UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BPI LABS, LLC,
PETITIONER,

v.

ELI LILLY AND COMPANY
PATENT OWNER.

Case IPR2025-01346
Patent 9,474,780

PETITION FOR *INTER PARTES* REVIEW OF USPN 9,474,780 UNDER 35 U.S.C. §§ 311 *ET SEQ.* AND 37 C.F.R. § 42.100 *ET SEQ.*

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LIST OF EXHIBITS[1]

Exhibit No	Description
1001	U.S. Patent No. 9,474,780.
1002	Declaration of Virginia Cornish, PH.D. in support of IPR2025-01024.
1003	*Intentionally left blank.*
1004	Prosecution History (Excerpts) of U.S. Patent No. 9,474,780.
1005	WO 2016/111971 Search Report.
1006	WO 2016/111971 Written Opinion.
1007	WO 2011/119657 A1 Publication (Alsina-Fernandez).
1008	WO 2013/164483 A1 Publication (Just).
1009	WO 2006/097537 A2 Publication (Lau)
1010	WO 2014/202727 A1 Publication.
1011	Fields G. B. Introduction to peptide synthesis. *Current protocols in protein science*, *Chapter 18*, 2002; 18.1.1–18.1.9.
1012	US 2015/0299281 A1 Publication.
1013	SAXENDA (liraglutide) injection drug label (Dec. 2014) ("SAXENDA") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf.
1014	Nelson, D. L., *et al.*, Chapters 4-5, 7, *Lehninger Principles of Biochemistry*, 3rd ed. (eds. Ryan, M., *et al.*, Worth Publishers) 2000.
1015	Segaloff, D. L., *et al.*, Chapter 9: Internalization of Peptide Hormones and Hormone Receptors, *Hormones and their Actions, Part I*, (eds. Cooke, B. A., *et al.*, Elsevier) 1988, 133-149.
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1017	WO 2010/011439 A1 Publication (DiMarchi).

[1] For ease of reference Petitioner uses the same exhibit numbering scheme as used in IPR2025-01024 for the same exhibits.

Exhibit No	Description
1018	Merrifield R. B. Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc.* 1963; 85:2149–2154.
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Exhibit No	Description
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1054	BYETTA (exenatide) injection drug label (Apr. 2005) ("BYETTA") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021773lbl .pdf.
1055	TRULICITY (dulaglutide) injection drug label (Sept. 2014) ("TRULICITY") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000Lbl.pdf.
1056	ADLYXIN (lixisenatide) injection drug label (Jul. 2016) ("ADLYXIN") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471Orig1s000lbl.pdf.
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Exhibit No	Description
	there is minimal effect of truncating exendin-4 in anaesthetized pigs. *Regulatory Peptides*. 2013 Feb 10;181:17-21.
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1075	WO 2015/067715 A2 Publication.
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1084	Declaration of Dr. Zhaohui Sunny Zhou, PH.D. in support of IPR2025-01346
1085	*Curriculum Vitae* of Dr. Zhaohui Sunny Zhou, Ph.D.

I. INTRODUCTION

BPI Labs, LLC ("Petitioner") requests *inter partes* Review pursuant to 35 U.S.C. §§ 311 *et seq.* and 37 C.F.R. §§ 42.100 *et seq*., of claims 1-2, 4-7, 9-10, 12-18 (the "Challenged Claims") of U.S. Patent No. 9,474,780 ("the '780 Patent"). *See* EX1001.

The '780 Patent is also being challenged in IPR2025-01024 filed by a different petitioner, Empower Clinic Services LLC ("Empower IPR"). *See* EX1080 and EX1081. The ground of rejection in the instant Petition is different than the ground raised in the Empower IPR. Petitioner here relies on the teachings of WO 2010/011439 to DiMarchi. ("DiMarchi"), which is not cited in the Empower IPR. DiMarchi's teachings are highly relevant to the claims of the '780 Patent as DiMarchi teaches ways to increase the efficacy of co-GIP/GLP-1 agonists while reducing immunogenicity.

As set out in this Petition, the Challenged Claims are unpatentable as obvious over the combination of WO 2011/119657 to Alsina-Fernandez ("Alsina-Fernandez") in view of DiMarchi and WO 2006/097537 to Lau, et al. ("Lau"). Therefore, the Board should institute this IPR.

II. OVERVIEW OF THE ARGUMENT

The '780 Patent purports to have invented dual incretin peptide mimetic compounds that activate receptors for both human glucose-dependent insulinotropic

polypeptide ("GIP") and glucagon-like peptide-1 ("GLP-1"). EX1001 at 1:3-8. However, the '780 Patent admits that peptides with dual agonist GIP/GLP-1 activity were known in the art, and cites to Alsina-Fernandez as one such example. EX1001 at 1:55-57. [2] The '780 Patent merely applies well-known peptide design and modification strategies taught by DiMarchi and Lau to the peptide disclosed in Alsina-Fernandez.

As evidenced by the declaration of Dr. Zhaohui Sunny Zhou, Ph.D, ("Dr. Zhou")[3], a person of ordinary skill in the art ("POSA") at the time of the invention was motivated to develop GLP-1/GIP co-agonist compounds for the treatment of diabetes mellitus, as well as weight loss, since the dosing of GLP-1 agonist compounds alone was limited by the nausea and vomiting preventing these single agonist compounds from reaching their full efficacy for glycemic control and weight loss. EX1081 at ¶113. The prior art relied on in this petition (Alsina-Fernandez, DiMarchi, and Lau) provided guidance to a POSA on how to develop and improve

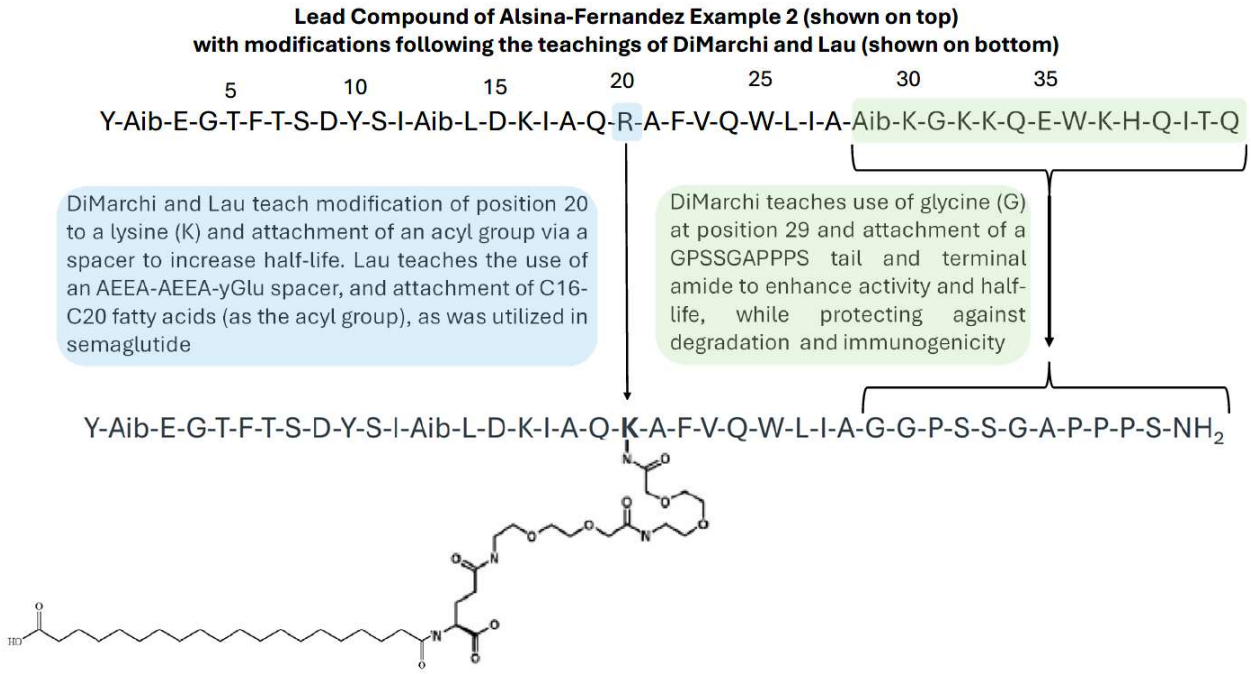
[2] Alsina-Fernandez is assigned to Patent Owner and has two inventors in common with the '780 Patent (Alsina-Fernandez and Bokvist). *Compare* EX1001 *with* EX1007.

[3] Dr. Zhou is an expert with over thirty years of experience in the areas of polypeptides and proteins, including extensive work on peptide drugs including GIP and GLP-1 receptor agonists. EX1084 at ¶1.

GLP-1/GIP co-agonist compounds in the form of well-known structural substitutions and modifications that represented rational design strategies. *Id*.

Particularly in view of a POSA's background knowledge in this well studied field, a POSA would have been motivated to (1) solve/mitigate the issues associated with nausea and vomiting caused by selective GLP-1 agonist compounds; (2) minimize any potential immunogenicity associated with regular administration of the GLP-1/GIP co-agonist compounds; and (3) provide for a longer half-life and duration of effect, allowing for less frequent injections of the medication (e.g., weekly vs daily). *Id*.

The illustration below provides the straightforward modifications a POSA would make to the Alsina-Fernandez GLP-1/GIP co-agonist peptide provided in his Example 2 based on the teachings of DiMarchi and Lau to arrive at a compound within the scope of the claims of the '780 Patent.



As explained herein, a POSA would have been motivated to combine Alsina-Fernandez, DiMarchi, and Lau to implement these structural changes illustrated above and would have a reasonable expectation of success in doing so.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

Petitioner satisfies each requirement for *Inter Partes* Review of the '780 Patent pursuant to 37 C.F.R. § 42.8(a)(1).

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The Petitioner and real-party-in-interest is BPI Labs, LLC with a physical address at 12393 Belcher Rd S., Suite 450, Largo, FL 33773-3097. An additional real-party-in-interest is Belcher Pharmaceuticals, LLC.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

The ’780 Patent is being challenged in IPR2025-01024 in petition filed by Empower Clinic Services, LLC. The petitioner of the instant IPR, BPI Labs, LLC is neither a real-party in interest nor a privy with respect to IPR2025-01024 and the parties involved. *See Applications in Internet Time, LLC* v. *RPX Corporation*, 897 F.3d 1336 (Fed. Cir. 2018).

To the best of Petitioner’s knowledge, the ’780 Patent is not involved in any other proceedings including district court litigation.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner is represented by the following counsel:

Lead Counsel	Backup Counsel[4]
James P. Murphy Reg. No. 55,474 Polsinelli PC 1000 Louisiana Street Suite 6400 Houston, Texas 77002 Tel: (713) 374-1631 jpmurphy@polsinelli.com	Corey Casey Reg. No. 66,950 Polsinelli PC 900 West 48th Place Suite 900 Kansas City, Missouri 64112 Tel: (816) 572-4439 ccasey@polsinelli.com

Pursuant to 37 C.F.R. § 42.10(b), Powers of Attorney have been filed with this Petition.

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Physical mailing service information for lead and back-up counsel is as follows:

James Murphy
Polsinelli PC
1000 Louisiana Street
Suite 6400
Houston, Texas 77002

Petitioner also consents to service by e-mail at the above e-mail addresses provided for lead and backup counsel.

[4] Petitioner intends to seek *pro hac vice* admission for Mr. Chad Landmon also with Polsinelli PC as an additional back-up counsel at the appropriate time.

E. Payment of Fees Under 37 C.F.R. § 42.15

All required fees have been paid with the filing of this Petition. Petitioner further authorizes the U.S. Patent & Trademark Office to charge Deposit Account No. 50-1662 for any fees, including the fee set forth in 37 C.F.R. § 42.15(a) for this Petition.

F. Certification of Word Count Under 37 C.F.R. § 42.24(d)

Petitioner certifies that the word count in this Petition, including all footnotes and annotations, is 13,993 words as counted by the word-processing program (Microsoft Word for Office 365) used to generate this Petition, where such word count excludes the table of contents, mandatory notices, certificate of service, list of exhibits, and this certificate of word count. This Petition is in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24(a)(1)(i).

IV. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that the '780 Patent is available for *inter partes* review. Petitioner is not barred or estopped from requesting an *inter partes* review of the '780 Patent claims on the grounds identified in this Petition. 37 C.F.R. § 42.104(a).

V. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(b)(1)

Petitioner asserts that claims 1-2, 4-7, 9-10, 12-18 are rendered obvious under 35 U.S.C. §103 by Alsina-Fernandez in view of DiMarchi and Lau.

VI. HOW THE CHALLENGED CLAIMS ARE TO BE CONSTRUED UNDER 37 C.F.R. § 42.104(b)(3)

Petitioner does not believe that any term requires construction to resolve the invalidity grounds presented in this Petition as the prior art renders the Challenged Claims unpatentable under any reasonable interpretation.

VII. OVERVIEW OF THE '780 PATENT

The '780 Patent is generally directed to "dual incretin peptide mimetic compounds that agonize receptors for both human and glucose-dependent insulinotropic polypeptide (GIP) and Glucagon-like peptide-1 (GLP-1), and may be useful for treating type 2 diabetes mellitus (T2D)." *Id*. at 1:1-8. GIP and GLP-1 are natural incretins secreted from the gut following a meal to enhance insulin secretion, nutrient disposal, and sensation of satiety. *Id*. at 1:20-36.

The '780 Patent acknowledges that use of these incretins individually was known but asserts that dosing of GLP-1 analogues was limited by adverse effects, such as nausea and vomiting, often preventing dosing from reaching full efficacy. *Id*. at 1:36-40 and 2:13-22. The '780 Patent also acknowledges it was known that native GIP and GLP-1 are inactivated rapidly by the ubiquitous DPP-IV protease, making them useful only for short-term metabolic control. *Id*. at 1:41-44.

The '780 Patent admits that GIP analogues with dual GIP/GLP-1 activity were known in the art and that known structural modifications of these compounds have specific effects on properties and functions of these compounds. *Id*. at 1:55-57. For

example, the use of fatty acid side chains as albumin binding motifs extend the half-life of these compounds. *Id*. at 2:4-11; *see also* EX1008, at 49:3-50:2 ("it is thought that the lipophilic substituent binds albumin in the blood stream, thus shielding the compounds employed in the context of the invention from enzymatic degradation which can enhance the half-life of the compounds") and 50:24-31.

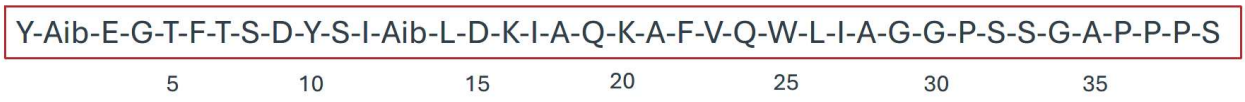
Despite the admitted disclosure of existing co-agonists of GIP and GLP-1, the '780 Patent asserts that a need still existed for a "balanced" co-agonism of GIP and GLP-1 receptors that could provide weight loss, have stability against deactivation by DPP-IV, and support once-weekly dosing. *Id*. at 1:45-54 and 2:28-41.

The '780 Patent presents "an embodiment" in the form of "a compound of Formula I," illustrated below:

$YX_1EGTFTSDYSIX_2LDKIAQKAX_3VQWLIAGGPSSGAPPPS$;

> wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_a$-CO—$(CH_2)_b$—CO_2H wherein a is 1 to 2 and b is 10 to 20; X_3 is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11), or a pharmaceutically acceptable salt thereof.

Id. at 2:53-65. When X_1 is Aib, X_2 is Aib, and X_3 is Phe (F), the compound of Formula I has the following base structure, which is consistent with SEQ ID Nos. 3 and 11 provided in the '780 Patent:



VIII. BACKGROUND OF TECHNOLOGY[5]

A. General Knowledge Regarding Peptide Chemistry

Peptides are short strings of at least two amino acids linked by covalent peptide bonds (i.e., amide bonds). EX1084 at ¶59; EX1011 at 18.1.1. Both natural and engineered peptides can trigger a signaling pathway by interacting with the receptor for that signaling pathway. EX1014 at 118-119, 203, Fig. 5-5. Some signaling peptide ligands act as peptide hormones. *See* EX1015.

Proteinogenic Amino Acids

Proteins in the body are naturally formed using 20 common amino acids as building blocks. EX1084 at ¶60. Figure 2.26 below shows the chemical structures of these amino acids, as reproduced in the prior art.

[5] Cited references not named in a ground of rejection are cited for the purpose of showing the state of the art and the background knowledge of a POSA. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

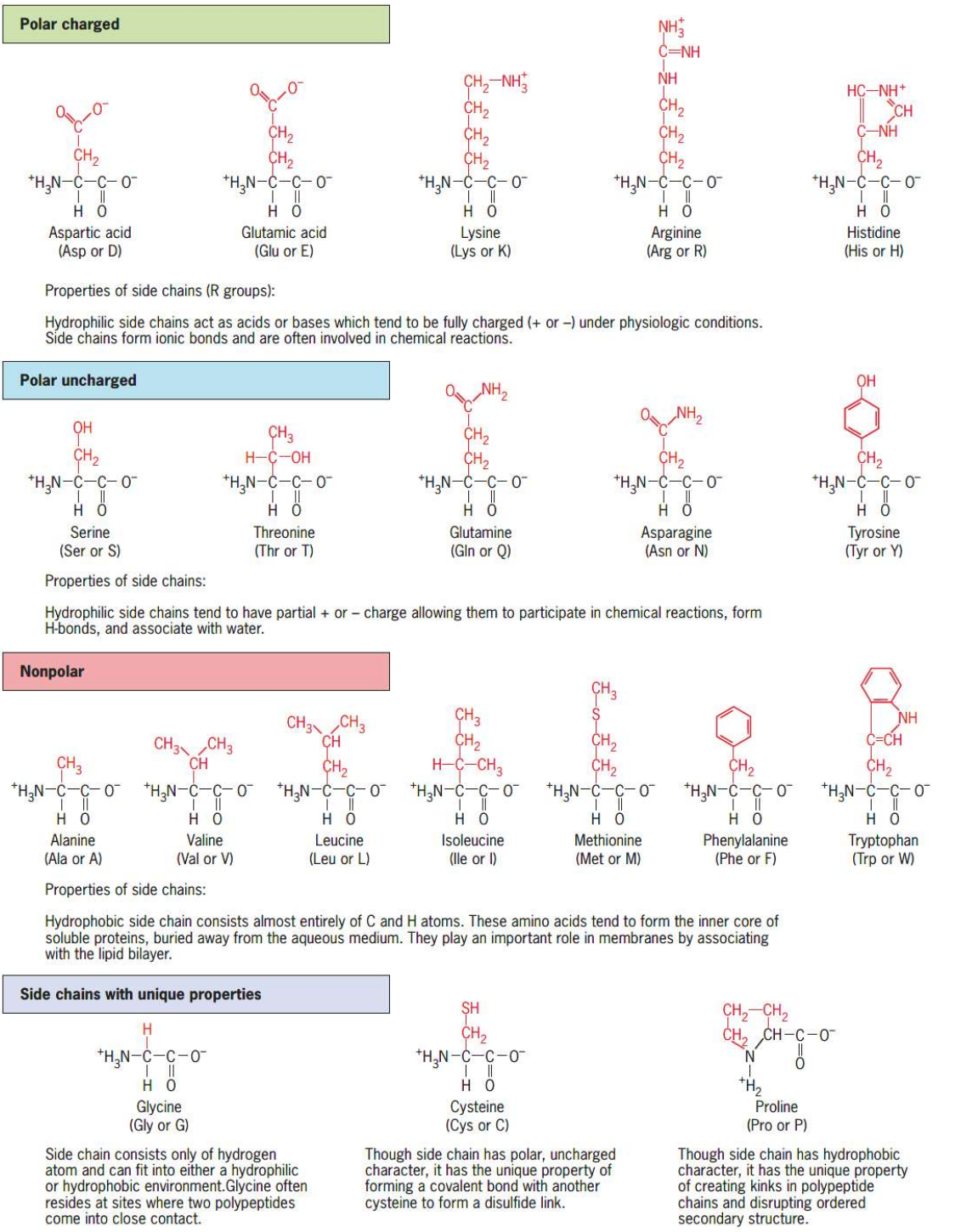


Figure 2.26 **The chemical structure of amino acids.** These 20 amino acids represent those most commonly found in proteins and, more specifically, those encoded by DNA. Other amino acids occur as the result of a modification to one of those shown here. The amino acids are arranged into four groups based on the character of their side chains, as described in the text. All molecules are depicted as free amino acids in their ionized state as they would exist in solution at neutral pH.

EX1078 at 52.

As shown above, the portion of each structure shown in black represents "the backbone," which is common to all amino acids. EX1084 at ¶61. The portion of the structures provided in red indicate the side chains, which are the primary source of differentiation among the different amino acids. *Id*.

These amino acid residues were regularly described using a three-letter code or a one-letter code, as illustrated in this chart:

Full	3-Letter	1-Letter	Full	3-Letter	1-Letter
Glycine	Gly	G	Phenylalanine	Phe	F
Alanine	Ala	A	Tyrosine	Tyr	Y
Valine	Val	V	Tryptophan	Trp	W
Leucine	Leu	L	Lysine	Lys	K
Methionine	Met	M	Arginine	Arg	R
Isoleucine	Ile	I	Histidine	His	H
Serine	Ser	S	Asparagine	Asn	N
Threonine	Thr	T	Glutamine	Gln	Q
Cysteine	Cys	C	Aspartate	Asp	D
Proline	Pro	P	Glutamate	Glu	E

EX1084 at ¶62; EX1014 at 118, Table 5-1. The side chains of the amino acids can alter the chemical characteristics of different amino acids, sometimes impacting the function of the amino acid, and, consequently, the peptides containing these amino acids. EX1084 at ¶63.

Synthetic Analogues of Peptides as Drugs

Peptide synthesis was described as early as 1901 and was continually improved upon up to the time of the invention. EX1084 at ¶¶64-66. By late 2014, modification of peptides for the purpose of improving pharmacokinetics and pharmacodynamics was routine. EX1084 at ¶67. Skilled artisans routinely modified peptides to stabilize them against proteolysis and degradation. *Id*. One approach involved PEGylation (the process whereby polyethylene glycol (PEG) is covalently attached to another molecule). *Id*. However, this approach was known to result in undesirable immunogenicity. *Id*. Specifically, in 2012, Garay reported that, in contrast to the common thinking that PEG is non-immunogenic and non-antigenic, up to 25% of healthy blood donors (*i.e.*, no indication of being previously treated with a PEGylated drug), and up to 89% of patients treated with a PEGylated drug have anti-PEG antibodies that can elicit responses to PEGylated drugs or compounds. *Id*.; EX1022 at Abstract, 1320. The response elicited by these PEG antibodies can result in decreased therapeutic efficacy and reduced tolerance to PEGylated drug compounds. *Id*.; EX1022 at Abstract, 1320. Consequently, a POSA approached PEGylation strategies with caution (particularly for chronic and repeated dosing), and would have been focused on other peptide development strategies. *Id*.

A more desirable approach involved conjugation of the peptide to a lipophilic moiety. EX1084 at ¶68. Knudsen et al. reported that the addition of fatty acid chains

to the Lys^{20} residue of liraglutide, a GLP-1 receptor agonist peptide, promotes reversible binding of the peptide to albumin in the blood, decreasing degradation by DPP-IV and protracting circulation and therapeutic effect. *Id*.; EX1023 at 5. Ward et al. disclosed that "site-specific lipidation alone could generate balanced, high potency co-agonism in glucagon-based peptides." *Id*.; EX1024 at 475. Further, Zhang et al. explained that lipidation is commonly employed to improve metabolic stability, membrane permeability, and bioavailability of peptide drugs. *Id*.; EX1025 at Abstract. Therefore, a POSA viewed conjugation with lipophilic moieties (e.g., fatty acid chains) to be a more desirable peptide synthesis strategy, as it avoided the unwanted immunogenicity reported to be present with PEGylation, while at the same time imparting advantageous properties on the peptide, including decreased degradation by DPP-IV and prolonging circulation and therapeutic effect of the peptide (thereby extending the half-life and allowing for less frequent administration of the peptide). *Id*.

Incretin GPCR Ligands – GIP and GLP-1

GIP and GLP-1 are both incretins that exist naturally in the body to activate the GIP and GLP-1 receptors. EX1084 at ¶¶69-70. In 1987, Mosjov and others discovered that the 37-residue GLP-1 peptide was actually a pro-peptide that was activated by cleavage of the first six N-terminal residues, leaving a conserved histidine as the N-terminal residue of the active forms of GLP-1(7-37) and GLP-1(7-

36). EX1084 at ¶¶71-72; EX1025 at Abstract. These two N-terminally truncated products (GLP-1(7-37) and GLP-1(7-36) amide) are the active species *in vivo*, are equipotent to one another, are the major physiological incretin in humans, and are commonly referred to as the endogenous form of GLP-1. EX1084 at ¶72; EX1030 at 27. Accordingly, amino acid residue numbering for endogenous GLP-1 often is performed using the convention of positions (1-30) or (1-31)—referring to the positions of the active peptide—rather than positions (7-36)/(7-37) of the pro-peptide. *Id*. In addition to increasing insulin secretion and expression, endogenous GLP-1 inhibits pancreatic beta-cell apoptosis, promotes beta-cell neogenesis, reduces glucagon secretion, delays gastric emptying, promotes satiety, and increases peripheral glucose disposal, thus playing a central role in controlling postprandial blood sugar levels. EX1084 at ¶72; EX1030 at 27-28.

Due to its impact on blood glucose, GLP-1 was considered a potential therapeutic for the treatment of diabetes, but there were two primary limitations on the use of exogenous GLP-1 for the treatment of diabetes and other disease states: (1) a very short half-life (only a few minutes); and (2) rapid degradation, with functional loss by DPP-IV-catalyzed cleavage of the two N-terminal residues (1-2) of the active form (residues 7-8 of the pro-peptide). EX1084 at ¶73; EX1030 at 28; EX1046 at Abstract. Though some forms of endogenous peptide cleavage activate GLP-1 (i.e., cleaving N-terminal residues 1-6 of the pro-peptide), other forms

essentially deactivate it. *Id*. In particular, studies identified a dipeptidyl peptidase (DPP)-IV cleavage site at pro-peptide residue 8 (Ala), where active GLP-1 is cleaved into GLP-1(9-37) or GLP-1(9-36) amide,[6] a much less active form with lower affinity for the GLP-1 receptor. EX1084 at ¶73; EX1047 at 753754; EX1048 at 3587, Figure 1; EX1049 at 21204, Table I. In parallel, Kieffer et al. demonstrated the absence of both GLP-1 and GIP degradation and improved GIP/GLP-1 activity in DPP-IV deficient rodents. EX1048 at 3587, Figure 1. Kieffer and Mosjov's work thus paved the way for using modified synthetic GLP-1 and GIP peptides (substituted at position 2 of the activated peptide to decrease DPP-IV cleavage) for therapeutic use in diabetes, obesity, and cardiovascular health. EX1084 at ¶73.

Diabetes and Obesity Treatment Using GLP-1 Agonists

(i) Incorporation of the Exendin Tail to Minimize DPP-IV Degradation and Extend Half-Life

By the 1980's, researchers discovered the endogenous GLP-1-receptor agonist exendin-4, which is resistant to DPP-IV cleavage largely because the Ala^2 is replaced with Gly^2, a DPP-IV resistant amino acid. EX1084 at ¶74; EX1030 at 28. Discovery of exendin led to rapid exploration of the structure activity relationship (SAR) explaining both the superior potency and proteolytic stability of the exendin-

[6] The numbering in GLP-1(9-37) and GLP-1(9-36) refers to the positions in the pro-peptide.

3 and -4 (sequences shown below) peptides as compared to GLP-1 and GIP. *Id*.; EX1069 at Abstract, 7 (GIP and GLP-1 "differ little in their susceptibility to proteolysis by these ectopeptidases"), 8 (the GLP-1 homologs exendin-3 and -4 both "share the biological properties of GLP-1" with only 50% homology to GLP-1, and with exendin-4 being "much more potently insulinotropic than GLP-1") and Table 4 (initial rates of proteolysis were 655 M/min/mg BBMM for GLP-1, 600 for GIP, 1 for Exendin-4, and 0.82 for Exendin-3).

Exendin-3 and -4 differ from one another only by the residues employed at positions 2 and 3. The annotated figure below shows the differing amino acid residues of Exendin-3 and Exendin-4 (highlighted in yellow), and also the shared C-terminal motif (highlighted in blue).

EXENDIN-3	HSDGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS
EXENDIN-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

EX1069 at 6, Table 1.

The superior metabolic stability and GLP-1 receptor agonist activity of exendins was also traced specifically to the C-terminal motif, which forms a Trp-cage motif or fold. EX1084 at ¶75; EX1072 at Abstract, 157. Adding the C-terminal motif (i.e., the exendin extension) to DPP-IV-resistant GLP-1 significantly improved its affinity and biological activity for GLP-1 receptor agonism as well as its metabolic stability against neutral endopeptidases. *Id*.; EX1072 at Abstract, 155-

157. The formation of the Trp-cage fold by the C-terminal motif additionally was understood to provide metabolic stability to the peptides, by reducing the rate at which the peptides were cleared by the kidneys and peripheral tissues. EX1084 at ¶75; EX1073 at Abstract. Adding the C-terminal motif to GLP-1 significantly reduced its rate of clearance while maintaining GLP-1 receptor binding and activation properties resembling native GLP-1. *Id*.; EX1073 at Abstract, Table 2, and 17-20 ("The present study clearly indicates that the COOH-terminal extension of EX-4 must provide some protection, since the renal clearance of GLP-1 was reduced to an amount closer to and not significantly different from the glomerular filtration rate when this sequence was added to GLP-1."). Researchers hypothesized that the reduced clearance rate of the extended GLP-1 analogue (employing the C-terminal motif of exendin) may result from reduced receptor-endocytosis-mediated clearance. *Id*.; EX1073 at 21.

Researchers subsequently demonstrated that the C-terminal motif similarly improved proteolytic resistance and insulinotropic activity of GIP without adversely affecting binding potency or functional activity at the GIP receptor relative to native GIP or DPP-IV-resistant GIP. EX1084 at ¶76; EX1074 at Abstract, 75-79, 82-84 & Table 1 (discussing C-terminally extended GIP analogue AC163794). Researchers proposed that the random, flexible coil provided by the endogenous GIP C-terminal motif was responsible for undesirable lipogenic activity of GIP, and thus proposed

replacing it with the exendin C-terminal motif to avoid undesirable lipogenesis. *Id*.; EX1074 at 82 ("GIP tail is a flexible random coil, recently suggested to have lipogenic function....The replacement of this tail region with a unique C-terminus tail of exenatide resulted in AC163794...with a significantly longer duration of insulinotropic action compared with native GIP or the DPP-IV resistant D-Ala^2 GIP1-42 peptide.").

The knowledge of the advantages of the exenatide C-terminal tail (which, as noted, forms the Trp-cage motif) resulted in the development of multiple peptide drug compounds utilizing this very strategy, such as lixisenatide (Lyxumia® and Adlyxin®) and exenatide (originally approved by the FDA in 2005 as Byetta® and later as an extended release formula, Bydureon®). EX1084 at ¶¶77-78; *see* EX1054. The exenatide peptide utilized in Byetta® and Bydureon® is a synthetic form of the naturally existing 39-amino acid exendin-4 peptide isolated from the saliva of the Gila monster. *Id*. Compared to human GLP-1, exenatide binds to the receptor with similar affinity, yet is refractory to *in vivo* degradation, thereby having a much longer half-life. *Id*. As discussed above in relation to exendin, exenatide's superior resistance to degradation by the DPP-IV peptidase is attributed to the difference in the second amino acid (Ala in GLP-1 and Gly in exenatide), and the additional stability of the peptide structure conferred by the C-terminal extension or tail in exenatide (which forms the Trp-cage motif, specifically between the Trp^{25} and the

C-terminal sequence -GGPSSGAPPPS). *Id*. Exenatide was reported as having a half-life of approximately 2.4 hours, significantly longer than that of native GIP and GLP-1, which have half-lives on the order of minutes. EX1054 at 3.

The lixisenatide peptide utilized in Lyxumia® and Adlyxin® also includes the exendin tail motif. EX1084 at ¶79. Though lixisenatide (derived from exendin-4) first received FDA approval for diabetes after the January 2015 priority date, it was heavily discussed in the literature before the January 9, 2015 critical date. EX1056 at 1-2, 11; EX1058 at Abstract, 2. As with exenatide, exendin tail of the lixisenatide peptide forms the Trp-cage motif, rendering the peptide more resistant to degradation by DPP-IV, and also extends the half-life of the compound. EX1084 at ¶79.

(ii) Conjugation with Lipophilic Fatty Acids to Enhance Albumin Binding and Further Extend the Half-Life

While the incorporation of the C-terminal exendin tail motif was a common design choice to protect against DPP-IV degradation, and to extend the half-life of GLP-1 agonist peptides, other design peptide design strategies had also become commonplace before the January 9, 2015 critical date. EX1084 at ¶80. In 2007, Madsen examined the impact of conjugating fatty acids, and fatty acid chain length on the half-life and duration of GLP-1 compounds. *See* EX1079. Specifically, Madsen assessed various peptide derivatives, all of which were derivatized at the

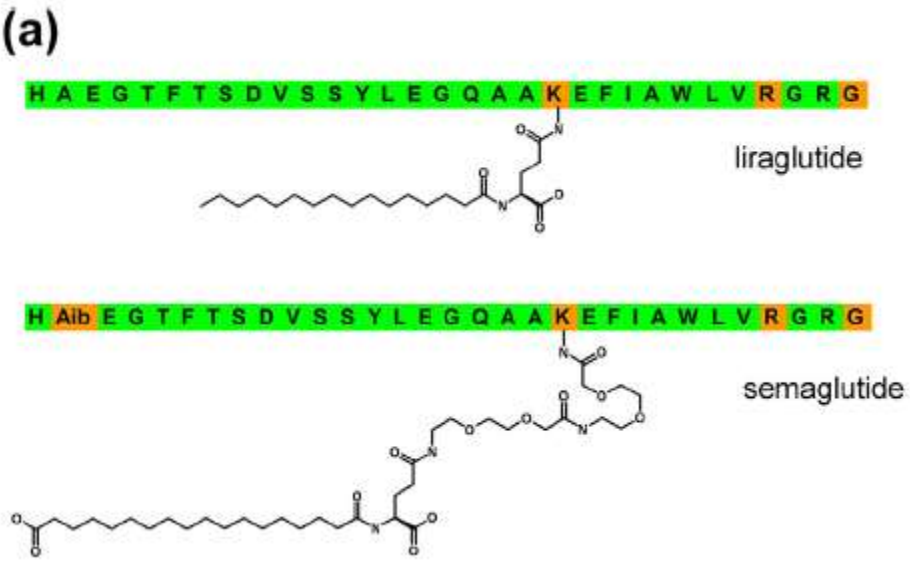
lysine (K) at position 26 of the native GLP-1 sequence (corresponding to position 20 of the GLP-1 agonist compound sequence, as discussed previously) with a spacer and an acyl group. EX1084 at ¶80; EX1079 at 6126-6127. This is the same conjugation strategy discussed previously. *Id*. Additionally, Madsen utilized a γ-Glu spacer, which was attached to fatty acids of varying lengths, including C10, C11, C12, C14, C16, and C18 fatty acids (corresponding to Compounds 1, 2, 3, 4, 5, and 6, respectively). *Id*.. Madsen found that, as the length of the fatty acid attached to the spacer increases, the compound's half-life also increases, with half-life values of 0.8 hours for the C10 fatty acid; 5.1 hours for the C11 fatty acid; 7.6 hours for the C12 fatty acid; 9 hours for the C14 fatty acid; 16 hours for the C16 fatty acid; and 21 hours for the C18 fatty acid. *Id*.

In view of this additional research and understanding, as exemplified by Madsen, many peptide drug compounds began to incorporate fatty acids as a strategy to further extend the half-life of GLP-1 agonist peptides. EX1084 at ¶81. One such example is the synthetic GLP-1 agonist liraglutide, which was developed and engineered to have 97% sequence identity to the active portion of endogenous GLP-1 (amino acids 7-37), the sole difference being the substitution of an arginine amino acid in place of a lysine amino acid at position 28 of the aligned peptide (pro-peptide position 34). EX1084 at ¶79.; EX1050 at 1, 11-12; EX1013 at 1, 14; EX1051 at Abstract, S59. Liraglutide further includes a C-16 fatty acid (palmitic acid) attached

to the peptide with a gamma glutamate ($_{\gamma}$Glu) spacer at the epsilon-amino group of the lysine at position 20 (pro-peptide position 26) of the peptide base sequence. *Id*.

Additionally, it was known by December 2014 that semaglutide was a GLP-1 derivative for once-weekly administration that was under development by Novo Nordisk A/S. EX1084 at ¶82; EX1010 at 1:21-23; EX1009 at Example 4. Semaglutide is a 31 amino acid peptide hormone, with two amino acid substitutions as compared to native GLP-1, namely Ala is substituted with Aib at position 2 (pro-peptide position 8), and Lys is substituted with Arg at position 28 (pro-peptide position 34). EX1084 at ¶82; EX1078 at 4014. Semaglutide also incorporates a C18-fatty acid[7] chain attached via an AEEA-AEEA-γGlu spacer to the Lys at position 20 (pro-peptide position 26). EX1084 at ¶82; EX1078 at 4014. To illustrate, the structures of both liraglutide and semaglutide are shown below:

[7] As Dr. Zhou discusses in his declaration, a POSA would know and understand that the terms "fatty acid" and "fatty diacid" have the same meaning in the context of the fatty acid chain conjugated to the GIP/GLP-1 peptides. EX1084 at ¶82 The prior art also uses these terms interchangeably. *See* EX1078 at 4014 (which refers to semaglutide's conjugation with a "fatty acid," but illustrates in Fig. 2a that a C18 fatty diacid is conjugated).



EX1084 at ¶82; EX1078 at 4014, Fig. 2a.

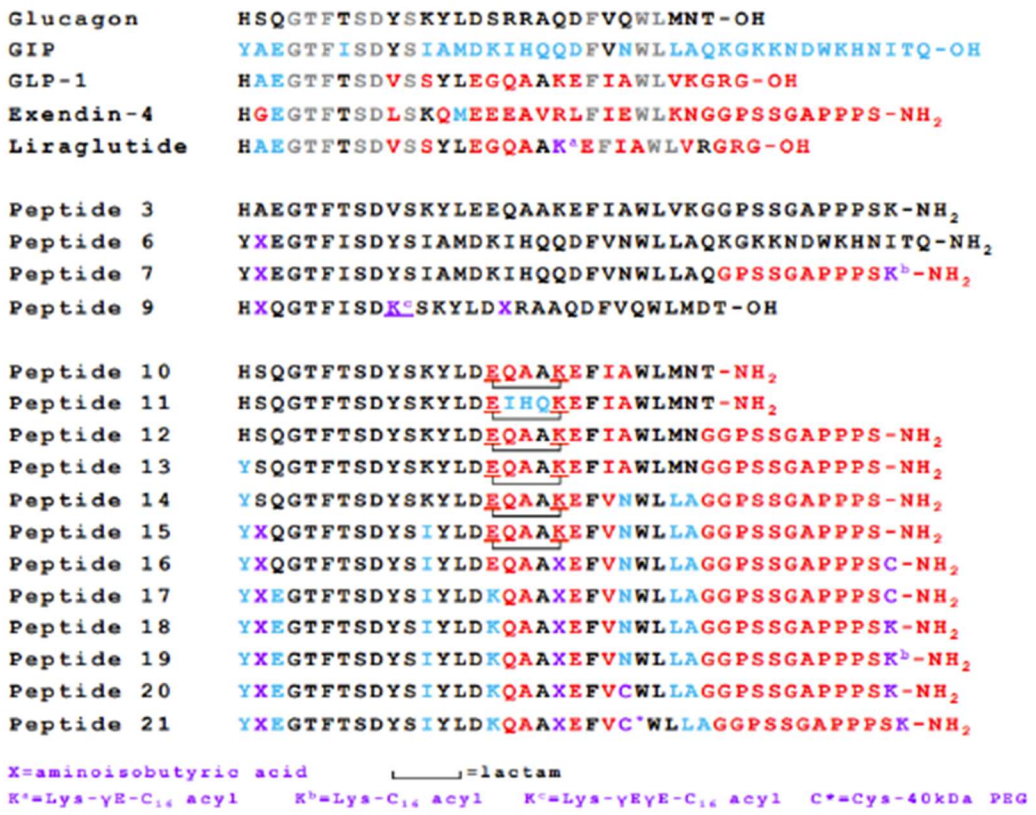
The development of liraglutide and semaglutide, both with prolonged half-lives, represented a growing trend in the field of peptide design and synthesis, namely the conjugation of lipophilic fatty acids to GLP-1 agonist peptides (specifically at the lysine 20 position) to prolong the half-life and allow for extended dosing schedules. EX1084 at ¶83. As explained by Lorenz, fatty acid conjugation was a well-established strategy to prolong the action of peptides by facilitating binding to serum albumin, thereby reducing the renal clearance of the peptide. EX1076 at 4014. Liraglutide and semaglutide are two examples of this design strategy. EX1084 at ¶83. As noted, liraglutide includes a C16 fatty acid conjugated to the Lys at position 20 via a glutamate spacer, resulting in extensive binding to serum albumin (~99%), leading to increased enzymatic stability towards DPP-IV, while reducing renal clearance. *Id.*; EX1076 at 4014. This increased stability and

reduced clearance results in a plasma half-life of 11-13 hours, which is substantially longer than native GLP-1 (known to have a short half-life of ~ 2 minutes). *Id*.; EX1076 at 4013-14. Semaglutide similarly includes a C18-diacid fatty acid chain also conjugated to the Lys at position 20, resulting in significant serum albumin binding, and an even longer half-life of ~160 hours. EX1084 at ¶83; EX1076 at 4014.

B. Rational Design of GLP-1/GIP Co-Agonists

By late 2014, GLP-1 and GIP co-agonist peptides were being explored, both *in vitro* and *in vivo*. EX1084 at ¶84; EX1059 at 754, Figure 5-6; *see* EX1061. Notably, Finan et al. described a GLP-1/GIP co-agonist that exhibited "enhanced antihyperglycemic and insulinotropic efficacy relative to selective GLP-1 agonists." EX1061 at Abstract, 1. Many other references had also begun to investigate and disclose various GIP/GLP-1 co-agonists, including Alsina-Fernandez, DiMarchi, and Just, among others. EX1007; EX1009; EX1017. In particular, Finan describes refining the duration of action of the co-agonists through site-specific lipidation to support less frequent administration. EX1061 at Abstract, 5-6. Finan also describes core sequences that produce GLP-1/GIP co-agonism without glucagon agonism, and

described these sequences in Supplemental Figure 1:



EX1084 at ¶84; EX1061 at Supplemental Figure 1. As can be seen in Supplemental Figure 1, Finan incorporated the exendin C-terminal tail (i.e., Trp cage motif) in the majority of its peptide compounds (e.g., peptides 12-21), similar to the strategy adopted in the development of exenatide and lixisenatide. EX1084 at ¶85.

Additionally, DiMarchi, another reference focused on GIP/GLP-1 co-agonists, had also begun to investigate these same peptide design strategies as early as 2009. EX1084 at ¶86. Specifically, DiMarchi discloses that increased activity at the GLP-1 receptor is provided by adding a C-terminal extension peptide such as GPSSGAPPPS or XGPSSGAPPPS to the C-terminus (i.e., the exendin C-terminal

tail). *Id*.; EX1017 at 5:7-11. In particular, DiMarchi discloses that glucagon peptides having a glycine substitution for threonine at position 29 and the C-terminal extension of GPSSGAPPPS is *four times* as potent at the GLP-1 receptor as native glucagon modified to include the C-terminal extension. *Id*.; EX1017 at 55:10-15.

DiMarchi further teaches that the peptide compounds can be modified to "[i]ncreas[e] solubility and/or duration of action or half-life in circulation and/or delaying the onset of action by acylation or alkylation of the glucagon peptide, as described herein." EX1084 at ¶87; EX1017 at 8:12-14. DiMarchi explains that the peptides can be acylated via a spacer, and that the acyl group can include fatty acids ranging from C4 to C30 fatty acids. *Id*.; EX1017 at 7:7-12, 8:12-14, and 64:7-13.

Consequently, while the development of GIP/GLP-1 co-agonists was in its earlier phases prior to January 2015, the art was clear that these co-agonists could be developed with efficacy for the treatment of diabetes and for weight loss. *See, e.g.*, EX1007, 2:9-10 ("certain compounds of the invention provide effective treatments to reduce body weight"), 3:32-33 ("the present invention also provides a method of treating diabetes mellitus in a patient comprising administering to a patient in need of such treatment an effective amount of a peptide of the invention"); EX1017, 2:17-19 ("peptides having both GIP activity and GLP-1 activity are particularly advantageous for inducing weight loss or preventing weight gain, as well as for treating hyperglycemia, including diabetes"). It was also clear to a POSA that

certain primary rational design strategies were being utilized in the development GLP-1 selective peptide compounds, namely:

- the incorporation of the C-terminal exendin tail to protect against degradation by DPP-IV, increase potency and structural stability, and to extend half-life; and
- conjugation (preferably at the lysine 20 position) with a lipophilic fatty acid to promote albumin binding and further extend the half-life.

EX1084 at ¶88.

Based on the utilization of these design strategies in the development of other FDA-approved drug compounds, these strategies would have been a primary focus for a POSA looking to achieve similar results related to protecting against degradation by DPP-IV and extending the peptide's half-life. EX1084 at ¶89.

IX. PRIOR ART QUALIFIES UNDER 35 USC §§102 and 103

The relevant teachings of Alsina-Fernandez, DiMarchi, and Lau as applied to the claims is provided in the analysis below. All three are prior art under at least §§102 and 103 since they were all published more than one year before the earliest filing date of the '780 Patent. *See* EX1007 (Alsina-Fernandez published September 29, 2011), EX1009 (Lau published September 21, 2006), and EX1017 (DiMarchi published January 28, 2010).