to make putative CRF1 receptor antagonists and test each one to determine whether any perform the claimed functions.

80. This iterative, trial-and-error process would require years of research at considerable costs. EX1032, 62. For example, a POSA would need to synthesize and screen a large number of putative CRF1 receptor antagonists for their individual binding kinetics and functional inhibition properties at the CRF1 receptor. Once a POSA identified putative CRF1 receptor antagonists, a POSA would then need to assay each of those compounds *in vitro* for their ability to antagonize CRF1 receptor binding. Although some commercially available high-throughput assays are available, the amount of experimentation to test an untold number of putative CRF1 receptor antagonists would be extensive. Finally, because the claims require treating CAH in a human, the only way to determine whether the remaining putative CRF1 receptor antagonists worked to do so would be to conduct time-consuming and expensive clinical trials in individuals with a rare disease.

81. In addition, it is my opinion that none of the examples in the '166 patent provide adequate enabling disclosure for the board scope of the claims because all the examples in the '166 patent are directed to tildacerfont. Specifically, Example 1 describes 200 mg tildacerfont in size 1 white hard gelatin capsules. EX1001, 34:50-56. Example 2 provides stability data for 1 mg, 5 mg, 50 mg, and 200 mg tildacerfont capsules packaged in either plastic blister packs or bottles. *Id.*, 34:57-36:57. Of course, neither of these examples provide guidance

to a POSA as to which CRF1 receptor antagonists could be used to treat CAH in humans.

82. The remaining examples, Examples 3-8, relate to clinical studies of tildacerfont and do not provide guidance to a POSA as to which other CRF1 receptor antagonists could be used to treat CAH in humans. EX1001, 36:58-48:61. Specifically, Examples 3 and 4 provide data from Phase 1 and Phase 2 clinical studies of tildacerfont. Examples 5 and 6 provide proposed examples for other Phase 2 clinical studies of tildacerfont, and Examples 7 and 8 provide proposed examples for Phase 3 clinical studies of tildacerfont.

83. In the '166 patent, Example 3 describes Phase 1 clinical studies of the safety, tolerability, and pharmacokinetics (PK) of tildacerfont in healthy adult volunteers. The results of Example 3 showed that “single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 [tildacerfont] were well-tolerated by healthy male and female subjects.” EX1001, 42:30-32. Examples 4, 5, and 6 relate to Phase 2 clinical studies. Example 4 was designed to test the safety, PK, and pharmacodynamics (PD) of tildacerfont in patients with classic CAH. *Id.*, 42:35-67. The results of Example 4 show that 80% of patients experienced reduced ACTH levels, 80% experienced reduced 17-OHP levels, and that 100% of patients experienced reduced A4 levels. *Id.*, 44:42-67. Example 5 is a proposed study example designed to test the safety and efficacy of tildacerfont in patients

with classic CAH over a three-month period. EX1001, 45:1-60. Example 6 is a proposed Phase 2 proof of concept study for treating adolescents with classic CAH. *Id.*, 45:62-47:12. Finally, Examples 7 and 8 are proposed examples of Phase 3 clinical studies. Example 7 is a proposed study example designed to test tildacerfont for the treatment of class CAH with the primary outcome measure being the efficacy of tildacerfont in reducing A4 and 17-OHP levels in patients with CAH. *Id.*, 47:15-48:20. Example 8 is a proposed study example designed to test whether CAH patients can have their dose of glucocorticoid progressively reduced from a supraphysiologic dose to a lower dose at or close to a dose equivalent to a physiologic does of glucocorticoid while taking tildacerfont. *Id.*, 48:25-61.

84. Just as with Examples 1 and 2, it is my opinion that none of examples 3-8 provide adequate guidance to a POSA as to which other CRF1 receptor antagonists are capable of treating CAH in a human by reducing glucocorticoid dosing and reducing an A4, ACTH, or 17-OHP level from baseline. It would take years of experimentation for a POSA to have followed Examples 3-8 to test a putative CRF1 receptor antagonist, much less all of the CRF1 receptor antagonists, falling within the claimed class of CRF1 receptor antagonists for the claimed functions.

85. Put differently, even if a POSA screened for putative CRF1 receptor antagonists *in vitro* or in an animal model as described above, the only way to determine whether those putative CRF1 receptor antagonists worked for treating CAH in a human would be to conduct time-consuming and expensive clinical trials. It is well known in the art that *in vitro* screening methods and animal models do not necessarily translate to efficacy in humans, because of the complexities of biological mechanisms underlying human diseases and possible differences between CRF1 receptors across species. *See* EX1066, 7. For example, even though a putative CRF1 receptor antagonist may bind to and inhibit CRF1 receptor *in vitro*, a POSA would understand that the putative CRF1 receptor antagonist would not necessarily be safe to administer in humans, nor would it necessarily achieve the claimed glucocorticoid reduction and reduction in A4, ACTH or 17-OHP, and would be not necessarily be therapeutically effective to treat CAH in a human as claimed.

86. Clinical trials involve years of study and millions of dollars to perform. EX1065, 117-18. Generally, clinical studies typically proceed through three sequential phases: Phase 1, Phase 2, and Phase 3. Phase 1 clinical studies usually include only a small number of healthy volunteers who are tested to establish safe dosages of a potential drug and to gather information on the pharmacokinetics (e.g., absorption, distribution, metabolism, and excretion) of the

potential drug. Phase 2 clinical studies progress to include patients who have the disease or condition that the potential drug is targeted to treat. Phase 2 clinical studies are designed to obtain evidence on safety, pharmacokinetics, pharmacodynamics (e.g., proposed drug mechanism of action), and to obtain preliminary data on efficacy for the targeted disease or condition. Phase 3 clinical studies are large-scale trials designed to establish the efficacy of a proposed drug and to discover side effects that occur infrequently.

87. In my experience, clinical trials for orphan diseases such as CAH are especially challenging because it is difficult to recruit enough patients to achieve statistically significant data. This is particularly true in pediatric studies, which have added complexities that make it more difficult to recruit and retain pediatric patients. Here, the claims are not limited to an adult or pediatric patient, they recite treating CAH in “a human” by administering a therapeutically-effective amount of a CRF1 receptor antagonist to “said human.” EX1001, 48:62-49:19.

88. Without statistically significant data, a POSA could not determine whether or not a putative CRF1 receptor antagonist was safe and effective for treating CAH. In my experience, drugs that may be safe and effective in even preclinical trials may not be shown to be safe and effective in clinical trials in humans. The many years and costs involved in getting to clinical trials in the first place demonstrates the extensive length of experimentation needed to develop

CRF1 receptor antagonists for treating CAH. As I explain above, when Spruce carried out a Phase 3 clinical trial of tildacerfont, it failed and did not show clinical efficacy. EX1058. Specifically, Spruce announced that tildacerfont did not provide an absolute change in glucocorticoid dosing in its Phase 3 clinical trial. *Id.* Because of this, Spruce announced that it was discontinuing its investment in tildacerfont for treating CAH. *Id.*

89. As I discuss above, there is a high level of unpredictability and knowledge in the field as to whether any putative CRF1 receptor antagonist could treat CAH in a human by reducing glucocorticoid dosing and A4, ACTH, or 17-OHP levels from baseline. Scientists have been searching for compounds capable of acting as antagonists of the CRF1 receptor for many years, including for treatment of diseases/disorders as anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse, as discussed above. As further stated above, Williams illustrates this unpredictability in the art by reporting that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.” EX1029, 1065. Thus, a POSA would not have necessarily expected any CRF1 receptor antagonist to work for any clinical indication, much less for treating a complex disease like CAH.

90. As I also discuss above, at the time of the '166 patent, there was no information in the art on what particular structural features of a CRF1 receptor

antagonist would be important for CAH treatment. The scientific literature showed that CRF1 receptor antagonists displayed a wide variety of structural features. Spruce's own publication, EX1041, described tildacerfont as a "second-generation CRF1 antagonist" having "unique structural features" compared to other CRF1 receptor antagonists. EX1041, 4667. But nothing in the '166 patent informs a POSA what these "unique structural features" are, nor guides the POSA in making and using other CRF1 receptor antagonists that might share these "unique structural features."

91. As I also discuss above, a POSA would expect differences in therapeutic effectiveness among different CRF1 receptor antagonists based on that particular antagonist's receptor affinity of the antagonist. But the '166 patent does not guide the POSA in determining which structures could result in greater receptor affinity. *Compare* EX1001 *with* EX1006, ¶¶ [0078]-[0083].

92. Moreover, although some CRF1 receptor antagonists reported had been characterized in the scientific literature at the time of the '166 patent, as I discuss above, it was unpredictable which of those CRF1 receptor antagonists—if any—would have the function of treating CAH in a human by reducing glucocorticoid dosing and A4, ACTH, or 17-OHP levels from baseline without conducting clinical trials. Indeed, Spruce's Phase 3 clinical studies of tildacerfont

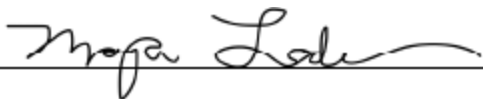
failed, and Spruce discontinued its investment in tildacerfont for treating CAH because tildacerfont did not provide an absolute change in glucocorticoid dosing.

93. In summary, it is my opinion that the '166 patent discloses only a starting point for further iterative research in an unpredictable and still-developing field. There would be no way for a POSA to determine which CRF1 receptor antagonists would have the claimed functions of treating CAH in a human by reducing glucocorticoid dosing and reducing the levels of A4, ACTH, or 17-OHP other than extensive trial-and-error experimentation. The '166 patent only provides one example of a CRF1 receptor antagonist that supposedly has these abilities— tildacerfont—yet claims an unknowable number of putative CRF1 receptor antagonists. Thus, it is my opinion that the claims that Neurocrine is challenging in this proceeding are not enabled for their full scope.

94. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

95. I currently hold the opinions expressed in this declaration. My analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in additional observations. I reserve the right to offer additional opinions regarding the subject matter set forth in this declaration, including in response to any argument raised by Spruce, or in response to expert opinions offered on behalf of Spruce.

Date: 2/10/2025

By: 

Maya Lodish, M.D.

APPENDIX A

University of California, San Francisco

CURRICULUM VITAE

Name: Maya Beth Lodish, MD

Position: Professor of Clinical Pediatrics, Step 2
Pediatrics
School of Medicine

Selna L. Kaplan Chair Distinguished Professorship in Pediatric
Endocrinology/Diabetes

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Mission Hall 550 16th St., 4th Floor, Box 0434
San Francisco, CA 94143
Voice: Tel: (415) 476-3310
Email: maya.lodish@ucsf.edu

EDUCATION

1994 - 1998	Dartmouth College, Hanover NH	B.A.	Cum Laude, Biochemistry and Molecular Biology
1999 - 2003	Yale University School of Medicine, New Haven, CT	M.D.	
2003 - 2006	Johns Hopkins Hospital, Baltimore, MD	Intern/ Resident	Internship & Residency in Pediatrics
2006 - 2009	National Institutes of Health, Bethesda, MD	Fellow	Fellowship in Pediatric Endocrinology
2010 - 2013	Duke University, Durham NC	M.H.Sc.	

LICENSES, CERTIFICATION

2006	Diplomate, American Board of Pediatrics
2006	Maryland Board of Physicians, License # 1124596
2009	Diplomate of the American Board of Pediatrics Sub-board of Pediatric Endocrinology
2011	Commonwealth of Virginia, Board of Medicine License #0101246122
2018	Medical Board of California, License #155103

PRINCIPAL POSITIONS HELD

2018 - present	UCSF	Professor of Clinical Pediatrics; Selna Kaplan Distinguished Professorship	Pediatrics
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OTHER POSITIONS HELD CONCURRENTLY

1998 - 1999	Boston Children's Hospital	Research Assistant	Division of Hematology- Oncology
2009 - 2012	National Institute of Child Health and Human Development (NICHD)	Assistant Clinical Investigator	Program on Developmental Endocrinology and Genetics (PDEGEN)
2009 - 2014	NICHD	Deputy Program Director	Fellowship in Pediatric Endocrinology
2012 - 2017	NICHD	Staff Clinician	PDEGEN
2015 - 2018	NICHD	Program Director	Fellowship in Pediatric Endocrinology
2017 - 2018	NICHD	Associate Research Physician	Developmental Endocrine Oncology and Genetics
2019 - present	UCSF	Chief, Division of Endocrinology	Pediatrics

HONORS AND AWARDS

1997	Tucker Foundation Community Service Fellowship	Dartmouth College
1998	Cum Laude	Dartmouth College
1998	Presidential Scholar	Dartmouth College
2000	NIH Medical Student Research Training Fellowship	Yale University School of Medicine
2003	William U. Gardner Thesis Prize	Yale University School of Medicine
2008	Clinical Category Poster Competition Award	Endocrine Society

2009	Presidential Poster Award	Lawson Wilkins Pediatric Endocrine Society
2012	Mentor Award	National Institute of Child Health and Human Development
2013	Merit Award for exceptional clinical support and management of in pediatrics	National Institute of Child Health and Human Development
2014	Elected to Society for Pediatric Research	Society for Pediatric Research
2014	Outstanding Reviewer Recognition Award	The Journal of Clinical Endocrinology and Metabolism
2015	Certificate of Appreciation for Valuable Contribution as IRB Member	Combined NeuroScience IRB
2015	John D. Crawford Visiting Professor	Massachusetts General Hospital
2016	Nominated by the NIH Fellows Committee for the Distinguished Clinical Teacher Award	Fellows Committee, NIH
2018	Society For Endocrinology Journal award: Endocrine Related Cancer	Society for Endocrinology
2020	President's Innovation Fund-San Francisco (PIF-SF) Grant Award	UCSF
2023	Invited Professorship, Sick Kids Hospital	University of Toronto, Sick Kids Division of Pediatric Endocrinology
2023	Excellence in Teaching Award in health professions education	UCSF Academy of Medical Educators
2024	Fellows leadership and advocacy group mentorship award	Fellows leadership and advocacy group, UCSF

CLINICAL ACTIVITIES

CLINICAL ACTIVITIES SUMMARY

My clinical activities at UCSF include creating an interdisciplinary pediatric thyroid center dedicated to the unique medical needs of children and adolescents with thyroid disease. I collaborate with the UCSF hereditary cancer clinic for management of children with a predisposition to endocrine tumors. I build collaborative endeavors with the division of pediatric oncology, providing endocrine care to survivors of childhood cancer and to neuro oncology patients. I provide mentorship to fellows, residents and medical students on the intricacies of clinical research and quality improvement.

CLINICAL SERVICES

2009 - 2018	Teaching Attending, Pediatric Endocrinology Service, NIH Clinical Center	3 months per year
2009 - 2018	Attending, Fellow's Outpatient Endocrine Clinic, NIH Clinical Center	44 sessions per year
2018 - present	Inpatient consult attending, Pediatric Endocrinology Service, Benioff Children's Hospital and Children's Hospital Oakland	1 month per year
2018 - present	Neuro-oncology multidisciplinary clinic team Endocrinologist	once per month
2018 - present	Outpatient clinical endocrinology attending physician, Benioff Children's Hospital SF and Benioff Children's Hospital Oakland	3-4 sessions per week

PROFESSIONAL ACTIVITIES**MEMBERSHIPS**

2002 - present	American Academy of Pediatrics
2006 - present	Endocrine Society
2008 - present	Pediatric Endocrine Society
2011 - present	Children's Oncology Group
2014 - present	Society for Pediatric Research
2018 - present	American Thyroid Association
2019 - present	American Diabetes Association
2021 - present	International Thyroid Oncology Group

SERVICE TO PROFESSIONAL ORGANIZATIONS

2010 - 2017	Hope for Hypothalamic Hamartoma	Board Member
2014 - 2017	Pediatric Endocrine Society	Leader, Sub-committee on Fellow Education
2015 - 2018	The Endocrine Society	Member, Clinical Endocrine Education Committee
2017 - 2020	Pediatric Endocrine Society	Leader, Sub-committee on Regional Meetings

2017 - present	The Endocrine Society	Strategic Planning Committee Invited Member
2017 - present	American Multiple Endocrine Neoplasia Support	Member, Medical Advisory Board
2017 - present	The Endocrine Society	Abstract Review
2018 - 2018	The Endocrine Society Annual Meeting Session: Pituitary Function and dysfunction	Session co-chair/moderator
2018 - 2018	NIH Center for Cancer Research: Cancer, Autoimmunity and Immunology, Autoimmune Endocrinopathies	Session co-chair/moderator
2019 - present	Children's Oncology Group Long-Term Follow-Up Guidelines Taskforce, Endocrine Late Effects Working Group – Pituitary Thyroid-Adrenal Silo	Member
2019 - present	Children's Oncology Group Executive Committee	Member
2019 - present	Endocrine Society Leadership Task Force	Member
2020 - present	American Thyroid Association Education Leadership Committee	Member
2021 - present	Children's Oncology Group Long-Term Follow-Up Guidelines Taskforce, Late Effects Working Group New Anticancer Agents	Silo Leader
2021 - 2022	THE GROWTH HORMONE RESEARCH SOCIETY: Safety of growth hormone replacement in survivors of cancer and intra-cranial and pituitary tumours	Committee member
2021 - 2022	Prolactin-Secreting Adenomas Consensus Workshop, the Pituitary Society	Committee Member
2023 - present	Pediatric Endocrine Society Annual Meeting Planning Committee	Committee Member
2023 - present	Pediatric Endocrine Society TRENDS Special Interest Group (Tumor Related Endocrine and Neuroendocrine Disorders)	co-chair

SERVICE TO PROFESSIONAL PUBLICATIONS

2012 - 2016	Editorial Board Member Journal of Clinical Endocrinology & Metabolism
2012 - present	Ad Hoc Reviewer Pediatric Blood & Cancer
2013 - present	AdHoc Reviewer PLOS ONE
2015 - present	AdHoc Reviewer Journal of Clinical Oncology
2016 - present	AdHoc Reviewer Molecular and Cellular Endocrinology
2016 - present	AdHoc Reviewer The Journal of Pediatrics (2016, 2017, 2018)

2016 - present AdHoc Reviewer Endocrinology, Diabetes and Metabolism Case Reports
 2017 - present AdHoc Reviewer Endocrine (2017)
 2017 - present AdHoc Reviewer BMC Medical Genetics (2017)
 2017 - present AdHoc Reviewer Endocrine-Related Cancer (2017)
 2017 - present AdHoc Reviewer Endocrine (2017)
 2018 - present AdHoc Reviewer Thyroid (2018)
 2018 - present AdHoc Reviewer JNCI Cancer Spectrum
 2019 - present AdHoc Reviewer The Lancet
 2021 - present Ad-Hoc Reviewer Journal of the American Medical Association

INVITED PRESENTATIONS - INTERNATIONAL

2009	European Society for Paediatric Endocrinology and Lawson Wilkins Pediatric Endocrine Society	Poster
2011	The Endocrine Society	Invited Speaker
2015	The Endocrine Society	Invited Speaker
2015	Joint meeting of International Society for Pediatric and Adolescent Diabetes & Australasian Paediatric Endocrine Group	Invited Speaker
2016	European Congress of Endocrinology	Invited Speaker
2017	10th International Meeting of Pediatric Endocrinology	Poster
2018	The Endocrine Society	Speaker, Poster, Session Moderator
2020	The Endocrine Society	Invited Speaker
2022	The Pituitary Society	Invited Speaker
2023	McGill University	Invited Speaker
2023	University of Toronto	Invited Speaker
2023	Mexican Society of Pediatric Endocrinology	Invited Speaker
2023	The Endocrine Society	Invited Speaker
2024	The Endocrine Society	Invited Speaker

INVITED PRESENTATIONS - NATIONAL

2010	Children's Tumor Foundation	Invited Speaker
2010	Life With Cancer	Invited Speaker
2011	Childhood Cancer Survivorship Conference	Invited Speaker

2013	Department of Pediatrics-Division of Academics and Research Children's Hospital of the Greenville SC Hospital System	Invited Speaker
2014	Pediatric Academic Society	Invited Speaker
2014	Johns Hopkins University School of Medicine	Invited Speaker
2015	Society of Inborn Errors of Metabolism	Invited Speaker
2015	University of Maryland, Division of Endocrinology	Invited Speaker
2015	Massachusetts General Hospital	Invited Speaker
2015	Cornell University School of Medicine	Invited Speaker
2015	Riley Hospital for Children, Indiana University School of Medicine,	Invited Speaker
2017	Thyroid Cancer Survivors' Association	Invited Speaker
2017	University of California, San Francisco	Invited Speaker
2018	National Cancer Institute, Bethesda Maryland NCI Cancer Moonshot Initiative: Medullary Thyroid Cancer	Invited panel member
2018	Thyroid Cancer Survivor's Association	Invited Speaker
2018	St. Jude Children's Research Hospital	Invited Speaker
2018	Children's Hospital of Philadelphia Neuroendocrinology Symposium	Invited Speaker
2018	Children's Hospital Oakland Research Institute	Invited Speaker
2019	52nd Annual Advances & Controversies in Clinical Pediatrics	Invited Speaker
2019	Pediatric Academic Society Meeting	Invited Speaker
2019	Baylor College of Medicine, Texas Children's Hospital	Invited Speaker
2020	Pediatric Endocrine Society Meeting	Invited Speaker
2021	PEARL Pediatric Endocrine Association for Research and Learning, Seattle, Washington	Invited Speaker
2022	Pediatric Endocrinologists of the Rocky Mountains Annual Meeting October 2022	Invited Speaker
2023	Pediatric Grand Rounds New York University School of Medicine	Invited Speaker
2023	Pediatric Endocrine Society Meeting	Symposium Leader
2023	American College of Surgeons Annual Meeting, Boston, MA	Invited Speaker
2024	Pediatric Endocrine Society Meeting	Symposium Leader

INVITED PRESENTATIONS - REGIONAL AND OTHER INVITED PRESENTATIONS

2010	NICHHD Scientific Retreat for Investigators	Invited Speaker
2013	NICHHD Exchange: "Pediatric Cancer: Perspectives and Promises"	Invited Speaker
2014	NIH Research Festival	Invited Speaker
2014	Combined Neuroscience IRB Retreat	Invited Speaker
2016	NIH Clinical Center Grand Rounds	Invited Speaker
2016	National Cancer Institute Symposium on Cancer Health Disparities	Invited Speaker
2017	Johns Hopkins University School of Medicine and National Institutes of Health Joint Perioperative Medicine Conference.	Invited Speaker
2017	Children's National Health Systems Pediatric Endocrine Conference	Invited Speaker
2017	NIH Clinical Center Pediatric Nursing Team	Invited Speaker
2017	Pediatric Endocrinology Metabolism and Genetics Research Conference	Invited Speaker
2018	Symposium to honor Dr. Felix Conte	Invited Speaker
2019	Advances and Controversies in Clinical Pediatrics	Invited Speaker
2019	Pediatric Oncology Grand Rounds UCSF	Invited Speaker
2020	Pediatric Genetics Educational Conference	Invited Speaker
2021	Pediatric Grand Rounds, Benioff Children's hospital Oakland	Invited Speaker
2021	Child and Adolescent Health Equity in Scholarship (SIP) Session Speaker	Invited Speaker
2021	Early Career Forum (ECF) Workshop. Your session, Know Your Options: Career Paths within Clinical Endocrinology and Research, Endocrine Society	Invited Speaker
2022	Annual meeting of the Organization of Pediatric Endocrinologists (OPEC)	Invited Speaker

CONTINUING EDUCATION AND PROFESSIONAL DEVELOPMENT ACTIVITIES

2018	Academy of Medical Educators: Narrative in Medicine Workshop, UCSF
2018	Research-Related Resources Symposium at UCSF
2018	Completed courses in Collaborative Institutional Training Initiative to be approved as an investigator in CTEP / Children's Oncology Group
2020	Diversity, Equity, and Inclusion Championing Training

2020 Leadership Development Course through Pediatric Endocrine Society

GOVERNMENT AND OTHER PROFESSIONAL SERVICE

2009 - 2018	Graduate Medical Education Committee, NIH Clinical Center	Member
2014 - 2014	European Research Council	Grant Reviewer
2016 - 2016	NIDDK Institutional K12	Grant Review Committee Member
2016 - 2016	Luxembourg National Research Fund	Grant Reviewer
2018 - 2018	Children with Cancer UK Clinical PhD & Training Studentships	Grant Reviewer
2018 - present	UpToDate	Peer Reviewer
2018 - 2018	Association for Clinical and Translational Science	Mock Study Section Member
2019 - 2019	Fanconi Anemia Research Fund 2019 grant review process	Grant Reviewer
2020 - 2020	French National Research Agency	Grant Reviewer
2021 - 2021	NIDDK T32 Training Grant	Grant Reviewer
2022 - 2022	NIDCR Study Section	Invited Member

UNIVERSITY AND PUBLIC SERVICE

SERVICE ACTIVITIES SUMMARY

Between July 1 2021 and present, my main service to the university has been as Division Chief of Pediatric Endocrinology. Our division is thriving with an excellent fellowship program that successfully renewed its T32 training grant in 2022 and we continue to recruit and retain stellar trainees. I am proud of our division's growth, since 2021 we have recruited 8 new faculty including a Benioff Endowed Chair, to lead our Diabetes programs across both Benioff Children's Hospitals, as well as a new leader for the Child and Adolescent Gender Center. In the past 3 years our division has made meaningful strides in health equity and advocacy. Our team has been recognized for leading the Novel Interventions in Children's Healthcare (NICH) program that helps our most vulnerable youth with chronic disease. NICH launched at UCSF in 2020 and takes a unique hands-on approach to help youth facing both complex medical conditions and significant psychosocial vulnerabilities . We continue to partner with the development office and successfully have raised over 2.6 million dollars to support our division over the past 3 years. Our division has successfully united our mission with cross-bay collaboration and initiatives that include representation of diverse staff and faculty.

Since my last advancement, I have been asked to join the Department of Pediatrics Senate Series Promotion Committee as well as Department of Pediatrics Compensation Committee, and I continue to serve on both of these committees. Additional service to the university includes my role on the Pediatric Endocrinology Fellowship Program Evaluation Committee. I

give back to the community through my role as camp physician at Bearskin Meadows, a camp for children with diabetes, for one week each summer. I also am an open water swimmer for the Swim Across America team that raises awareness for childhood cancer and helps to fund the childhood cancer survivor clinic at UCSF.

SCHOOL OF MEDICINE

2018 - present	UCSF Pediatric Residency Selection Committee	Interviewer for residency candidates
2018 - present	Pediatric Endocrinology Fellowship Program Annual Evaluation Committee	Committee Member
2019 - present	CMC preceptorship for medical students	preceptor
2021 - 2021	Search Committee for the Director of the Diabetes Center	Selection Committee Member
2023 - present	Search Committee for Adult Endocrinology Faculty Position	Selection Committee Member

DEPARTMENTAL SERVICE

2019 - present	Division Chief, Pediatric Endocrinology	Division Chief
2021 - 2021	Search Committee, Division Chief of Pediatric Hematology	committee member
2020 - 2021	Department of Pediatrics Faculty Incentive Committee	committee member
2022 - present	Department of Pediatrics Senate Series Promotion Committee	committee member
2023 - present	Department of Pediatrics Compensation Committee	committee member

SERVICE AT OTHER UNIVERSITIES

2004 - 2006	Johns Hopkins Pediatric Residency Curriculum Committee Member	Baltimore, MD
2006 - 2008	NICHD annual fellows retreat steering committee member	Bethesda, MD
2007 - 2009	NICHD Quality Assurance Committee Fellows Representative	Bethesda, MD
2009 - 2018	Member, Graduate Medical Education Committee, National Institutes of Health Clinical Center (NIH CC)	Bethesda, MD
2010 - 2015	Member, Combined Neuroscience Institutional Review Board, NIH CC	Bethesda, MD

2012 - 2018	Member, Tenure and Promotion Committee, National Institute of Child Health and Human Development	Bethesda, MD
2014 - 2018	Member, Pediatric Care Committee, NIH Clinical Center	Bethesda, MD
2017 - 2018	Member, NICHD Scientific Retreat Planning Committee	Bethesda, MD
2022 - 2023	Member, Scholarship Oversight Committee, Children's Hospital of Philadelphia	Philadelphia, PA

COMMUNITY AND PUBLIC SERVICE

2006 - 2006	Mercy Medical Mission / Johns Hopkins Tropical Medicine Elective	Physician member team in Chulucanas, Peru
2013 - 2013	Johns Hopkins Women's Pre-Health Leadership Society	Invited Speaker
2013 - 2015	Montgomery County Public Schools	Led STEM classes for first graders
2015 - 2016	The Children's Inn at NIH	Marathon Team Member
2016 - 2018	Montgomery County Public Schools Health Council	Physician Member
2017 - 2017	American Red Cross	Blood Drive Leader
2018 - 2018	The Gift of Life Bone Marrow Registry	Leader of Drive to enroll participants into registry
2018 - present	Swim Across America	Team member
2019 - present	Bearskin Meadow Diabetes Camp	camp physician
2019 - 2019	Berkeley High School "STEMINISM" club	invited speaker

CONTRIBUTIONS TO DIVERSITY

CONTRIBUTIONS TO DIVERSITY Contributions to Diversity, Equity & Inclusion Guidance

As chief, I have made one of our division's priorities improving equitable clinical outcomes, access, and experience for children with diabetes. As a leader of the division, I am not afraid to put controversial topics related to social justice front and center, for example, presenting data to the hospital board on our disparities in access to diabetes technology comparing our publicly and privately insured patient populations. Even after SES adjustment, marked disparities in diabetes treatment outcomes exist between black versus Latin-X and white children at UCSF. It is only by speaking openly about the challenges and inequities that we face that we can hope to bring awareness to these issues and galvanize more resources to tackle the problem. I have made it a priority to restructure the education of our fellows in pediatric endocrinology so that they spend part of their first year at Benioff Children's Hospital in Oakland, where they work with a larger proportion of families from underserved communities. When teaching students, I bring concepts of equity into the classroom and clinical realm and encourage scholarly activity related to these topics. For example, we established an A1c Health Equity taskforce including

diabetes educators, nutritionists, nurses, physicians, and fellows in training, to evaluate drivers of disparities and potential solutions. The aim is to address inequities in achieving optimal glycemic control, as measured by the marker hemoglobin A1c, and to use quality improvement methodology to deliver equitable care amongst patients and families. Our goal is reduction of the hemoglobin A1c gap between public and private pay patients, for FY 2021 the gap was 1.3. We are testing whether presenting a Continuous Glucose Monitor (CGM) option and/or providing a written CGM patient education hand-out to T1D patients not on CGM will increase interest and use of CGM in that patient population and subsequently improve A1cs and quality of life. We were awarded a Diversity, Equity & Inclusion award from Benioff Childrens Hospital Oakland to support this work (Awarded to Barbara Liepman, RN, CDCES).

Examples of scholarly activity related to DEI:

Reed A, Noya CE, Wagner DV, Lim JH, Glocker V, Bal KS, Gonzales Granados M, Stone A, McGrath MT, Harris MA, Lodish M, Wong JC. Improvement in Psychosocial Functioning of Youth with Diabetes and their Caregivers With Multiple Social Risk Factors. Poster presentation accepted for the American Diabetes Association's 83rd Scientific Sessions; Jun 23-26, 2023; San Diego, CA.

- On April 8, 2023, our division led the first family camp for youth with type 2 diabetes and their families at MetWest High School in Oakland. Type 2 Diabetes disproportionately impacts children of color in our community, with a much higher prevalence in black and LatinX youth. Many trainees, including medical students, residents, fellows, and nursing students participated in this event.

- On February 10-12 2023 our division led Campamento Familiar en Español at Camp Arroyo in Livermore, CA, which provides a unique opportunity for Spanish speaking families with children experiencing Type 2 diabetes to join together in a weekend of education and support. This program also provides educational opportunities for our fellows and students.

TEACHING AND MENTORING

TEACHING SUMMARY

Since joining the faculty at UCSF, I have been invited to teach medical students, residents, and fellows in formal courses. I find this to be the most rewarding part of my career and continue to seek out more opportunities to teach. I attend in the pediatric endocrinology clinic and on the inpatient pediatric endocrinology consult service (with medical students, residents, and fellows. I am a preceptor for the Clinical Microsystems Clerkship MS1 and MS2) and Specialty Practice Ambulatory subinternship (SPAN, MS4). I teach didactic lectures to students, residents, nursing students, and pediatric endocrinology fellows, as well adult endocrinology and reproductive endocrinology fellows. My overall teaching effectiveness score at UCSF is 4.78/5 (N=49; 2019-2023). Nationally, I am a member of the American Thyroid Association Education Leadership committee and the Pediatric Endocrine Society Committee on Fellow Education, as well as the Society for Pediatric Research. I helped to draft the curriculum content guidelines for the American Board of Pediatrics subspecialty content in Pediatric Endocrinology. Since 2019, I have spent one week per summer as the Diabetes Youth Foundation Camp Lead Physician mentoring residents, medical students, and fellows at Bearskin Meadows as part of their UCSF endocrinology elective. This provides hands-on teaching in a real-life situation. In 2022, I was invited to give the introductory first year medical student lecture on Type 2 diabetes by the leaders of the Renal, Endocrine, Gastroenterology, and Nutrition (REGN) block. I was honored in 2022 when

selected to be a mentor for a 4th year medical student for her Specialty Practice Ambulatory Sub-Internship to precept in the clinical outpatient setting for 12 half day sessions.

FORMAL TEACHING

	Academic Yr	Course No. & Title	Teaching Contribution	School	Class Size
	2019 - 2019	Pediatrics 110 Small Group Teaching	Small Group leader	Medicine	15
	2020 - 2022	121C Small Group Teaching	small group leader	Medicine	15
	2021 - 2021	Foundations 1 Course IDS 122A Renal, Endocrine, GI, Nutrition (REGN)	Small Group Leader	Medicine	15
	2022 - 2023	Foundations 1 Course IDS 121C REGN MS1 core lecture on Diabetes	Lecture	Medicine	120
	2023 - present	Foundations 1 Course IDS 121C REGN MS1 core lecture on Thyroid, core lecture on disorders of Adrenal, Pituitary and Hypothalamus	Lecture	Medicine	120

INFORMAL TEACHING

2007 - 2011 Becoming an Effective Scientist, Lecture and Journal Club Leader at NIH CC

2009 - 2015 Clinical Protocol Mechanics- Advanced Nursing Seminar at NIH CC

2009 - 2018 2-3 months per year in-patient teaching attending for Pediatric Endocrinology at NIH CC

2009 - 2018 Supervision of fellows, visiting residents, rotating medical students in the Pediatric Endocrinology Outpatient Clinic, 44 sessions per year

2009 - 2018 Weekly Pediatric Endocrinology rounds, Research Conference, Endocrine grand Rounds, and Research conference, 4 hours per week

2009 - 2018 Lectures to pediatric endocrine and adult endocrine fellows, as well as board - review interactive question sessions 2 hours per week

2009 - 2018 Consultations from referring physicians at NIH Clinical Center

2018 - present weekly case conference + monthly journal club

- 2018 - present Adolescent health Seminar, Division of Adolescent and Young Adult Medicine lecture on Abnormal Puberty for Nursing School
- 2018 - present Pediatric Residency Noon Conference
- 2019 - present Endocrinology Fellowship Didactic Series
- 2021 - 2022 Preceptor for IDS 125 SPAN: Specialty Practice Ambulatory Sub-Internship for a 4th year medical student

MENTORING SUMMARY

In my career thus far have mentored over 40 students and fellows in training, many of whom have had first author publications and have gone on to successful academic careers. Since my last advancement, served as faculty mentor to UCSF resident in pediatrics for the 2021-2022 academic year as part of the new pediatric resident mentorship program. I have had the privilege of serving as the primary research and scholarly project mentor for 3 fellows in the pediatric endocrinology training program at UCSF. These trainees have gone on to have faculty positions at academic institutions. I have served as the primary mentor for 2 residents in pediatrics for their scholarly projects. I have served as the primary research mentor for one StARR scholar awardee (stimulating access to Research in Residency) As a new initiative in pediatric faculty development, each junior faculty member has their own faculty mentoring committee. I currently serve on 4 such junior faculty mentoring committees for faculty in our division. As division chief, I have made it my priority to meet in person with every faculty member to formally go over faculty development plans on an annual basis. I am looking forward to incorporating the new Department wide annual review template as a way to better structure this mentoring process. From 2021-2023 I served as mentor to Dr. Priya Srivistrava who published a first author paper in the Journal of Pediatric Urology. I currently mentor Dr. Tina Hu who is a second-year med/peds endocrine fellow and she is working with me on our pediatric thyroid cancer registry project to characterize the mutational landscape of pediatric thyroid cancer.

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Program or School	Mentor Type	Role	Current Position
2011 - 2011	Brooke (Lokie) Clampitt	Penn State College of Medicine Summer Internship Program at NIH	Research/Scholarly Mentor	Mentor for scholarly activity, on BMD in NF-1	Resident in Pediatrics, Children's Hospital of Oklahoma
2011 - 2013	Urania Dagalakis	Albany College of Medicine Intramural Research Training Award NIH	Research/Scholarly Mentor	Mentor for scholarly activity on puberty and tumor growth in NF-1	Medical student, Albany College of Medicine

Dates	Name	Program or School	Mentor Type	Role	Current Position
2012 - 2012	Eitan Bornstein	U. of Michigan Summer student	Research/Scholarly Mentor	Supervise summer research project: vandetanib and thyroid function	Resident in internal medicine, University of Colorado in Denver
2012 - 2012	Laura Libuit	Howard U. Medical Student	Research/Scholarly Mentor	Supervise summer research project: Gender differences in pediatric Cushing disease	Resident in General Surgery, Georgetown University
2013 - 2013	Juliana Biro	Bard College Undergraduate Summer Student	Research/Scholarly Mentor	Supervise summer research project: Ectopic ACTH/CRH tumors	Medical Student, Florida Atlantic University
2013 - 2013	Paola Chrysostomou	U. of Maryland Undergraduate Senior Project mentee	Research/Scholarly Mentor	Supervise Senior Project Adrenal Gland in PPNAD	Masters Degree in Toxicology, Colorado State U.
2015 - 2017	Cynthia Tsay	Medical Student, Yale University	Research/Scholarly Mentor	Thesis advisor: Genetics of pituitary adenomas in Harvey Cushing's collection	Fellow in Gastroenterology, Johns Hopkins University
2015 - 2015	Sara Rahman	Medical Student, Quinnipiac University	Research/Scholarly Mentor	Supervise clinical research project: Kidney Stones in pediatric Cushing Syndrome	Resident in Obstetrics and Gynecology, George Washington University School of Medicine

Dates	Name	Program or School	Mentor Type	Role	Current Position
2015 - 2016	Leah Birdwell	U. of Maryland Undergraduate Senior Project mentee	Research/Scholarly Mentor	Supervise clinical research project: Coagulation abnormalities in pediatric Cushing Syndrome	Medical student, Edward Via College of Osteopathic Medicine
2016 - 2016	Rebecca Boden	High School Student, BCC, Bethesda MD	Research/Scholarly Mentor	Supervise clinical research project: Lymphocyte function in Cushing disease	Undergraduate, Haverford College
2016 - 2017	Hailey Blain	Undergraduate, Bowdoin College	Research/Scholarly Mentor	Supervise clinical research project: Cardiac MRI in Cushing disease	High School Science Teacher, Madiera School Virginia
2021 - 2022	Taylor Vasquez	Medical Student UCSF	Co-Mentor/Clinical Mentor	SPAN mentor	Resident in Pediatrics, Stanford University

POSTDOCTORAL FELLOWS AND RESIDENTS MENTORED

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2009 - 2010	Radha Nandagopal	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Clinical Assistant Professor, Elson S. Floyd College of Medicine, Washington State University, Spokane, Washington

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2009 - 2011	Angela Delaney	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Staff Clinician, Unit on Genetics of Puberty and Reproduction, NICHD, Bethesda, MD.
2009 - 2011	Melissa Crocker	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical Supervision	Instructor in Pediatrics, Division of Pediatric Endocrinology, Children's Hospital Boston, Boston MA.
2009 - 2012	Fariha Kamran	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Pediatric Endocrinologist DUS Family Medical Practice, Greenbelt, MD
2009 - 2012	Alison Boyce	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Staff Clinician in the Skeletal Clinical Studies Unit at National Institutes of Health
2010 - 2013	Youn Hee Jee	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Senior Fellow, Section on Growth and Development, NIHCD

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2010 - 2013	Evgenia Gourgari	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Clinical supervision, research mentor adrenal phenotype in PCOS	Assistant Professor of Pediatrics, Division of Pediatric Endocrinology, Georgetown University School of Medicine
2011 - 2014	Lars Ola Nilsson	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Assistant Professor, Department of Women's and Children's Health Karolinska Institute, Stockholm, Sweden
2011 - 2014	Aikaterini Nella	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision, research mentor on cushing syndrome in patient with MTC	Assistant Professor of Pediatrics, Division of Pediatric Endocrinology University of Texas Medical Branch, Galveston, Texas
2012 - 2015	Mary Scott Ramnitz	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision, Research mentor review on racial disparities in puberty	Medical Research Scientist, Ultragenyx Pharmaceuticals, San Francisco, CA

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2012 - 2015	Andrea Estrada	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Assistant Professor of Pediatrics, Department of Pediatric Endocrinology, at George Washington, University School of Medicine, Children's National Medical Center
2013 - 2015	Mihail Zilbermint	Adult Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, Genetics of Adrenal Hyperplasia	Assistant Professor of Medicine, Johns Hopkins University
2013 - 2016	Ovidiu Galescu	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Medical Officer, Division of Metabolism and Endocrinology Products, Center for Drug and Evaluation and Research, Food and Drug Administration
2013 - 2014	Roopa Kanakatti Shankar	Genetics Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, abnormalities in Fanconi Anemia	Assistant Professor, Children's Hospital of Richmond at VCU

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2014 - 2017	Cemre Robinson	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision, Research mentor BMD in GVHD	Assistant Professor of Pediatrics, Department of Pediatric Endocrinology, Yale University School of Medicine
2014 - 2017	Miranda Broadney	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical Supervision	Senior Research Fellow NICHD
2014 - 2015	Alexander Karageorgiadis	Research Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, Ectopic ACTH/CRH tumors and cardiac myxoma in CNC	Resident in Pediatrics, Georgetown University
2014 - 2015	Maria Bastis	Research Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, ADHD and pheochromocytoma	Resident in Pediatrics, Children's Medical Center Dallas
2014 - 2015	Ricardo Corra	Adult Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, ARMC-5 in PPNAD	Endocrinology Fellowship Program Director The University of Arizona College of Medicine
2015 - 2018	Marissa Lightbourne	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision	Staff Clinician, NIDDK

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2016 - 2018	Christina Tatsi	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, Autoimmune disorders, lymphocyte Count infection Risk in Cushing Syndrome Chromosomal Abnormalities in Pediatric Pituitary Corticotropinomas	Staff Clinician, NICHD
2017 - 2018	Maria Zhadina	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision	Asst. Professor of Pediatrics, Children's Hospital of Philadelphia
2017 - 2018	Rebecca Persky	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision	Asst. Professor of Pediatrics, George Washington School of Medicine
2017 - 2018	Abby Meyers	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision	Instructor, Childrens National Medical Center
2017 - 2017	Carolina Saldarriaga	Research Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, Postoperative Diabetes Insipidus and Hyponatremia in Children after Transsphenoidal Surgery	Resident in pediatrics, INOVA Fairfax residency
2017 - 2018	Angeliki Makri	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, Pheochromocytoma in children with MEN2, Lipoprotein Particles In Patients With Pediatric Cushing Disease	Asst. Professor of Pediatrics, McGill University

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2018 - 2020	Armaiti Mody	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research mentor 11-oxygenated steroids in PCOS, Obesity in Pediatric Cancer Survivors	Assistant Professor, UC Davis
2018 - present	Caroline Schulmeister	Pediatric Endocrinology Fellow	Research/Scholarly Mentor	Career Mentor SOC Member	In training
2019 - present	Angel Alvarez	Resident in Pediatrics, BCH Oakland	Project Mentor	PLUS project mentor	In training
2020 - 2020	Namrata Patel	Pediatric Gastroenterology Fellow	Project Mentor	SOC Member	In training
2020 - present	Su Ying Nip	Resident in Pediatrics, UCSF	Project Mentor	incidence of DKA during emerging adulthood in the California State Registry 2014-2018	In training
2021 - 2023	Kevin Yen	Fellow in Pediatric Endocrinology, UCSF	Project Mentor	SOC Member	in training
2021 - 2023	Priya Srivastava	Fellow in Pediatric Endocrinology, UCSF	Project Mentor, Career Mentor	SOC Member	In training
2022 - present	Tina Hu	Adult/Pediatric Endocrinology Fellow, UCSF	Research/Scholarly Mentor, Project Mentor	Pediatric Differentiated Thyroid Cancer	In training

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AND CREATIVE ACTIVITIES SUMMARY

Since joining the faculty at UCSF in August 2018, my research has shifted towards health equity and diabetes. In 2020 I partnered with philanthropy and am the recipient of the Cohen-Klebanoff Juvenile Diabetes Fund, a current use fund totaling nearly 1 million dollars, to support research on the early adoption of diabetes technology in the most vulnerable youth with type 1

diabetes. This funding was able to support a junior faculty member and one of our pediatric endocrinology fellows to complete a pilot study Pilot Study of Early Adoption of Automated Insulin Delivery in Under-Resourced Youth, abstract presented at the American Diabetes Association 2023 meeting and published in Diabetes 2023.

Our division has brought to UCSF an innovative behavioral health program and alternative payment model that has empirical support for both its clinical success and ability to decrease costs for third-party payers. The program targets youth with medical complexity and psychosocial vulnerability, who are repeatedly hospitalized with avoidable complications. These youth have been demonstrated to be the largest spend in pediatric care. This program, Novel Interventions in Children's Healthcare (NICH), has been implemented at Oregon Health & Science University (OHSU) with Oregon public and private payors, and we have successfully piloted the program here at both UCSF Benioff Hospital Mission Bay and BCH Oakland. We presented our pilot data to UCSF BCH leadership in 2022 and as a result BCH has agreed to sustain the costs of leading the bulk of the program moving forward. We successfully renewed a grant with Alameda Alliance for Health and have a contract in place with the San Francisco Health Plan for Enhanced Care Management finding to allow us to grow and sustain this program.

I continue to serve as a clinical investigator for studies of novel therapeutics in pediatric endocrinology, with two active protocols that I currently lead. I am the site PI for a RCT for a new corticotropin releasing hormone receptor antagonist for the treatment of children with congenital adrenal hyperplasia, and UCSF has successfully recruited 6 participants with this rare condition. Funds have allowed for the salary support of a junior faculty member and a clinical research coordinator who supports our division as a whole.

I continue to lead a protocol for the study of pediatric thyroid cancer and in 2013, UCSF successfully joined the Pediatric Thyroid Cancer Consortium, CATC, a multi-institutional cooperative research program dedicated to the study of pediatric thyroid disorders. The mission of the CATC is to share clinical and research data from a consortium of centers with multidisciplinary pediatric thyroid expertise, and to share results from these institutes with other CATC member institutions and world-wide scientific and medical communities. At UCSF, I have successfully secured a grant from Lilly pharma to allow us to continue to build our pediatric thyroid cancer registry and perform genetic testing on thyroid tissue to search for actionable mutations. I am currently mentoring one of our pediatric endocrinology fellows in her research project analyzing this registry database.

RESEARCH AWARDS - CURRENT

1. NBI-74788-CAH2006 Award	Primary Investigator	2% % effort	Lodish (PI)
ID: 132532A			
Neurocrine Pharma		06/24/2021	12/15/2027
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinicerfont (NBI-74788) in Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment		\$ 135,106.73 direct/yr 1	\$ 232,878.42 total
Clinical Trial of novel oral medication in children with CAH			
PI			

2. Award ID 139743A	Primary Investigator	0.5% % effort	Lodish (PI)
IBSA		08/10/2022	present
A Randomized Comparative Study Between Liquid (Tirosint®-SOL) and Tablet Formulations of Levothyroxine in Neonates and Infants with Congenital Hypothyroidism (CH)		\$ 63,913.77	\$ 95,151.39 total
A research study comparing Tirosint®-SOL oral solution as thyroid hormone (TH) replacement therapy in infants with Congenital Hypothyroidism (CH) to the conventional treatment with crushed levothyroxine sodium (LT4) tablets.			
PI			
3. A140562	Primary Investigator	0% % effort	Lodish (PI)
Alameda Alliance for Health		07/01/2022	6/30/2023
AGREEMENT between NOVEL INTERVENTIONS IN CHILDREN'S HEALTH CARE and ALAMEDA ALLIANCE FOR HEALTH		\$ 428,000	\$ 428,000 total
Grant to support program at UCSF to provide wrap-around care for children with chronic illness and high burden of social needs			
PI			
4. A140504	Primary Investigator	0% % effort	Lodish (PI)
Lily Pharma		10/10/2022	10/10/2023
UCSF pediatric thyroid cancer experience registry		\$ 125,953	
Funding to allow for data entry and specimen processing and tissue analysis to study pediatric thyroid cancer			
Primary Investigator			

RESEARCH AWARDS - PAST

1. L30 Research Career Program	Clinical Fellow and Associate Clinical Investigator	100% % effort	Lodish (PI)
NIH office of Intramural Loan Repayment		07/01/2006	06/30/2011
L30 Research Career Program		\$ 20,000	\$ 90,000 total
The NIH Intramural loan repayment program covered the costs of medical school loans while I served as a clinical fellow and Associate Clinical Investigator			
Served as Clinical Fellow and ACI with research contributing to the LRP mission			
2. Bench-to-Bedside	Co-investigator	20 % effort	Stratakis (PI)
Office of Research on Women's Health, NIH		06/01/2010	06/01/2012
Adrenal Hyperplasia Among Adolescent Patients with Polycystic Ovarian Syndrome		\$ 135,000	\$ 270,000 total
direct/yr 1			

Androgen excess may be adrenal and/or ovarian in origin; we hypothesized that a subgroup of patients with polycystic ovarian syndrome (PCOS) may have some degree of abnormal adrenocortical function. The objective of the study was to evaluate the pituitary adrenal axis with an oral low- and high-dose dexamethasone-suppression test (Liddle's test) in women with PCOS. This was a case-control study conducted at the National Institutes of Health Clinical Center. A total of 38 women with PCOS and 20 healthy volunteers (HV) aged 16-29 years participated in the study.

Led clinical care of patients with PCOS, mentored fellow (Dr. Gourgari) on study design and analysis plan, after Dr. Gourgari graduated from fellowship, I took on the role of primary investigator of the clinical protocol.

3. 1ZIAHD008894	PI	50 % effort	Lodish (PI)
National Institute of Child Health and Human Development		10/30/2011	10/30/2013
Detection and treatment of endocrine abnormalities in childhood cancer survivors		\$ 120,796 direct/yr 1	\$ 537,688 total
Endocrine dysfunction is increasingly recognized as one of the most important aspects of quality of life issues, physical and psychosocial development and overall prognosis in pediatric patients diagnosed with neoplasms, as well as in patients s/p bone marrow transplant throughout their lifespan. In addition, several of the new, molecularly designed therapies for neoplasms may interact with endocrine signaling; these include receptors and/or their ligands for growth and/or proliferation factors, and disruptors of steroid hormone interaction. One of the aims of this protocol is in training our fellows, residents and students in the identification and management of endocrine abnormalities developing in patients who have been diagnosed with and treated for neoplasms and/or who have received HSCT at the NIH-Clinical center.			
Wrote protocol, web-based case report forms, responsible for all aspects of the protocol including patient care, IRB submission and renewal			
4. CRADA	PI	20 % effort	Lodish (PI)
Corcept Therapeutics		06/01/2012	06/01/2014
An open-label study of the safety, pharmacokinetics and pharmacodynamics of mifepristone in children with refractory Cushing disease		\$ 200,000 direct/yr 1	\$ 400,000 total
Study objectives are to characterize the safety profile of mifepristone in children with Cushing's disease, to determine the pharmacokinetics of mifepristone in children with Cushing's disease, and to obtain pharmacodynamic data on the effect of mifepristone on glucose metabolism, body weight and the growth-hormone-IGF-1 axis in children with refractory Cushing Disease			
As Primary Investigator of the clinical trial, I wrote the protocol, submitted it to the IRB, trained nurses and physicians on protocol related issues, and led the patient care team.			
5. HHSN2752013000231/27500003	Associate Investigator	20 % effort	Mills (PI)
Division of Intramural Population Health Research (DIPHR), NIH		07/01/2014	01/01/2018
Genetic Factors in Cushing Disease: Whole Exome Sequencing		\$ 78,381 direct/yr 1	\$ 365,738 total

The major goal of this research initiative is to employ large scale genome analytic approaches to identify genetic factors associated with CD, associated phenotypes and clinical factors such as response to therapy

As primary investigator of the clinical study entitled "A CLINICAL AND GENETIC INVESTIGATION OF PITUITARY AND HYPOTHALAMIC TUMORS AND RELATED DISORDERS" at the NIH Clinical center, I am responsible for all aspects of the clinical protocol. We have stored samples from pediatric patients with Cushing Disease and have performed WES on these samples. We are identifying genetic variants are associated with phenotypic changes and clinical factors. My role is to link clinical data to genetic data, specifically, to see if gene variants are related to factors such as levels of cortisol, ACTH, response to provocative tests, facial dysmorphic features, tumor size, response to therapy and clinical features including growth trajectory, blood pressure, height percentile, and glucose tolerance.

6. 1ZIEHD008944	PI	50 % effort	Lodish (PI)
NIH		01/01/2015	06/29/2018
Pediatric Endocrine Training Program		\$ 1,539,035 direct/yr 1	\$ 4,481,953 total
3 Year ACGME accredited fellowship program in pediatric endocrinology Oversight of fellowship training, mentor trainees in their scholarly activities			

7. CRADA 03193	PI	20 % effort	Lodish (PI)
Pfizer		11/30/2017	01/01/2018

An open-label phase 2 study of the safety and efficacy of pegvisomant in children with refractory growth hormone excess

The objectives of the study are to characterize the safety profile of the pegvisomant in children with growth hormone excess, and to obtain pharmacodynamic data on the effect of pegvisomant on the growth-hormone-IGF-1 axis in children with refractory gigantism, as well as on their linear growth rate.

As the primary investigator on this study, I wrote the study protocol, submitted the draft for scientific review and to the IRB, am working with the FDA to obtain an IND, and will be responsible for all aspects of the protocol.

8. PVO-1A-202	Associate investigator	5% % effort	Hsiao (PI)
		11/01/2019	present

A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RAR γ -Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

PEER REVIEWED PUBLICATIONS

1. 1999 Crispino JD, **Lodish M**, MacKay JP, Orkin SH 1999 Use of altered specificity mutants to probe a specific protein-protein interaction in differentiation: the GATA-1:FOG complex. *Molecular cell* 3:219-228. PMID: 10078204
2. 2001 Crispino JD, **Lodish M**, Thurberg BL, Litovsky SH, Collins T, Molkentin JD, Orkin SH 2001 Proper coronary vascular development and heart morphogenesis depend on interaction of GATA-4 with FOG cofactors. *Genes & development* 15:839-844. PMID: 11297508
3. 2002 Chang AN, Cantor AB, Fujiwara Y, **Lodish M**, Droho S, Crispino JD, Orkin SH 2002 GATA-factor dependence of the multitype zinc-finger protein FOG-1 for its essential role in megakaryopoiesis. *Proceedings of the National Academy of Sciences of the United States of America* 99:9237-9242. PMID: 12077323
4. 2008 **Lodish M**, Powell AC, Abu-Asab M, Cochran C, Lenz P, Libutti SK, Pingpank JF, Tsokos M, Gorden P 2008 Insulinoma and gastrinoma syndromes from a single intrapancreatic neuroendocrine tumor. *The Journal of clinical endocrinology and metabolism* 93:1123-1128. PMID: 18252785
5. 2009 Drori-Herishanu L, Horvath A, Nesterova M, Patronas Y, **Lodish M**, Bimpaki E, Patronas N, Agarwal S, Salvatori R, Martari M, Mericq V, Stratakis CA 2009 An Intronic mutation is associated with prolactinoma in a young boy, decreased penetrance in his large family, and variable effects on MEN1 mRNA and protein. *Hormone and metabolic research* 41:630-634. PMID: 19391077
6. 2009 **Lodish M**, Sinaii N, Patronas N, Batista DL, Keil M, Samuel J, Moran J, Verma S, Popovic J, Stratakis CA 2009 Blood pressure in pediatric patients with Cushing syndrome. *The Journal of clinical endocrinology and metabolism* 94:2002-2008. PMID: 19293264
7. 2009 Nguyen JH, **Lodish M***, Patronas NJ, Ugrasbul F, Keil MF, Roberts MD, Popovic J, Stratakis CA 2009 Extensive and largely reversible ischemic cerebral infarctions in a prepubertal child with hypertension and Cushing disease. *The Journal of clinical endocrinology and metabolism* 94:1-2. PMID: 19126630. (*corresponding author)

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BOOKS AND CHAPTERS

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9. 2017 **Lodish M**, Keil M, Stratakis C, Cushing Syndrome in Childhood Pediatric Endocrinology: A Practical Clinical Guide, 3ed. 2017 Springer (in press)
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11. 2018 Almeida M, **Lodish M**, Stratakis C Cushing’s Syndrome 2018 edition of Conn's Current Therapy, edited by Edward T. Bope and Rick D. Kellerman. Elsevier

OTHER PUBLICATIONS

1. 2017 Rivkees SA, Kelly M, **Lodish M**, Weiner D 2017 The Pediatric Medical Student Research Forum: Fostering Interest in Pediatric Research. *J Pediatr*;188:3-4. PMID: 28645440

SIGNIFICANT PUBLICATIONS

1. 2016 Merchant MS, Wright M, Baird K, Wexler LH, Rodriguez-Galindo C, Bernstein D, Delbrook C, **Lodish M**, Bishop R, Wolchok JD, Streicher H, Mackall CL 2016 Phase I Clinical Trial of Ipilimumab in Pediatric Patients with Advanced Solid Tumors. *Clinical cancer research: an official journal of the American Association for Cancer Research* 22:1364-1370

This study was the first in children examining the safety, pharmacokinetics, and immunogenicity, and immune correlates of ipilimumab, an immune checkpoint inhibitor approved for treatment of metastatic melanoma. Ipilimumab was administered to pediatric patients using management algorithms for immune-related toxicities, and I served as an associate investigator and the pediatric endocrinologist on the protocol assessing the patients for endocrine- immune-related adverse events. The timing of toxicities in pediatric patients and the link to objective response in terms of tumor burden is a topic of ongoing investigation with immune-modulating therapies.

2. 2016 Birdwell L, **Lodish M**, Tirosh A, Chittiboina P, Keil M, Lyssikatos C, Belyavskaya E, Feelders RA, Stratakis CA 2016 Coagulation Profile Dynamics in Pediatric Patients with Cushing Syndrome: A Prospective, Observational Comparative Study. *J Pediatr* 177:227-231

I mentored University of Maryland Undergraduate Leah Birdwell in her senior year research project that led to this first-authored publication for her. In this prospective, observational study we measured coagulation profiles in 54 patients with Cushing syndrome, before and 6-12 months after surgery and compared with normocortisolemic children. Children with Cushing syndrome had elevated procoagulants, antifibrinolytics, and anticoagulants at baseline compared with controls; normalization of coagulation measures was seen after surgical cure. Despite the increase in anticoagulants, hypercortisolemia is associated with a hypercoagulable state in children, as is the case in adults. This finding has potential implications for prevention of venous thromboembolism in children with Cushing syndrome, whether iatrogenic or endogenous.

3. 2017 Tatsi C, Boden R, Sinaii N, Keil M, Lyssikatos C, Belyavskaya E, Rosenzweig S, Stratakis C, **Lodish M**. 2017 Decreased Lymphocyte Count and Increased Infection Risk are Common in Pediatric Endogenous Cushing Syndrome" Pediatric Research - 2018 Feb;83(2):431-437

I initiated this study to investigate the relationship between elevated cortisol and the immune system, specifically looking at infection risk. I mentored Christina Tatsi, pediatric endocrine fellow, who chose this as her scholarly project for fellowship. We describe the changes of the WBC lineages in pediatric endogenous hypercortisolemia, their associations with the markers of disease severity, and the presence of infections in 197 children with endogenous CS compared to 66 controls. The absolute lymphocyte count of CS patients was significantly lower than that of controls, while the total WBC and the absolute neutrophil counts were significantly higher. These changes correlated with several markers of CS severity and improved after resolution of hypercortisolemia. Infections were identified in 35 patients (17.8%), and their presence correlated to elevated serum morning cortisol, midnight cortisol, and urinary free cortisol levels, as well as with the decrease in absolute lymphocyte count. Children with endogenous CS have abnormal WBC counts, which correlate with the severity of CS, and normalize after cure. Infections are common in this population; clinicians should be aware of this complication of CS and have low threshold in diagnosis and treating infections in CS

4. 2018 Kraft IL, Akshintala S, Zhu YJ, Lei H, Derse-Anthony C, Dombi E, Steinberg SM, **Lodish M**, Waguespack S, Kapustina O, Fox E, Balis FM, Merino MJ, Meltzer PS, Glod J, Shern JF, Widemann BC. Outcomes of Children and Adolescents with Advanced Hereditary Medullary Thyroid Carcinoma Treated with Vandetanib. Clin Cancer Res.2018 Feb 15;24(4):753-765

For the past 10 years, I have served as the pediatric endocrinologist on this collaborative study with the NCI, responsible for endocrine management of the 16 patients enrolled in study. We conducted the first phase I/II trial of vandetanib for children and adolescents with Medullary Thyroid Cancer to define a recommended dose and assess antitumor activity.

5. 2018 Saldarriaga, C, Lyssikatos C, Belyavskaya E, Keil M, Chittiboina P, Sinaii N, Stratakis CA, **Lodish M**. Postoperative Diabetes Insipidus and Hyponatremia in Children after Transsphenoidal Surgery for Adrenocorticotropin Hormone and Growth Hormone Secreting Adenomas. The Journal of Pediatrics. 2018 Apr;195:169-174

Post-operative management for children undergoing transsphenoidal surgery may be challenging. I initiated this study to o define the incidence and risk factors of postoperative sodium alterations in pediatric patients undergoing transsphenoidal surgery for adrenocorticotropic hormone and growth hormone secreting pituitary adenomas.Among 160 children who underwent TSS for pituitary adenomas, the incidence of DI and SIADH after TSS was 26% and 14%, respectively. Combined risk factors for DI and/or SIADH include female sex, manipulation of and/or tumor invasion into the PP, and CSF leak or lumbar drain. I mentored medical student Carolina Saldarriaga in all aspects of this project.

CONFERENCE ABSTRACTS

- 2011 **Lodish M**, Sinaii N, Prodanov T, Ferguson C, Dicker S, Sullivan S, Vanderhoof V, Nelson L. "Compared to Secondary Amenorrhea, Primary Amenorrhea in Patients with Primary Ovarian Insufficiency Is Not Associated with Increased Prevalence of Major Depressive Disorder, yet Is Associated with Lower Estradiol Levels, and Smaller Ovarian and Uterine Size" 93rd Annual Meeting of The Endocrine Society, June 6 2011, Boston MA
- 2014 Karageorgiadis A, Gourgari E, Lyssikatos C, Stratakis C, **Lodish M**. Growth Hormone and Prolactin Secretion in Patients with Carney Complex ICE/ENDO June 21-24 2014, Chicago, IL
- 2014 Alwazeer M, Olutoye O, Margolin J, Castro E, Williams J, Quezado M, **Lodish M**, Stratakis C, Balazs A. Cushing Syndrome Secondary to Bronchial Carcinoid Tumor in a 14-Year- Old Female: Challenges in Diagnosis and Treatment ICE/ENDO June 21-24 2014, Chicago, IL
- 2015 Correa R, Batsis M, Chittiboina P, Raghavan P, Papadakis G, Belyavskaya E, Lyssikatos C, **Lodish M**, Stratakis C. "Cushing Disease Due to Pituitary Macroadenoma: Biochemical Characteristics in a Pediatric Cohort" ICE/ENDO March 4-8 2015, San Francisco, CA
- 2015 Jameson C, Lyssikatos C, Shawker T, **Lodish M**, Stratakis C. "Incidence of Thyroid Abnormalities in Peutz-Jeghers Syndrome" ICE/ENDO March 4-8 2015, San Francisco, CA
- 2016 Broadney M, Keil M, **Lodish, M**, Stratakis C. "Decreased Corticotropin (ACTH) Levels Associated with Propofol Infusion" ICE/ENDO April 1-4 2016, Boston, MA

- 2016 Hannah-Shmouni F, Beckers P, Trivellin G, Lyssikatos C, Josefson J, **Lodish M**, Stratakis C. "Neurofibromatosis 1 and Growth Hormone Excess" ICE/ENDO April 1-4 2016, Boston, MA
- 2016 Rahman S, **Lodish M**, Appelman-Dijkstra N, Papadakis G, Stratakis C. "Low Bone Mineral Density Is Associated With Kidney Stones in Children with Cushing's Disease" Pediatric Academic Society Meeting (PAS) April 30-May 3, 2016, Baltimore MD
- 2017 Blain H, Tirosh A, Sandfort V, Bluemke D, Arai A, Bandettini P, Stratakis C, **Lodish M**. Carotid MRI in Children with Cushing Syndrome: A Window into a Marker of Early Cardiovascular Disease ENDO April 1-4 2017, Orlando, FL
- 2017 Makri A, Raygada M, **Lodish M**. "Neurofibromatosis-1 Presenting with Gigantism and Precocious Puberty" ENDO April 1-4 2017, Orlando, FL
- 2017 Tatsi C, Alrezk R, Xekouki P, Lyssikatos C, Belyavskaya E, **Lodish M**, Stratakis C. "Report of a Patient with Severe Glucocorticoid Resistance Successfully Managed with High Dose Dexamethasone" IMPE September 14-17, 2017 Washington D.C.
- 2018 Zilbermint M, Gaye A, Berthon A, Hannah-Shmouni F, Faucz F, Davis A, Gibbons GH, **Lodish M**, Stratakis CA ARMC5 Variants And Risk Of Hypertension In African-Americans: Minority Health-GRID Study. ENDO 2018, March 17-20, Chicago, Il.
- 2018 Keil M, **Lodish M**, Tirosh A, Belyavskaya E, Lyssikatos C, Stratakis, CA. Quality Of Life Physical Health Scores Are Associated With Disease Severity In Children With Cushing Disease. ENDO 2018, March 17-20, Chicago, Il.
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- 2019 Mody A, Murphy T, Johns C, **Lodish M**, Goldsby R. Obesity in Childhood Cancer Survivors. North American Symposium on Late Complications after Childhood Cancer, June 20-21 2019, Atlanta GA.
- 2020 Mody A, **Lodish M**, Auchus R, Huddelston H. 11-Oxygenated C19 Steroids in Polycystic Ovarian Syndrome. ENDO 2020, June 8-22, virtual due to COVID19

ACADEMIC LEADERSHIP

From January 2015 - June 2018, I served as director of the fellowship in Pediatric Endocrinology at the NIH. The fellowship is sponsored by the NICHD and Children's National Health Systems (CNHS) and is based at the NIH Clinical Center. I continue to expand my role as clinical educator and investigator; in 2013, I earned my masters degree in the NIH-Duke Training Program in Clinical Research, and in 2014 I became a member of the Society of Pediatric Research. I have been recognized as a leader in the field of medical education in pediatric endocrinology as an invited member of the Education Committee of the Pediatric Endocrine Society as well as the Clinical Education Committee of the Endocrine Society. Currently I serve as Division Chief of Pediatric Endocrinology at UCSF.