For the Patent Owner
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Paper No. __

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Coalition For Affordable Drugs V LLC
Petitioner
v.

Hoffman-LaRoche Inc.
Patent Owner

_____

Case: Unassigned
Patent 8,163,522
Title: HUMAN TNF RECEPTOR

_____

Petition

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Inter partes review is requested under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-80 & 42.100-123, for Claims 1-10 of US 8,163,522 (**Ex. 1001**). This Petition shows there is a reasonable likelihood that the petitioner will prevail on at least 1 challenged claim, based on one or more patents or printed publications.

I. MANDATORY NOTICES

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

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Coalition For Affordable Drugs V LLC ("CFAD"), Hayman Credes Master Fund, L.P. ("Credes"), Hayman Orange Fund SPC – Portfolio A ("HOF"), Hayman Capital Master Fund, L.P. ("HCMF"), Hayman Capital Management, L.P. ("HCM"), Hayman Offshore Management, Inc. ("HOM"), Hayman Investments, L.L.C. ("HI"), nXn Partners, LLC ("nXnP"), IP Navigation Group, LLC ("IPNav"), J Kyle Bass, and Erich Spangenberg are the real parties in interest (collectively, "RPI"). The RPI hereby certify the following information: CFAD is a wholly owned subsidiary of Credes. Credes is a limited partnership. HOF is a segregated portfolio company. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative general partner of Credes and HCMF. HI is the general partner of HCM. J Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD, Credes, HOF and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF

and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is the Manager and majority member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the Manager and majority member of IPNav. Other than HCM and J Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD, Credes, HOF, HCMF, HCM, HOM, HI, nXnP or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition will be borne by HCM, CFAD, Credes, HOF and/or HCMF.

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

To the best of Petitioner's knowledge there are no other matters which would affect or be affected by a decision in this proceeding, but for completeness we mention *Sandoz Inc. v. Amgen Inc.*, No. CV-13-2904 MMC, 2013 U.S. Dist. LEXIS 161233, (N.D. Cal. Nov. 12, 2013), aff'd, 773 F.3d 1274 (Fed. Cir. 2014).

C. Designation of Lead and Backup Counsel 37 C.F.R. § 42.8(b)(3)

Petitioner identifies its lead and backup counsel below. A Power of Attorney is being filed concurrently herewith in accordance with 37 C.F.R. § 42.10(b).

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

Direct correspondence to counsel at the above address. Petitioner consents to email service at: rhahl@neifeld.com, rmihail@neifeld.com and general@neifeld.com.

II. FEES 37 C.F.R. § 42.15(a)

Petitioner authorizes charging the 37 C.F.R. 42.15(a) fee and any other fees associated with this Petition to Deposit Account **502106**. The fee is: $23,000.

III. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing 37 C.F.R. § 42.104(a)

Petitioner certifies that the '522 patent is available for *inter partes* review. Petitioner also certifies that it is not barred or estopped from challenging the '522 patent on the Grounds identified in this Petition. 37 C.F.R. § 42.104(a)

B. Challenge and Precise Relief Requested 37 C.F.R. § 42.104(b)

1. Patents and Printed Publications 37 C.F.R. 42.104(b)(2)

1. US 6,004,781 ("*Seed,*" **Ex. 1006**) is a continuation of 08/057,952, Apr. 12, 1993, which is a continuation of 07/896,781, Jun. 9, 1992, which is a continuation of 07/299,596, Jan. 23, 1989, which is a continuation-in-part of 07/147,351, Jan. 22, 1988. *Seed* is available under 35 U.S.C. §102(e).

2. US 5,395,760 ("*Smith,*" **Ex. 1003**) was filed May 10, 1990. This application is a continuation-in-part of 07/421,417, filed Oct. 13, 1989, now abandoned, which is a continuation-in-part of 07/405,370, filed Sep. 11, 1989, now abandoned, which is a continuation-in-part of 07/403,241, filed Sep. 5, 1989, now abandoned. *Smith* is available under 35 U.S.C. §102(e).

3. US 5,116,964 ("*Capon,*" **Ex. 1002**), filed Nov 22, 1989 is a continuation-in-part of 07/315,015, filed Feb. 23, 1989. *Capon* is available under 35 U.S.C. §102(e).

2. Specific Statutory Grounds for Challenge 42.104(b)(2)

Ground 1: Claims 1-10 are unpatentable under 35 U.S.C. §103 as obvious over *Seed* (**Ex. 1006**) in view of *Smith* **(Ex. 1003),** and in view of *Capon* **(Ex. 1002)**.

None of these references is cumulative. *Seed* was not of record in the 08/444,791 application. *Smith* discloses a TNF receptor **Ex. 1003** 2:38-41. *Seed* teaches CD4 linked to an IgG_1 "upstream of the hinge region." **Ex. 1006**, 14:6-9. *Capon* also teaches CD4 receptors linked to IgG_1 "just upstream of the hinge region," but the "hinge" is defined functionally: "These truncated proteins are all joined to a human heavy chain gamma 1 region just upstream of the hinge domain (H) such that these chimeras contain the two cysteine residues (C) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions." **Ex. 1002**, 40:43-48. So, while the *Seed* and *Capon* Fc regions are similar, *Capon* defines the "hinge" domain functionally. **Ex. 1004**, ¶26.

IV. UNPATENTABILITY OF U.S. 8,163,522

A. Brief overview of the ‘522 Patent

The ‘522 patent claims are directed to polynucleotides encoding hybrid proteins, methods for producing an expression product of the polynucleotide construct containing part of a human tumor necrosis factor p75 receptor (TNF-R) fused to immunoglobulin Fc regions, related expression vectors, and mammalian host cells. The fusion proteins are said to be useful for therapeutic and diagnostic methods involving TNF binding. **Ex. 1001** 10:23-29. The ‘522 makes no claim to any proteins, *per se,* produced by the methods disclosed. **Ex. 1004, ¶**18.

B. Prosecution History of the ‘522 Patent

US 8,163,522 issued from 08/444,791, filed 05/18/1995, which is a divisional of 08/095,640, now US 5,610,279 (expired). The allowance was mailed 02/15/2012 (**Ex. 1026**, p. 1). The IFW contains 3530 pages but it is only necessary to review the rejection over *Smith* in view of *Capon* to understand this case. As discussed below the Examiner argued that it would have been obvious to modify the IgG constant region of *Smith* by omitting the CH1 domain, thereby changing *Smith’s* tetrameric TNF-binding assembly into a dimeric TNF-binding assembly.

Capon described polynucleotides encoding chimeric [ligand-binding partner]-immunoglobulin fusions with a modified IgG heavy chain omitting the CH1 domain. *Capon* states, “Typically, such fusions retain at least functionally

active hinge, CH2 and CH3 of the constant region of an immunoglobulin heavy chain." **Ex. 1002**, 10:10-12. Thus *Capon* taught [ligand-binding partner]-hinge-CH_2-CH_3 (*i.e.*, receptor-Fc) hybrids. **Ex. 1002**, 4:43-47; **Ex. 1004,** ¶26.

The Examiner's *Smith*/*Capon* rejection was framed incorrectly. Rather than arguing that it would have been obvious to make a TNF-R-Fc fusion by using *Capon's* method to clone *Smith's* TNF receptor, the Examiner focused on *Smith's* final product, arguing that it would have been obvious to modify *Smith's* TNF-R-IgG hybrid by removing the CH1 domain, creating an Fc region (*i.e.,* TNF-R-Fc), which should self-assemble into a dimer. The Examiner argued:

> *Smith* et al. teach DNA encoding an Ig fusion molecule. *Smith* et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor wherein the Ig portion lacks the first domain of the constant region. *Capon* et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). *Capon* et al. teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). *Capon* et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain…It would have been prima facie obvious…to have created the claimed invention because *Smith* et al. teach the nucleic acid sequence encoding an insoluble (eg. membrane bound) 75kD TNF receptor and DNA encoding Ig fusion proteins containing said molecule while *Capon* et

> al. teach DNA encoding soluble Ig/ligand binding fusion proteins wherein…the Ig portion…can contain at least the hinge, CH2 and CH3 domains …One…would have been motivated to do the aforementioned because *Capon* et al. teach that the ligand binding portion…can be derived from a wide variety of different known cell surface receptors…and that said fusion proteins have a variety of uses (see column 4)." **Ex. 1019**, p. 8-9.

A similar rejection was made at **Ex. 1023**, p. 9 - 10.

The Examiner's argument that TNF-R-IgG → TNF-R-Fc may seem reasonable to a patent practitioner, but it is not what a person of ordinary skill in the art ("POSITA") would have thought when the '522 patent was filed, because *Capon* had disclosed a general method for making [ligand-binding partner]-Fc fusions. Once *Smith* had disclosed the TNF-R gene, a POSITA would have used *Capon's* method to make TNF-R-Fc with a reasonable expectation of success:

[X receptor]-Fc (dimer) → [TNF receptor]-Fc (dimer)

wherein [X receptor] is CD4 (**Ex. 1002,** 44:60-62; 45:6-12, Example 5 of *Capon*), or cell surface glycoprotein lymphocyte homing receptor or "LHR" (**Ex. 1002,** 15:4-8; 40:30-32, Example 4 of *Capon*). **Ex.1004, ¶**36. Instead, the Examiner framed the argument in terms of replacing *Smith's* unmodified IgG heavy chain with *Capon's* Fc region by omitting the CH1 domain. The Applicants responded that "there was no reason to select the species of IgG fusions encoded by the claimed polynucleotides from among the multitude of Ig fusions described in the

Capon Patent." (**Ex. 1020**, p. 40, lines 8-10), and argued that he had not established a prima facie case of obviousness – to which the Examiner had no effective answer since the rejection was withdrawn (after claim amendments and cancellation of claims). **Ex. 1026**, p. 6, lines 2-3; **Ex. 1023**, p. 9, line 8 – p. 13, line 12.

But the Applicants' argument about having to select the claimed polynucleotides from "among the multitude of Ig fusions" was wrong. It overlooked *Capon*'s "typical" approach (**Ex. 1002**, col. 10:10-12) used in Examples 4 and 5, and FIG. 8, and ignored a "particularly preferred" embodiment (LHR-Fc). **Ex. 1002**, 15:4-8. Modifying such chimeras by replacing their receptors with *Smith's* TNF-R required no selection from among multitudes. (It merely required using *Capon's* method for its intended purpose. **Ex. 1004, ¶**36)

Applicants also argued that *Smith* teaches away from their claimed invention:

> Moreover, the Smith Patent teaching of "unmodified constant regions" teaches one to prefer an embodiment that comprises the CH1 domain. Thus, the cited art teaches away from the particular species of Ig fusion proteins encoded and produced by the claimed constructs, which consist of the extracellular region of p75 TNFR and "all the domains of an immunoglobulin heavy chain constant region other than the first domain." **Ex. 1020**, p. 40, lines 2-6.

Applicants made this point again at **Ex 1022**, p. 24, lines 16-20; and again at **Ex. 1024**, p. 8 line 27-p. 9, line 7:

> For example, the Capon Patent states that a "preferred embodiment" retains the entire constant region (the ligand binding partner being substituted for the variable region of an antibody, see col. 5, ln. 37-41 and col. 15, ln. 9-25).…Applicants reminded the Examiner that MPEP §2144.08 requires that such teachings be considered because they "may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness."…The Examiner's only response was to quote MPEP §2123…suggesting that nonpreferred and alternative embodiments still constitute prior art. Action, p. 9. However, the mere fact that a compound could be made is not a sufficient reason to select it…" **Ex. 1024**, p. 8, line 27- p. 9, line 7.

The citation to *Capon* "col. 15, ln. 9-25" for the assertion that "retains the entire constant region" is "preferred" missed *Capon's* real meaning. *Capon* actually teaches omitting the CH1 domain is also preferred: "There are two preferred embodiments of this sort; in one, the entire heavy chain constant region is fused to a portion of the LHR; in another, a sequence beginning in the hinge region just upstream of the papain cleavage site which defines IgG Fc chemically (residue 216)." **Ex. 1002**, 15:8-13. Contrary to Applicants' argument at **Ex. 1020**, p. 40, lines 8-10, rather than a "multitude of Ig fusions" to select from, there are just two preferred IgG constructs: with or without the CH1 domain, the latter being "typical" (**Ex. 1002**, 10:10-12) and in one case: "A <u>particularly preferred</u> embodiment is a fusion of an N-terminal portion of a LHR, which contains the binding site for the endothelium of lymphoid tissue, to the C-terminal <u>Fc portion of</u>

an antibody, containing the effector functions of immunoglobulin G_1." **Ex. 1002**, 15:4-8 (emphasis added). This passage describes building LHR-hinge-CH1-CH2 (i.e., LHR-Fc) to give an "LHR having improved properties including enhanced specific activity and modified plasma half-life." **Ex. 1002**, 4:3-6; **Ex 1004**, ¶52a.

So the "teaching away" argument was incorrect. *Smith* did indeed mention unmodified IgG heavy chains, but the Applicants argued that this fact, in itself, teaches away from modified heavy chains. However, *Smith* disclosed this structure as just one embodiment, giving no reason why any other structure should be avoided, while the applicants supplied no such reason either. **Ex. 1020**, p. 40, lines 2-6; **Ex 1022**, p. 24, lines 16-20; **Ex. 1024**, p. 9, lines 16-18.

Applicants then argued in the alternative that, even if a prima facie case had been made out it should be withdrawn, due to alleged unexpected properties of an expressed protein (**Ex. 1020**, p. 33, line 13 – p. 36, line 28; **Ex. 1022**, p. 31, line 1 – p. 34, line 16, **Ex. 1024**, p. 12, line 1 – p. 13, line 14). However, none of the '522 patent claims is directed to a protein (**Ex. 1004**, ¶18) and the Examiner did not say that unexpected results supported allowance. **Ex. 1023**, p.13, line 12 - p.20, line 15.

The prima facie case of obviousness in Ground 1 cannot be overcome by the properties of a protein (even if unexpected) because that doctrine requires the claims be commensurate in scope with the unexpected results. *In re Clemens*, 622 F.2d 1029, 1036, (CCPA 1980). See also *In re Peterson*, 315 F.3d 1325, 1329-31,

(Fed. Cir. 2003). Claims 1 – 10 are not commensurate in scope with any protein because: 1) they are directed to either polynucleotides, host cells, vectors, or methods of protein expression, but not to proteins *per se*, and 2) all of the claimed subject matter has alternative uses that were obvious over *Seed*, *Smith,* and *Capon*.

Capon taught "The novel polypeptides of this invention are useful in diagnostics or in purification of the ligand binding partner by immunoaffinity techniques known per se. Alternatively, in the purification of the binding partner, the novel polypeptides are used to adsorb the fusion from impure admixtures, after which the fusion is eluted and, if desired, the binding partner is recovered from the fusion, e.g., by enzymatic cleavage." **Ex. 1002**, 17:54-61. Thus, *Capon's* hybrid proteins can be used to make the ligand binding partner itself, while the Fc region facilitates protein purification and provides chemical reagents. **Ex. 1004**, ¶35

Likewise *Smith* taught that IgG "TNF-R derivatives can be used as immunogens, reagents in receptor based immunoassays, or as binding agents for affinity purification procedures of TNF or other binding ligands" **Ex. 1003**, 8:1-4. Prof. Greene testifies that neither reference discourages the POSITA from using *Capon's* method to make *Smith's* TNF-R. **Ex. 1004**, ¶53, ¶76, ¶98.

In sum, the Examiner failed to properly articulate what *Capon* and *Smith* really taught, and the Applicants failed to show that their DNA constructs, vectors, host cells, and methods have unexpected properties, even though the principal

difference between the '522 patent claims and *Capon*'s method is just the identity of the ligand-binding partner. **Ex. 1004,** ¶53, ¶76, ¶98.

C. The Effective Filing Date of Claims in the '522 Patent

The '522 patent issued on application 08/444,791, filed May 19, 1995, which is a divisional of 08/095,640, filed on July 21, 1993, now US 5,610,279, which is a continuation of 07/580,013, filed on Sept. 10, 1990, now abandoned. It claims priority to four foreign applications filed on: Sep. 12, 1989 (CH) 3319/89 (**Ex. 1027**; English translation **Ex. 1028**); Mar. 8, 1990 (CH) 746/90 (**Ex. 1029**; English translation **Ex. 1030**); Apr. 20, 1990 (CH) 1347/90 (**Ex. 1031**; English translation **Ex. 1032**); and Aug. 31, 1990 (EP) 90116707 (**Ex. 1033**; English translation **Ex. 1034**). The effective date of Claims 1 - 10 is no earlier than Aug.31, 1990, the filing date of (EP) 90116707 (**Ex. 1033**; certified English translation **Ex. 1034**), because the documents filed before Aug. 31, 1990 fail to describe an Ig heavy chain containing "all of the domains of the constant region of a human IgG [or IgG_1] immunoglobulin heavy chain other than the first domain of said constant region," as required by all claims in the '522 patent. **Ex. 1004**, ¶10.

D. Person of Ordinary Skill in the Art

The level of ordinary skill in the art of the '522 patent may be determined by reviewing the patent itself, relevant prior art, the nature of problems it was intended to solve, and the education level of active professionals in the field in

1989-1990. **Ex. 1004**, ¶11. Petitioner relies on an expert declaration by Prof. James Greene, who has spent over 34 years in academic research, pharmaceutical consulting, and special government and public service activities in biotechnology. **Ex. 1004**, ¶¶3-5. Prof. Greene attests that the field of the '522 patent is: recombinant DNA processes for the production, isolation, and use of chimeric proteins. **Ex. 1004**, ¶8. A person of ordinary skill in the art when the putative inventions claimed in the '522 patent were made would most likely have held an advanced degree, such as a Ph.D., in cell biology, biochemistry, or biophysics. **Ex. 1004**, ¶9. Prof. Greene is familiar with the knowledge, experience, and resourcefulness of a POSITA during the relevant time period. **Ex. 1004**, ¶¶11-12.

E. Claim Construction

"TNF Receptor"

The '522 specification describes the claimed TNF receptors as "proteins of the present invention are non-soluble proteins, i.e. for example membrane proteins or so-called receptors, and soluble or non-soluble fragments thereof, which bind TNF (TNF-BP), in homogeneous form," **Ex. 1001**, 4:14-18. Thus, "TNF receptor" should be construed as "soluble or non-soluble proteins, or fragments thereof, which bind TNF, in homogeneous form." **Ex. 1004**, ¶21.

"All of the Domains of the Constant Region of a Human IgG Except…"

The ‘522 specification states, “[t]his invention comprises DNA sequences which combine two partial DNA sequences, one sequence encoding soluble fragments of TNF binding proteins and the other partial sequence encoding all domains except the first domain of the constant region of the heavy chain of human immunoglobulin IgG, IgA, IgM, or IgE, and the recombinant proteins encoded by these sequences.” **Ex. 1001**, 2:37-43. Therefore the phrase “all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region” should be construed as “-hinge-CH2-CH3” region of an IgG (or IgG_1) immunoglobulin heavy chain. **Ex. 1004**, ¶22.

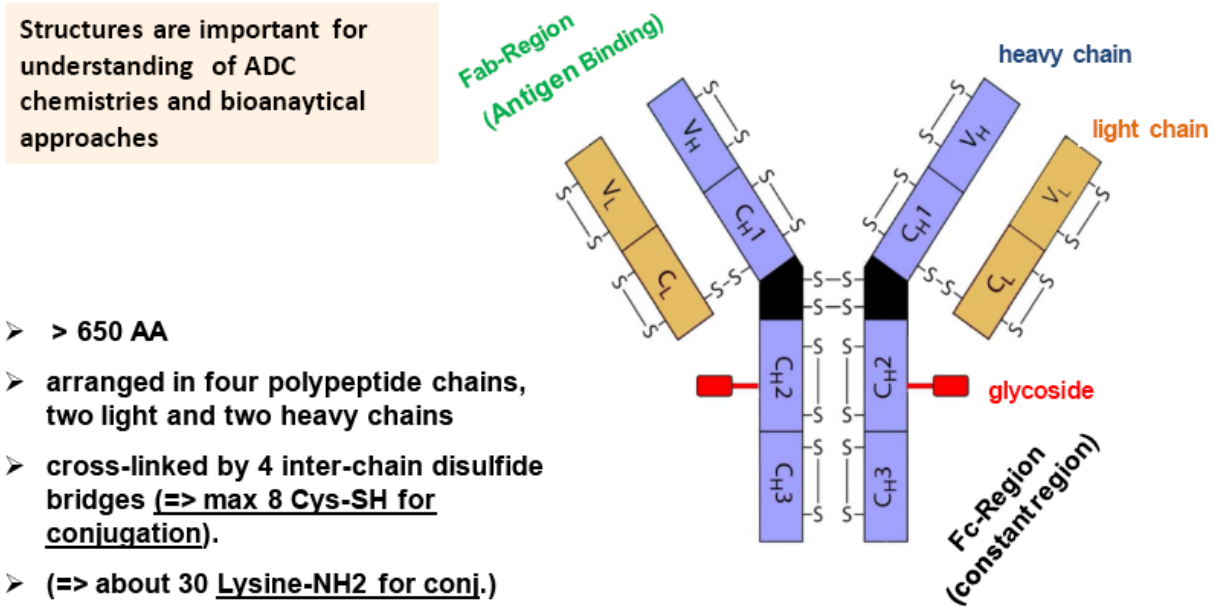
“About”

The ‘522 specification does not define the molecular weight range encompassed by the phrase “an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel.” Differences in such values depend on variations in glycosylation, and inherent imprecision of gel electrophoresis. The broadest reasonable construction of the claim term “about” is “approximately.” This construction is consistent with the plain and ordinary meaning of “about” as “approximately.” **Ex. 1004** ¶ 22a. ¶

Other claim terms should be given their plain and ordinary meaning.

F. Overview of Prior Art Reviewed by Prof. Greene

Immunoglobulin structure (**Ex. 1004**, ¶24):



Seed teaches polynucleotides encoding CD4 fused to an immunoglobulin heavy chain, their expression in transformed host cells, and use to treat HIV. **Ex. 1006**, 4:47-5:29. These fusions may be separated from the reaction mixture with an immobilized protein that binds specifically to the Fc portion. **Ex. 1006**, 8:54-57. *Seed* states that "the CH1 region of an immunoglobulin chain may be deleted" (**Ex. 1006**, 6:13-14), and shows that the extracellular portion of the CD4 molecule could be fused at three locations in a human IgG1 heavy chain constant region gene:

> Assembly of the chimeric genes by ligation afforded molecules in which either the variable (V) region, the V + CH1 regions, or the V, CH1 and hinge regions were replaced by CD4. In the last case, the chimeric molecule is expected to form a monomer structure, while in the former, a dimeric molecule is expected" **Ex. 1006**, 13:38-44.

In *Seed's* "second genetic construct" the V + CH1 regions are replaced by CD4, and contains "the DNA sequence which encodes CD4 linked to human IgG1 at the Esp site upstream of the hinge region." **Ex. 1006,** 14:6-9. A plasmid containing it was deposited at the ATCC. **Ex. 1006**, 14:9-12. *Seed's* second genetic construct has "all of the domains of the constant region of a human IgG_1 immunoglobulin heavy chain other than the first domain of said constant region." **Ex. 1004,** ¶25.

Capon discloses making Fc hybrids as a general method:

> …an object of this invention to produce ligand binding partners fused to moieties which serve to prolong the in vivo plasma half-life of the ligand binding partner, such as immunoglobulin domains or plasma proteins, and facilitate its purification by protein A. It is a further object to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding, cell receptor binding and the like. **Ex. 1002**, 4:38-47.

A [ligand-binding partner]-IgG fusion is described: "Typically, such fusions retain at least functionally active hinge, CH2 and CH3 of the constant region of an immunoglobulin heavy chain." **Ex. 1002**, 10:10-12. This immunoglobulin (-hinge-CH_2-CH_3) fragment is the "Fc" region. The term "functionally active hinge" refers to a hinge with at least the second and third cysteine moieties, which are important for dimer assembly via disulfide bridges. **Ex. 1004,** ¶26. *Capon* states, "**FIG. 9** illustrates that these molecules dimerize under non-reducing conditions

demonstrating that the hinge region is fully functional in these chimeras." **Ex. 1002**, 40:65-69. Prof. Greene testifies that *Capon's* Fc hybrids contain "all of the domains of the constant region of a human IgG [or IgG_1] immunoglobulin heavy chain other than the first domain of said constant region." **Ex. 1004,** ¶26.

Capon goes on to teach that Fc fusion proteins are secreted from host cells. **Ex. 1002**, 40:60-63.[1] **Ex. 1004,** ¶27

Smith describes IgG fusions containing the human TNF receptor (TNF-R) together with recombinant DNA methods for making them. The proteins bind to TNF and are useful in therapeutic and diagnostic methods. **Ex. 1003,** Abstract. *Smith* discloses soluble derivatives of the full-length TNF receptor:

> Soluble TNF-R" or "sTNF-R" as used in the context of the present invention refer to proteins, or substantially equivalent analogs, having an amino acid sequence corresponding to all or part of the extracellular region of a native TNF-R... **Ex.1003**, 4:12-16.

Smith teaches that "[s]uch compositions, however, are obtainable in practical yields only by cloning and expressing genes encoding the receptors using

[1] *Traunecker et al*. (**Ex. 1041**) co-authored by Josef Schneider of Hoffman-LaRoche (assignee of the '522 patent) cited at *Capon* **Ex. 1002**, 2:6-7, states "We have also noticed that hybrid molecules containing the CH1 domain, for example CD4-1gM chimaeras, are not secreted…" **Ex. 1041,** p.3, cols. 1-2. **Ex. 1004**, ¶27.

recombinant DNA technology." **Ex. 1003**, 2:22-25. The POSITA understood that *Smith's* soluble TNF receptor would be suitable as a ligand-binding partner in the hybrids of *Seed* and *Capon.* The need for "practical yields" would have motivated one to use *Seed* or *Capon* to express the TNF-R gene of *Smith*. **Ex. 1004**, ¶28.

Smith said that a dimeric assembly should enhance TNF binding affinity: "Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand." **Ex. 1003**, 10: 61-66; **Ex. 1004**, ¶29.

Seed teaches dimeric CD4-Fc constructs as "the fusion protein may be expressed in a mammalian cell which does not secrete other light or heavy Ig chains. When expressed under these conditions, the fusion protein may form a homodimer." **Ex. 1006**, 6:53-56. *Capon* also teaches dimeric constructs saying: "**FIG. 9** illustrates that these molecules dimerize under non-reducing conditions demonstrating that the hinge region is fully functional in these chimeras." **Ex. 1002**, 40:65-69. Enhanced TNF binding affinity would have motivated a POSITA to use *Seed* or *Capon* to provide dimeric TNF-R-Fc assemblies. **Ex. 1004**, ¶30.

Seed goes on to say that Fc fusions facilitate purification: "The fusion proteins and immunoglobulin-like molecules of the invention may be isolated and purified in accordance with conventional conditions, such as extraction,

precipitation,..." **Ex. 1006**, 8:50-58; **Ex. 1004**, ¶31. *Capon* also taught purification methodologies: "the protein A reactivity also allows for the purification of these chimeras to near homogeneity on protein A sepharose columns" (**Ex. 1002**, 40:69-41:2), and states that the CH1 domain is not necessary for affinity purification, "because CD4-IgG, LHR-IgG and CD4-IgG-LHR-IgG all contain an IgG Fc portion, they can all be precipitated directly by protein A by standard methods." **Ex. 1002**, 45:5-10. *Seed* and *Capon* taught "purifying an expression product of the polynucleotide from the cell mass or the culture medium." **Ex. 1004, ¶**32.

Seed discloses therapeutic utility: "The invention also relates to a method for preparing a medicament or pharmaceutical composition comprising the components of the invention, the medicament being used for therapy of HIV or SIV infection in animals." Ex. **1006**, 10: 31-34; **Ex. 1004, ¶**33. *Capon* also teaches therapeutic utility: "selection of ligand binding partners with specific affinity for particular tissues clearly enhances the ability to deliver therapeutic agents which are stable, have relatively long half-lives, and are capable of precise tailoring without undue experimentation" (**Ex. 1002,** 30:67 – 31:3); "[s]ustained release polypeptide preparations are implanted or injected into proximity to the site of inflammation or therapy for example adjacent to arthritic joints…" **Ex. 1002,** 31:45-48. Moreover, *Capon* taught that this approach could be adapted to a variety of therapeutic applications based on the identity of the ligand. Thus, a POSITA

knew that the identity of the ligand, ligand binding affinity, and plasma half-life are important for therapeutic utility. **Ex. 1004,** ¶34.

Seed disclosed reagents for use in immunoassays and the like: "…the immunoglobulin-like molecule or fusion protein may be labeled with any conventional label." **Ex. 1006**, 10:41-43. *Capon* also taught reagents: "The novel polypeptides of this invention are useful in diagnostics or in purification of the ligand binding partner by immunoaffinity techniques known per se…if desired, the binding partner is recovered from the fusion, e.g., by enzymatic cleavage." **Ex. 1002**, 17:54-61 **Ex. 1004,** ¶35.

Thus following *Seed's* initial work, *Capon* established a general method for making [ligand-binding partner]-Fc fusions. (Other therapeutic chimeric proteins made by fusing a ligand to IgG were also known before August 31, 1990, e.g., L-selectin-IgG. **Ex. 1045**, Abstract; **Ex. 1004**, ¶36) Once *Smith* had disclosed the TNF-R gene, a POSITA would have used *Seed* or *Capon's* method to make TNF-R-Fc with a reasonable expectation of success, as follows:

[X receptor]-Fc (dimer) → [TNF receptor]-Fc (dimer)

wherein [X receptor] = CD4 (**Ex. 1002,** 44:60-62; 45:11-12; and Example 5 of *Capon*) or LHR (**Ex. 1002,** 15:4-8, Example 4). That is because a POSITA wanted to: a) enhance the serum half-life of TNF-R, by fusing it to an Fc fragment for therapeutic purposes; b) enhance TNF binding affinity by fusing TNF-R to an Fc

fragment, to make a bivalent assembly for reagent and therapeutic purposes; and c) yield quantities of TNF-R itself, as a reagent. These goals entail the same DNA constructs, fusion proteins, vectors, mammalian host cells, and purification methods recited in Claims 1 – 10 of the '522 patent. **Ex. 1004**, ¶36.

Mammalian cells, and specifically CHO cells, are recited in certain claims of the '522 patent. Since immunoglobulins are glycosylated, it was common to express them in mammalian cells capable of complex glycosylation, whereas other cell types (*e.g.*, bacteria) are not. CHO cells were well known to be suited for the generation of stable cell lines. **Ex. 1037; Ex. 1004**, ¶37.

Regarding unexpected properties, *Smith* taught that high binding affinity was expected from TNF-R-Fc dimers, because "the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand." **Ex. 1003**, 10: 62-66. That was consistent with known properties of TNF itself: "TNF-α is predominantly a homotrimer and therefore intrinsically capable of multivalent binding." **Ex. 1038**, p.2, col.2, lines 13 -16; **Ex 1039,** Abstract. The POSITA knew that after a first binding event in a dimeric TNF receptor, another TNF molecule within the trimer will likely bind to the second receptor. **Ex. 1004**, ¶38. Because one expected enhanced TNF binding of dimeric TNF-R-Fc, it cannot be considered an unexpected result. Studies confirmed that the Fc region in

etanercept (Enbrel, Amgen) enhances serum half-life, per *Capon*, while the bivalent structure enhances TNF affinity, per *Smith*: "The Fc portion helps to retain the molecule in the circulation. By competitive inhibition, the two sTNFRII arms bind two of the three receptor-binding sites on the TNF trimer." **Ex. 1042**, p.6, 2:4-7; **Ex. 1004**, ¶38.

V. DETAILED EXPLANATION OF THE CHALLENGES

A. Ground 1: Claims 1-10 would have been obvious over *Seed* in view of *Smith,* and further in view of *Capon*

The rationale to support a conclusion that a claim would have been obvious is that all claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective function, and the combination yielded no more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc*., 550 U.S. 398, 416 (2007) (citing *United States v. Adams*, 383 U.S. 39, 40 (1966); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969); and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)). Obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

Claim 1: A method comprising the steps of: (a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of: (i) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and (ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and (b) purifying an expression product of the polynucleotide from the cell mass or the culture medium.

The preamble of claim 1 recites a "method" comprising "the steps of," without introducing what kind of method is involved; part (a) recites culturing a host cell, and part (b) recites purifying an expression product from the cell mass or the culture medium. This preamble introduces a method for expressing a protein in cell culture and then purifying the expressed protein. **Ex. 1004**, ¶39.

The first element of claim 1 requires **"[a] method comprising the steps of: (a) culturing a host cell comprising a polynucleotide wherein the polynucleotide encodes a protein."** *Seed* discloses: "The invention is directed to a protein gene which comprises 1) a DNA sequence which codes for CD4, or fragment thereof which binds to HIV gp120, fused to 2) a DNA sequence which encodes an immunoglobulin heavy chain. Preferably, the antibody has effector function." **Ex. 1006**, 5:33-39. *Seed* also discloses "A method of producing a fusion protein……characterized by cultivating in a nutrient medium under protein-producing conditions a host stain transformed with the vector…direct expression

of the said fusion protein, and recovering the fusion protein so produced". **Ex. 1006**, 4:56 – 5:1; **Ex. 1004,** ¶40.

Capon discloses: "The fusions of this invention are made by transforming host cells with nucleic acid encoding the fusion, culturing the host cell and recovering the fusion from the culture. Also provided are vectors and nucleic acid encoding the fusion, as well as therapeutic and diagnostic compositions comprising them." **Ex. 1002**, 5:61-66. *Smith* likewise discloses culturing a host cell to express proteins: "Recombinant TNF-R DNA is expressed or amplified in a recombinant expression system comprising a substantially homogeneous monoculture of suitable host microorganisms." **Ex. 1003**, 11:60-63; **Ex. 1004**, ¶41.

Seed, Capon and *Smith* show that culturing host cells comprising a polynucleotide that encodes a fusion protein was well known. **Ex. 1004**, ¶42.

The second element of claim 1 requires **"wherein the polynucleotide encodes a protein consisting of: (i) the extracellular region of an insoluble human TNF receptor."** *Smith* teaches, "[t]he mature full-length human TNF-R is a glycoprotein having a molecular weight of about 80 kilodaltons (kDa)." **Ex. 1003**, 3:47-49. *Smith* further discloses polynucleotides encoding the extracellular region of the insoluble TNF receptor: "Subunits of TNF-R may be constructed by deleting terminal or internal residues or sequences. Particularly preferred sequences include those in which the transmembrane region and intracellular

domain of TNF-R are deleted or substituted with hydrophilic residues to facilitate secretion of the receptor into the cell culture medium. The resulting protein is referred to as a soluble TNF-R molecule which retains its ability to bind TNF." **Ex. 1003**, 9:17-24; **Ex. 1004**, ¶43.

Seed teaches, "The invention relates to a gene comprising a DNA sequence which encodes a fusion protein comprising 1) CD4, or a fragment thereof which binds to HIV gp120." **Ex. 1006**, 4:47-50. Also, "The CD4 protein consists of a 370 amino acid extracellular region containing four immunoglobulin-like domains,…" **Ex. 1006**, 1:64-67; **Ex. 1004,** ¶44.

Capon teaches, "Construction of suitable vectors containing the desired coding and control sequences employ standard ligation techniques. Isolated plasmids or DNA fragments…form the plasmids required." **Ex. 1002**, 29:49-53. Also, "Ordinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof…The transmembrane regions…are preferably inactivated or deleted prior to fusion." **Ex. 1002**, 10:1-9. *Capon* also discloses:

> Inactivation of the transmembrane domain of the LHR and any other binding partner where one is present, <u>typically by deletion</u> or substitution of transmembrane domain hydroxylation residues, will facilitate recovery and formulation by reducing its cellular or

membrane lipid affinity and improving its aqueous solubility. **Ex. 1002,** 20:11-17 (emphasis added).

So *Capon* prefers deleting the transmembrane region of insoluble receptors "where one is present," while *Smith* teaches that deleting the transmembrane region applies to TNF-R: "Particularly preferred sequences include those in which the transmembrane region and intracellular domain of TNF-R are deleted." **Ex. 1003**, 9:17-24. So, the POSITA would have understood that deleting the transmembrane region of *Smith's* TNF-R would create an extracellular region compatible with the expression methods of *Seed* and *Capon* that specifically employ inactivation or deletion of transmembrane regions. Thus, the combined teachings of *Seed, Capon* and *Smith* would have motivated one to create a polynucleotide encoding a protein in which the transmembrane region of *Smith's* TNF receptor is deleted, resulting in an "extracellular region of an insoluble TNF receptor" as claimed. **Ex. 1004**, ¶45. Simple logic would also dictate such a structure because the extracellular domain binds to TNF, so one would be motivated to eliminate interference from other domains that are not directly involved in TNF binding by deleting domains, such as the transmembrane regions, which anchor the receptor in the cell. **Ex. 1004**, ¶45.

The third element of claim 1 requires **"wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel."** *Smith* discloses, "[t]he

mature full-length human TNF-R is a glycoprotein having a molecular weight of about 80 kilodaltons (kDa)" (**Ex. 1003**, 3:47-49), and "[t]he native human TNF-R molecules are recovered from cell lysates as glycoproteins having an apparent molecular weight by SDS-PAGE of about 80 kilodaltons (kDa)." **Ex. 1003**, 7:14-18. *Smith* further discloses that "FIGS. 2A-2B depict the partial cDNA sequence and derived amino acid sequence of the human TNF-R ...The N-terminal leucine of the mature TNF-R protein is underlined at position 1. The predicted transmembrane region from amino acids 236 to 265 is also underlined. The C-termini of various soluble TNF-Rs are marked with an arrow (↑)." **Ex. 1003,** 3:16-25. *Smith* also states that "[a] particularly preferred soluble TNF-R construct is TNF-RΔ235 (the sequence of amino-acids 1-235 of FIG. 2A), which comprises the entire extracellular region of TNF-R." **Ex. 1003,** 9:25-28; **Ex. 1004**, ¶46.

Thus *Smith* had underlined the "predicted transmembrane region from amino acids 236 to 265" (**Ex. 1003, 3:23-24)** and identified the entire extracellular region from amino acids 1-235. **Ex. 1003,** 4:12-21. In Prof. Greene's opinion, amino acids 1-235 of *Smith*'s FIG. 2A disclose polynucleotides encoding the extracellular (i.e., "soluble") region of an "insoluble human TNF receptor." So *Smith's* mature full-length human TNF-R "of about 80 kDa" reflects the same polynucleotide sequence as that encoding the "insoluble human TNF receptor ha[ving] an apparent molecular weight of the expressed proteins of about 75 kilodaltons as determined

on a non-reducing SDS-polyacrylamide gel," recited in claim 1. The difference in apparent molecular weights (80 kDa vs. 75 kDa) is probably due to the inherent imprecision of gel electrophoresis and/or differences in host cells used to express the proteins . Based on the nucleic acid and amino acid sequences shown in *Smith* FIG. 2A, it is apparent that *Smith's* TNF-R meets the claim element "an insoluble human TNF-R having an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel." **Ex. 1004**, ¶47.

The fourth element of claim 1 requires **"and comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10)."** (The '522 patent also gives SEQ. ID NO:10 in the equivalent three-letter code: "Leu Pro Ala Gln Val Ala Phe Xaa Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys.") **Ex. 1001**, 33:37-40. *Smith's* FIGS. 2A-2B "depict the partial cDNA sequence and derived amino acid sequence of the human TNF-R clone 1." **Ex. 1003**, 3:16-20. SEQ ID NO:10 can be seen within FIG. 2A of *Smith* at amino acids 1-18. The "Xaa" position in SEQ. ID NO: 10 is occupied by "Thr" (threonine) in Fig. 2A of *Smith*, at amino acid 8. The IUPAC definition for "Xaa" is any amino acid in that position. **Ex. 1010**. Therefore amino acid sequence 1-18 of Fig. 2A of *Smith* contains SEQ. ID NO:10. **Ex. 1004**, ¶48.

The fifth element of claim 1 requires **"all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first**

domain of said constant region." *Seed* teaches, "[p]referred immunoglobulin-like molecules which contain CD4, or fragments thereof, contain the constant region of an IgM, IgG1 or IgG3 antibody which binds complement at the Fc region." **Ex. 1006**, p7, 27-28. *Capon* teaches, "[s]uitable immunoglobulin combining sites and fusion partners are obtained from IgG-1, -2. -3, or -4 subtypes, IgA. IgE, IgD or IgM, but preferably IgG-1." **Ex. 1002**, 14:65-67. Thus *Seed* and *Capon* would have motivated a POSITA to select an IgG heavy chain. **Ex. 1004**, ¶49.

Seed teaches CD4 linked to IgG1 "upstream of the hinge region." (**Ex. 1006**, 14:6-9), which is encompassed by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," recited in claim 1. An example of this structure is a "CD4 linked to human IgG1 at the Esp site upstream of the hinge region (fusion protein CD4Eγ1) … depicted in Table 2." **Ex. 1006**, 14:6-9; **Ex. 1004**. ¶50.

Capon teaches that, "[o]rdinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof…Typically, such fusions retain at least functionally active hinge, CH2 and CH3 of the constant region of an immunoglobulin heavy chain." **Ex. 1002**, 10:1-12. Thus a POSITA would have known that chimeras containing a ligand binding partner (e.g., a receptor) fused with the N-terminus of an immunoglobulin "typically" use the Fc region (i.e., -hinge-CH2-CH3), which

structure is embraced by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," recited in claim 1. **Ex. 1004**, ¶51.

Capon's examples suggest that receptor-Fc fusions are indeed typical. Example 5 describes modifying a plasmid that had contained CH1: "The CD4-Ig plasmid is that described in *Capon* et al. supra, modified by the deletion of the coding region for the C_{H1} domain and a portion of the hinge region up to the first cysteine residue." **Ex. 1002,** 44:63-66. Other Fc fusions are in Example 4:

> The three truncated MLHR-IgG chimeras…are also shown in FIG. 8. These truncated proteins are all joined to a human heavy chain gamma 1 region <u>just upstream of the hinge domain (H)</u> such that these chimeras contain the two cysteine residues (C) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions…Junctional sites between the LHR and human IgG sequences was chosen such that the joining of the molecules near the hinge region resulted in chimeric molecules that were efficiently synthesized and dimerized in the absence of any light chain production. **Ex. 1002**, 40:38-59 (emphasis added).

Prof. Greene attests that the MLHR sequences above "joined to a human heavy chain gamma 1 region just upstream of the hinge domain" are each fused to a "constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region." Thus Example 4 and Figure 8 of *Capon* teach

hybrids containing a ligand binding partner in place of the variable region(s) of an IgG, and are embraced by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," claim 1. **Ex. 1004**, ¶52.

Prof. Greene further testifies that the only significant difference between the polynucleotide constructs used in the methods recited in claim 1 of the '522 patent, in *Seed's* second genetic construct pCD4Eγ1, and in *Capon's* Example 4 is the identity of the ligand-binding receptor region encoded by the polynucleotide. Both the *Seed* and *Capon* methods are used to express chimeras containing receptors much like *Smith's* soluble TNF receptor. Nothing in *Seed* or *Capon* discourages a POSITA from selecting the TNF receptor of *Smith*, and nothing in *Smith* discourages one from using *Seed* or *Capon's* methods for expressing TNF-R. This shows that neither *Seed*, nor *Capon* nor *Smith* teach away from the claimed fifth element of claim 1. **Ex. 1004**, ¶53.

Seed's plasmid pCD4Eγ1 and *Capon's* Examples 4 and 5 provide strong motivations to select the receptor-Fc construct as claimed. Primarily it is that these methods work consistently: first demonstrated by *Seed*, then again by *Capon* in Example 5 (once), and Example 4 (three times) where the chimeric molecules were "efficiently synthesized" and secreted "in the absence of any light chain production." **Ex. 1002**, 40:50-55; **Ex. 1004**, ¶54.

Another known benefit in using the *Seed* or *Capon* Fc fusion partners is that the proteins were expected to form dimers. **Ex. 1006**, 13:38-44; **Ex. 1002**, 40:43-48. *Smith* taught the importance of "bivalent" (*i.e.* dimeric) structures to enhance TNF binding affinity: "…the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand." **Ex. 1003**, 10:61-66. In Prof. Greene's opinion, a POSITA would have expected to enhance TNF binding affinity using *Seed* or *Capon's* Fc constructs because they both provide hybrid proteins having the receptor displayed bivalently. The POSITA would have also been motivated to make Fc fusions because *Capon* taught that they improve the circulating plasma half-life of ligand binding molecules, normally a desirable property of pharmaceuticals.[2] **Ex. 1002**, 1:10-11; **Ex. 1004**, ¶55.

The POSITA would have been motivated to create chimeras containing *Smith*'s TNF receptor fused to *Seed* or *Capon*'s Fc regions because each was expected to express the protein from host cells, to dimerize, resulting in a product

[2] The effect on half-life of Fc regions was explained in an earlier paper by *Capon et al.*, "We chose the IgG1 subtype to supply the Fc domain because IgG1 is the best compromise between Fc binding, C1q binding, and long half-life." **Ex. 1040**, p.4, col. 1; **Ex. 1004**, ¶56.

with enhanced TNF binding affinity compared to the soluble TNF receptor of *Smith,* and because the Fc region provides long serum half-life. **Ex. 1004**, ¶57.

The sixth element of claim 1 requires **"purifying an expression product of the polynucleotide from the cell mass or the culture medium."** *Seed* teaches that Fc regions facilitate purification of the expressed proteins: "The fusion proteins and immunoglobulin-like molecules of the invention may be isolated and purified in accordance with conventional conditions, such as extraction, precipitation,… For example, the IgG1 fusion proteins may be purified by passing a solution through a column which contains immobilized protein A or protein G which selectively binds the Fc portion of the fusion protein." **Ex. 1006**, 8:50-57. *Capon* likewise discloses, "[t]he novel polypeptide is recovered and purified from recombinant cell cultures by known methods, including...immunoaffinity chromatography….Other known purification methods within the scope of this invention utilize…complement domains. Moreover, reverse-phase HPLC and chromatography using ligands for the hybrid immunoglobulin are useful for the purification of the hybrid." **Ex. 1002**, 30:26-37; **Ex. 1004**, ¶58. *Smith* also teaches that hybrid IgG fusion proteins can be purified from cell cultures expressing the recombinant DNA ("reversed-phase high performance liquid chromatography (RP-HPLC) steps…can be employed to further purify a TNF-R composition.") **Ex. 1003**, 16:16-20; **Ex. 1004**, ¶58.

Purification methods mentioned in the ‘522 patent were standard (“the general methods of the state of the art used for the purification of proteins, especially of membrane proteins, such as, for example, ion exchange chromatography, gel filtration, affinity chromatography, HPLC and SDS-PAGE can be used.” **Ex. 1001**, 7:13-17). Thus *Seed*, *Smith*, *Capon* and the ‘522 patent all teach similar methods for “purifying an expression product of the polynucleotide from the cell mass or the culture medium” as claimed. **Ex. 1004**, ¶59. In short, there is nothing novel or surprising about the purification methods in claim 1 of the ‘522 patent. **Ex. 1004**, ¶59.

In sum, a POSITA would have been motivated to: culture a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of the extracellular region of an insoluble human TNF receptor having an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel, that comprises the amino acid sequence SEQ ID No:10, and which contains all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region; and then purify the expression product of the polynucleotide from the cell mass or the culture medium. **Ex. 1004**, ¶60. Thus, claim 1 would have been obvious over *Seed* in view of *Smith* and *Capon*.

Claim 2: The method of claim 1, wherein the host cell is a CHO cell.

Claim 2 depends on claim 1 and incorporates all its limitations. Claim 2 further requires, **"wherein the host cell is a CHO cell."** *Seed* discloses CHO cells suitable for expression of hybrids containing an IgG heavy chain: "Preferred hosts for fusion protein production are mammalian cells, grown in vitro in tissue culture or in vivo in animals. Mammalian cells provide post translational modification to immunoglobulin protein molecules which provide for correct folding and glycosylation of appropriate sites. Mammalian cells which may be useful as hosts include cells of fibroblast origins such as VERO or CHO-K1 or cells of lymphoid origin." **Ex. 1006**, 7:29-35. *Capon* discloses CHO cells suitable for expression of hybrids containing an IgG heavy chain, "[t]wo examples [of mammalian host cells] are CHO DHFR-cells and mouse LTK cells." **Ex. 1002**, 29:1-2. **Ex. 1004**, ¶61.

Smith also discloses CHO cells as mammalian host cells for expression of recombinant DNA constructs expressing TNF-R and IgG heavy chain polynucleotides. **Ex. 1003**, 10:57-64; 15:46-48. Because *Seed*, *Capon* and *Smith* teach the use of CHO cells to express similar fusions, a POSITA would have been motivated to use CHO cells to express the product of the DNA recited in claim 1. **Ex. 1004**, ¶62. Thus, claim 2 was obvious over *Seed* in view of *Smith* and *Capon*.

Claim 3: The method of claim 1, wherein the IgG heavy chain is an IgG_1 heavy chain.

Claim 3 depends on claim 1 and incorporates all of its limitations. Claim 3 further requires **"wherein the IgG heavy chain is an IgG_1 heavy chain."** *Seed*

teaches, "the IgG1 fusion proteins may be purified by passing a solution through a column which contains immobilized protein A or protein G which selectively binds the Fc portion of the fusion protein." **Ex. 1006**, 8:54-57. *Capon* specifically teaches IgG_1 as a preferred embodiment saying, "[s]uitable immunoglobulin combining sites and fusion partners are obtained from IgG-1. -2. -3, or -4 subtypes, IgA, IgE, IgD or IgM, but preferably IgG-1." **Ex. 1002**, 14:65-67. Thus subtype IgG-1 (also known as IgG1 and IgG_1) is *Capon's* preferred fusion partner for ligand binding proteins. The POSITA would have selected IgG_1 because *Seed* and *Capon* described this subtype as the principal method. In sum, a POSITA would have been motivated to select the IgG_1 heavy chain of *Capon* in the method of claim 3. **Ex. 1004**, ¶¶63-64. Thus, Claim 3 would have been obvious over *Seed* in view of *Smith* and *Capon*.

Claim 4: A polynucleotide encoding a protein consisting of: (a) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor (i) has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and (ii) comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and (b) all of the domains of the constant region of a human IgG_1 immunoglobulin heavy chain other than the first domain of said constant region.

The first element of claim 4 requires **"[a] polynucleotide encoding a protein consisting of: (i) the extracellular region of an insoluble human TNF receptor."** *Smith* teaches, "[t]he mature full-length human TNF-R is a glycoprotein having a molecular weight of about 80 kilodaltons (kDa)." **Ex. 1003**,

3:47-49. *Smith* further discloses a polynucleotide encoding the extracellular region of the insoluble TNF receptor: "Subunits of TNF-R may be constructed by deleting terminal or internal residues or sequences. Particularly preferred sequences include those in which the transmembrane region and intracellular domain of TNF-R are deleted or substituted with hydrophilic residues to facilitate secretion of the receptor into the cell culture medium. The resulting protein is referred to as a soluble TNF-R molecule which retains its ability to bind TNF." **Ex.1003**, 9:17-24; **Ex. 1004**, ¶65-66.

Seed teaches, "The invention relates to a gene comprising a DNA sequence which encodes a fusion protein comprising 1) CD4, or a fragment thereof which binds to HIV gp120." **Ex. 1006**, 4:47-50. Also, "The CD4 protein consists of a 370 amino acid *extracellular region* containing four immunoglobulin-like domains,…" **Ex. 1006**, 1:64-67 (emphasis added); **Ex. 1004**, ¶67.

Capon teaches, "[c]onstruction of suitable vectors containing the desired coding and control sequences employ standard ligation techniques. Isolated plasmids or DNA fragments…form the plasmids required." **Ex. 1002**, 29:49-53. Also, "[o]rdinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof…The transmembrane regions…are preferably inactivated or deleted prior to fusion." **Ex. 1002**, 10:1-9. *Capon* also discloses,

> "Inactivation of the transmembrane domain of the LHR and any other binding partner where one is present, typically by deletion or substitution of transmembrane domain hydroxylation residues, will facilitate recovery and formulation by reducing its cellular or membrane lipid affinity and improving its aqueous solubility."
> **Ex. 1002,** 20:11-17 (emphasis added)

So *Capon* prefers deleting the transmembrane region of insoluble receptors "where one is present," while *Smith* teaches that deleting the transmembrane region applies to TNF-R: "Particularly preferred sequences include those in which the transmembrane region and intracellular domain of TNF-R are deleted." **Ex. 1003**, 9:17-24. So, the POSITA understood that deleting the transmembrane region of *Smith*'s TNF-R would create an extracellular region compatible with the expression methods of *Seed* and *Capon* that specifically employ inactivation or deletion of transmembrane regions. Thus, the combined teachings of *Seed*, *Capon* and *Smith* would have motivated one to create a polynucleotide encoding a protein in which the transmembrane region of *Smith*'s TNF receptor is deleted, resulting in an "extracellular region of an insoluble TNF receptor" as claimed. Simple logic would also dictate such a structure because the extracellular domain binds to TNF, so one would be motivated to eliminate interference from other domains that are not directly involved in TNF binding by deleting domains, such as the transmembrane regions, which anchor the receptor in the cell. **Ex. 1004**, ¶68.

The second element of claim 4 requires **"wherein the insoluble human TNF receptor (i) has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel."** *Smith* discloses, "[t]he mature full-length human TNF-R is a glycoprotein having a molecular weight of about 80 kilodaltons (kDa)" (**Ex. 1003,** 3:47-49), and "[t]he native human TNF-R molecules are recovered from cell lysates as glycoproteins having an apparent molecular weight by SDS-PAGE of about 80 kilodaltons (kDa)." **Ex. 1003**, 7:14-18. *Smith* further discloses that "FIGS. 2A-2B depict the partial cDNA sequence and derived amino acid sequence of the human TNF-R ...The N-terminal leucine of the mature TNF-R protein is underlined at position 1. The predicted transmembrane region from amino acids 236 to 265 is also underlined. The C-termini of various soluble TNF-Rs are marked with an arrow (↑)." **Ex. 1003,** 3:16-26. *Smith* also states that "[a] particularly preferred soluble TNF-R construct is TNF-RΔ235 (the sequence of amino-acids 1-235 of FIG. 2A), which comprises the entire extracellular region of TNF-R." **Ex. 1003**, 9:25-28; **Ex. 1004**, ¶69.

Thus *Smith* had underlined the "predicted transmembrane region from amino acids 236 to 265" and identified the entire extracellular region as amino acids 1-235. **Ex. 1003**, 4:12-21. In Prof. Greene's opinion, amino acids 1-235 of *Smith*'s FIG. 2A disclose polynucleotides encoding the extracellular (*i.e.,* "soluble") region of an "insoluble human TNF receptor." **Ex. 1003**, 4:12-21; **Ex. 1004**, ¶70. So

Smith's mature full-length human TNF-R "of about 80 kDa" (Ex. 1003 3:47-49) reflects the same polynucleotide sequence as that encoding the "insoluble human TNF receptor ha[ving] an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel," recited in claim 4 of the '522 patent. The difference in apparent molecular weights of the proteins (80 kDa vs. 75 kDa) is probably due to the inherent imprecision of gel electrophoresis and/or differences in host cells used to express the proteins. Based on the nucleic acid and amino acid sequences shown in *Smith* FIG. 2A, it is apparent that *Smith's* TNF-R meets the claim element "an insoluble human TNF-R having an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel." **Ex. 1004**, ¶70.

The third element of claim 4 further defines the insoluble human TNF receptor as one which also **"comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10)."** (The '522 patent also gives SEQ. ID NO:10 in the equivalent three-letter code: "Leu Pro Ala Gln Val Ala Phe Xaa Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys.") **Ex. 1001**, 33:37-40. *Smith's* FIGS. 2A-2B "depict the partial cDNA sequence and derived amino acid sequence of the human TNF-R clone 1." **Ex. 1003**, 3:16-18. SEQ ID NO:10 can be seen within FIG. 2A of *Smith* at amino acids 1-18. The "Xaa" of SEQ. ID NO:10 stands for any amino acid, in this case for the "Thr" (threonine) of the sequence of FIG.

2A of Smith. Therefore amino acids1-18 of Fig. 2A of *Smith* is identical to SEQ. ID NO:10 of the '522 patent. **Ex. 1004**, ¶71.

The fourth element of claim 4 requires **"all of the domains of the constant region of a human IgG_1 immunoglobulin heavy chain other than the first domain of said constant region."** *Seed* teaches, "Preferred immunoglobulin-like molecules which contain CD4, or fragments thereof, contain the constant region of an IgM, IgG1 or IgG3 antibody which binds complement at the Fc region." **Ex. 1006**, 9:7-10. *Capon* specifically teaches, IgG_1 as a preferred embodiment saying, "[s]uitable immunoglobulin combining sites and fusion partners are obtained from IgG-1, -2. -3, or -4 subtypes, IgA. IgE, IgD or IgM, but preferably IgG-1." **Ex. 1002**, 14:65-67. Thus *Seed* and *Capon* would have motivated a POSITA to select an IgG1 heavy chain because both described this subtype as the principal method. **Ex. 1004**, ¶72.

Seed teaches CD4 linked to IgG1 "upstream of the hinge region." (**Ex. 1006**, 14:6-9), which is encompassed by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," recited in claim 4. An example of this structure is a "CD4 linked to human IgG1 at the Esp site upstream of the hinge region (fusion protein CD4Eγ1) … depicted in Table 2." **Ex. 1006**, 14:6-9; **Ex. 1004**, ¶73.

Capon teaches that, "[o]rdinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof…Typically, such fusions retain at least functionally active hinge, CH2 and CH3 of the constant region of an immunoglobulin heavy chain." **Ex. 1002**, 10:1-12. Thus a POSITA would have known that chimeras containing a ligand binding partner (e.g., a receptor) fused with the N-terminus of an immunoglobulin "typically" use the Fc region (i.e., -hinge-CH2-CH3), which structure is embraced by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," recited in claim 4. **Ex. 1004**, ¶74.

Capon's examples suggest that receptor-Fc fusions are indeed typical. Example 5 describes modifying a plasmid that had contained CH1: "The CD4-Ig plasmid is that described in *Capon* et al. supra, modified by the deletion of the coding region for the C_{H1} domain and a portion of the hinge region up to the first cysteine residue." (**Ex. 1002**, 44:63-66) Other Fc fusions are in Example 4:

> The three truncated MLHR-IgG chimeras…are also shown in FIG. 8. These truncated proteins are all joined to a human heavy chain gamma 1 region <u>just upstream of the hinge domain (H)</u> such that these chimeras contain the two cysteine residues (C) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions…Junctional sites between the LHR and human IgG sequences was chosen such that the joining of the molecules near

> the hinge region resulted in chimeric molecules that were efficiently synthesized and dimerized in the absence of any light chain production. **Ex. 1002**, 40:38-55 (emphasis added).

Prof. Greene attests that the MLHR sequences above "joined to a human heavy chain gamma 1 region just upstream of the hinge domain" are each fused to a "constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region." Thus Example 4 and Figure 8 of *Capon* teach hybrids containing a ligand binding partner in place of the variable region(s) of an IgG, and are embraced by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," claim 4. **Ex. 1004**, ¶75.

Prof. Greene further testifies that the only significant difference between the polynucleotide constructs recited in claim 4 of the '522 patent, in *Seed*'s second genetic construct pCD4Eγ1, and in *Capon's* Example 4 is the identity of the ligand-binding receptor region encoded by the polynucleotide. Both the *Seed* and *Capon* methods are used to express chimeras containing receptors much like *Smith's* soluble TNF receptor. Nothing in *Seed* or *Capon* discourages a POSITA from selecting the TNF receptor of *Smith*, and nothing in *Smith* discourages one from using *Seed* or *Capon's* methods for expressing TNF-R. This shows that neither Seed, nor Capon nor Smith teach away from the claimed fourth element of claim 4. **Ex. 1004**, ¶76.

Seed's plasmid pCD4Eγ1 and *Capon's* Examples 4 and 5 provide strong motivations to select the receptor-Fc construct as claimed. Primarily it is that these methods work consistently: first demonstrated by *Seed*, then again by *Capon* in Example 5 (once), and Example 4 (three times) where the chimeric molecules were "efficiently synthesized" and secreted "in the absence of any light chain production." **Ex. 1002**, 40:50-55; **Ex. 1004**, ¶77.

Another known benefit in using the *Seed* or *Capon* Fc fusion partners is that the proteins were expected to form dimers. **Ex. 1006**, 13:38-44; **Ex. 1002**, 40:43-48. *Smith* taught the importance of "bivalent" (*i.e*. dimeric) structures to enhance TNF binding affinity: "…the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand." **Ex. 1003**, 10: 61-66. In Prof. Greene's opinion, a POSITA would have expected to enhance TNF binding affinity using *Seed* or *Capon's* Fc constructs because they both provide hybrid proteins having the receptor displayed bivalently. The POSITA would have also been motivated to make Fc fusions because *Capon* taught that they improve the circulating plasma half-life of ligand binding molecules, normally a desirable property of pharmaceuticals. **Ex. 1002**, 1:10-11; **Ex. 1004**, ¶¶78-79.

The POSITA would have been motivated to create chimeras containing *Smith*'s TNF receptor fused to *Seed* or *Capon*'s Fc regions because each was

expected to efficiently express the protein from host cells, to dimerize, giving a product with enhanced TNF binding affinity compared to the soluble TNF receptor of *Smith,* and because the Fc region provides long serum half-life. **Ex. 1004**, ¶80.

In sum, when the claim 4 invention was filed, a POSITA would have been motivated to construct a polynucleotide encoding the extracellular region of an insoluble human TNF receptor, wherein the human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel, including the amino acid sequence disclosed in SEQ ID No. 10, and all the domains of the constant region of a human IgG_1 immunoglobulin heavy chain other than the first domain of said constant region. **Ex. 1004**, ¶81. Thus, the polynucleotide of claim 4 was obvious over *Seed*, *Smith* and *Capon*.

Claim 5: A vector comprising the polynucleotide of claim 4.

Claim 5 depends on claim 4 and incorporates all of its limitations, including IgG_1. Claim 5 further requires, **"a vector comprising the polynucleotide of claim 4."** *Seed* discloses, "[t]he invention also relates to vectors containing the gene of the invention and hosts transformed with the vectors." **Ex. 1006**, 4:54-55. Also, "a method of producing a fusion protein which comprises: cultivating…a host strain transformed with the vector containing the gene of the invention, said vector further comprising expression signals which are recognized by said host strain and direct express of said fusion protein." **Ex. 1006**, 4:56-67. Example 6 of *Seed* shows

the stable expression of fusion construct pCD4Eγ1 in baby hamster kidney cells, i.e., an IgG1 in a mammalian host cell. *Capon* discloses, "Construction of suitable vectors containing the desired coding and control sequences employ standard ligation techniques." **Ex. 1002**, 29:49-51. *Smith* discloses, "A preferred eukaryotic vector for expression of TNF-R DNA is disclosed below in Example 2." **Ex. 1003**, 15:53-54. *Smith* also teaches that "Such compositions, however, are obtainable in practical yields only by cloning and expressing genes encoding the receptors using recombinant DNA technology." **Ex. 1003**, 2:22-25. *Seed, Capon* and *Smith* all show that a POSITA would have been motivated to make and express vectors comprising the polynucleotides recited in claim 4, as a way to obtain TNF-R hybrids in practical yield. **Ex. 1004**, ¶82. Thus, the vector of claim 5 was obvious over *Capon* in view of *Smith* and *Capon.*

Claim 6: A mammalian host cell comprising the polynucleotide of claim 4.

Claim 6 depends on claim 4 and incorporates all of its limitations, including IgG_1. Claim 6 further requires, **"[a] mammalian host cell comprising the polynucleotide of claim 4."** *Seed*, *Capon* and *Smith* each disclose mammalian host cells transformed with vectors to insert polynucleotides. *Seed* discloses, "For mammalian hosts, several possible vector systems are available for expression. One class of vectors utilize DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus,

baculovirus, retroviruses (RSV, MMTV or MOMLV), or SV40 virus. Cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow selection of transfected host cells." **Ex. 1006**, 8:5-13. Example 6 of *Seed* shows the stable expression of fusion construct pCD4Eγ1 in baby hamster kidney cells, i.e., an IgG1 in a mammalian host cell. *Capon* discloses mammalian host cells which are suitable for expression of hybrids containing an IgG heavy chain, "[s]uitable eukaryotic host cells for expressing the hybrid immunoglobulin include…chinese hamster ovary cells-DHFR…human cervical carcinoma cells (HELA ATCC CCL 2)." **Ex. 1002**, 29:30-42. *Capon* teaches, "Suitable immunoglobulin combining sites and fusion partners are obtained from IgG-1. -2. -3, or -4 subtypes, IgA. IgE, IgD or IgM, but preferably IgG-1." **Ex. 1002**, 14:65-68. Subtype IgG-1 (also known as IgG1 and IgG_1) is preferred by *Capon* for expressing ligand binding proteins. **Ex. 1004**, ¶83.

Smith also discloses mammalian host cells which are suitable for expression of recombinant DNA constructs expressing TNF-R and an IgG heavy chain polynucleotide, "[e]xamples of suitable mammalian host cell lines include the COS-7 lines of monkey kidney cells…and other cell lines capable of expressing an appropriate vector including, for example, L cells, C127, 3T3, Chinese hamster ovary (CHO), HeLa and BHK cell lines." **Ex. 1003**, 14:10-15. Expression of the IgG_1 subtype is described, "For example, chimeric TNF-R/IgG_1 may be produced

from two chimeric genes…Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNF-R displayed bivalently." **Ex. 1003**, 10:57-64; **Ex. 1004**, ¶84.

In sum, *Seed, Capon* and *Smith* all teach the use of mammalian host cells as expression vehicles, which are suitable for expressing polynucleotides encoding a ligand binding protein fused to the constant region of a human IgG_1 heavy chain. By virtue of their well characterized features and demonstrated efficiency in expressing exogenous polynucleotides, a POSITA would have been motivated to select mammalian cells, such as CHO, HeLa or OCS cells, embraced by claim 6. **Ex. 1004**, ¶85. Thus claim 6 was obvious over *Seed* in view of *Smith* and *Capon.*

Claim 7: A method comprising the steps of: (a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of: (i) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor comprises the amino acid sequence of SEQ ID NO:27 and (ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and (b) purifying an expression product of the polynucleotide from the cell mass or the culture medium.

The preamble of claim 7 recites a "method" comprising "the steps of," without introducing what kind of method is involved; part (a) recites culturing a host cell, and part (b) recites purifying an expression product from the cell mass or culture medium. This preamble introduces a method for expressing a protein in cell culture and then purifying the expressed protein. **Ex. 1004**, ¶86.

The first element of claim 7 requires, **"[a] method comprising the steps of: (a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein."** *Seed* discloses: "The invention is directed to a protein gene which comprises 1) a DNA sequence which codes for CD4, or fragment thereof which binds to HIV gp120, fused to 2) a DNA sequence which encodes an immunoglobulin heavy chain. Preferably, the antibody has effector function." Ex. **1006**, 5:33-39. *Seed* also discloses "A method of producing a fusion protein……characterized by cultivating in a nutrient medium under protein-producing conditions a host stain transformed with the vector…direct expression of the said fusion protein, and recovering the fusion protein so produced". **Ex. 1006**, 4:56-67 – 5:1; **Ex. 1004**, ¶87.

Capon discloses: "The fusions of this invention are made by transforming host cells with nucleic acid encoding the fusion, culturing the host cell and recovering the fusion from the culture. Also provided are vectors and nucleic acid encoding the fusion, as well as therapeutic and diagnostic compositions comprising them." **Ex. 1002**, 5:61-66. *Smith* likewise discloses culturing a host cell to express proteins, "Recombinant TNF-R DNA is expressed or amplified in a recombinant expression system comprising a substantially homogeneous monoculture of suitable host microorganisms." **Ex. 1003**, 11:60-63; **Ex. 1004**, ¶87a.

Seed, Capon and *Smith* show that culturing host cells comprising a polynucleotide that encodes a fusion protein was well known. **Ex. 1004**, ¶88.

The second element of claim 7 requires **"wherein the polynucleotide encodes a protein consisting of: (i) the extracellular region of an insoluble human TNF receptor."** *Smith* teaches, "[t]he mature full-length human TNF-R is a glycoprotein having a molecular weight of about 80 kilodaltons (kDa)." **Ex. 1003**, 3:47-49. *Smith* further discloses polynucleotides encoding the extracellular region of the insoluble TNF receptor: "Subunits of TNF-R may be constructed by deleting terminal or internal residues or sequences. Particularly preferred sequences include those in which the transmembrane region and intracellular domain of TNF-R are deleted or substituted with hydrophilic residues to facilitate secretion of the receptor into the cell culture medium. The resulting protein is referred to as a soluble TNF-R molecule which retains its ability to bind TNF." **Ex. 1003**, 9:17-24; **Ex. 1004**, ¶89.

Seed teaches, "The invention relates to a gene comprising a DNA sequence which encodes a fusion protein comprising 1) CD4, or a fragment thereof which binds to HIV gp120." **Ex. 1006**, 4:47-50. Also, "The CD4 protein consists of a 370 amino acid *extracellular region* containing four immunoglobulin-like domains,…" **Ex. 1006**, 1:64-67 (emphasis added); **Ex. 1004**, ¶90.

Capon teaches, "Construction of suitable vectors containing the desired coding and control sequences employ standard ligation techniques. Isolated plasmids or DNA fragments…form the plasmids required." **Ex. 1002**, 29:49-53. Also, "Ordinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof…The transmembrane regions…are preferably inactivated or deleted prior to fusion." **Ex. 1002**, 10:1-9. *Capon* also discloses,

> Inactivation of the transmembrane domain of the LHR and any other binding partner where one is present, typically by deletion or substitution of transmembrane domain hydroxylation residues, will facilitate recovery and formulation by reducing its cellular or membrane lipid affinity and improving its aqueous solubility. **Ex. 1002,** 20:11-17 (emphasis added).

So *Capon* prefers deleting the transmembrane region of insoluble receptors "where one is present," While *Smith* teaches that deleting the transmembrane region applies to TNF-R: "Particularly preferred sequences include those in which the transmembrane region and intracellular domain of TNF-R are deleted." **Ex. 1003**, 9:17-24. So, the POSITA would have understood that deleting the transmembrane region of *Smith*'s TNF-R would create an extracellular region compatible with the expression methods of *Seed* and *Capon* that specifically employ inactivation or deletion of transmembrane regions. Thus, the combined teachings of *Seed, Capon*

and *Smith* would have motivated one to create a polynucleotide encoding a protein in which the transmembrane region of *Smith*'s TNF receptor is deleted, resulting in an "extracellular region of an insoluble TNF receptor" as claimed. Simple logic would also dictate such a structure because the extracellular domain binds to TNF, so one would be motivated to eliminate interference from other domains that are not directly involved in TNF binding by deleting domains, such as the transmembrane regions, which anchor the receptor in the cell. **Ex. 1004**, ¶91.

The third element of claim 7 requires **"the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor comprises the amino acid sequence of SEQ ID NO:27."** SEQ. ID NO:27 of the '522 patent contains a 461 amino-acid sequence **Ex. 1001** starting at col. 39, line 23, and continuing to col. 41, lines 1-26. *Smith* discloses the identical sequence in Figs. 2A-2B from amino acid -22 through 439. **Ex. 1004**, ¶92.

In Prof. Greene's opinion, the teachings of *Seed*, *Capon* and *Smith* discussed in the second element of claim 7 ("wherein the polynucleotide encodes a protein consisting of: (i) the extracellular region of an insoluble human TNF receptor."), would have motivated a POSITA to create a polynucleotide in which the transmembrane region of *Smith*'s TNF receptor is deleted leading to the sequence disclosed in *Smith* FIGS. 2A-2B (i.e., SEQ ID NO:27), because that is the extracellular region of an insoluble human TNF receptor. **Ex. 1004**, ¶93.

The fourth element of claim 7 requires **"all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region."** *Seed* teaches, "Preferred immunoglobulin-like molecules which contain CD4, or fragments thereof, contain the constant region of an IgM, IgG1 or IgG3 antibody which binds complement at the Fc region." Ex. **1006**, 9:7-10. *Capon* teaches, "Suitable immunoglobulin combining sites and fusion partners are obtained from IgG-1, -2. -3, or -4 subtypes, IgA. IgE, IgD or IgM, but preferably IgG-1." **Ex. 1002**, 14:65-67. Thus *Seed* and *Capon* would have motivated a POSITA to select an IgG heavy chain. **Ex. 1004**, ¶94.

Seed teaches CD4 linked to IgG1 "upstream of the hinge region." (**Ex. 1006**, 14:6-9), which is encompassed by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," recited in claim 7. An example of this structure is a "CD4 linked to human IgG1 at the Esp site upstream of the hinge region (fusion protein CD4Eγ1) … depicted in Table 2." **Ex. 1006**, 14:6-9; **Ex. 1004**, ¶95.

Capon teaches that, "[o]rdinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof…Typically, such fusions retain at least functionally active hinge, CH2 and CH3 of the constant region of an immunoglobulin heavy chain." **Ex. 1002**, 10:1-12. Thus a POSITA would have known that chimeras

containing a ligand binding partner (e.g., a receptor) fused with the N-terminus of an immunoglobulin "typically" use the Fc region (i.e., -hinge-CH2-CH3), which structure is embraced by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," recited in claim 7. **Ex. 1004**, ¶96.

Capon's examples suggest that receptor-Fc fusions are indeed typical. Example 5 describes modifying a plasmid that had contained CH1: "The CD4-Ig plasmid is that described in *Capon* et al. supra, modified by the deletion of the coding region for the C_{H1} domain and a portion of the hinge region up to the first cysteine residue." **Ex. 1002,** 44:63-66. Other Fc fusions are in Example 4:

> The three truncated MLHR-IgG chimeras…are also shown in FIG. 8. These truncated proteins are all joined to a human heavy chain gamma 1 region just upstream of the hinge domain (H) such that these chimeras contain the two cysteine residues (C) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions…Junctional sites between the LHR and human IgG sequences was chosen such that the joining of the molecules near the hinge region resulted in chimeric molecules that were efficiently synthesized and dimerized in the absence of any light chain production. **Ex. 1002**, 40:38-59 (emphasis added).

Prof. Greene attests that the MLHR sequences above "joined to a human heavy chain gamma 1 region just upstream of the hinge domain" are each fused to a

"constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region." Thus Example 4 and Figure 8 of *Capon* teach hybrids containing a ligand binding partner in place of the variable region(s) of an IgG, and are embraced by the phrase "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region," claim 7. **Ex. 1004**, ¶97.

Prof. Greene further testifies that the only significant difference between the polynucleotide constructs used in the methods recited in claim 7 of the '522 patent, in *Seed*'s second genetic construct pCD4Eγ1, and in *Capon's* Example 4 is the identity of the ligand-binding receptor region encoded by the polynucleotide. Both the *Seed* and *Capon* methods are used to express chimeras containing receptors much like *Smith's* soluble TNF receptor. Nothing in *Seed* or *Capon* discourages a POSITA from selecting the TNF receptor of *Smith*, and nothing in *Smith* discourages one from using *Seed* or *Capon's* methods for expressing TNF-R. This shows that neither *Seed*, nor *Capon* nor *Smith* teach away from the claimed fourth element of claim 7. **Ex. 1004**, ¶98.

Seed's plasmid pCD4Eγ1 and *Capon's* Examples 4 and 5 provide strong motivations to select the receptor-Fc construct as claimed. Primarily it is that these methods work consistently: first demonstrated by *Seed*, then again by *Capon* in Example 5 (once), and Example 4 (three times) where the chimeric molecules were

"efficiently synthesized" and secreted "in the absence of any light chain production." **Ex. 1002**, 40:50-55; **Ex. 1004**, ¶99.

Another known benefit in using the *Seed* or *Capon* Fc fusion partners is that the proteins were expected to form dimers. **Ex. 1006**, 13:38-44; **Ex. 1002**, 40:43-48. *Smith* taught the importance of "bivalent" (*i.e*. dimeric) structures to enhance TNF binding affinity: "…the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand." **Ex. 1003**, 10: 61-66. In Prof. Greene's opinion, a POSITA would have expected to enhance TNF binding affinity using *Seed* or *Capon's* Fc constructs because they both provide hybrid proteins having the receptor displayed bivalently. The POSITA would have also been motivated to make Fc fusions because *Capon* taught that they improve the circulating plasma half-life of ligand binding molecules, normally a desirable property of pharmaceuticals. **Ex. 1002**, 1:10-11; **Ex. 1004**, ¶100.

The POSITA would have been motivated to create chimeras containing *Smith*'s TNF receptor fused to *Seed* or *Capon*'s Fc regions because each was expected to efficiently express the protein from host cells, to dimerize, resulting in a product with enhanced TNF binding affinity compared to the soluble TNF receptor of *Smith,* and because the Fc region provides long serum half-life. **Ex. 1004**, ¶102.

The fifth element of claim 7 requires **"purifying an expression product of the polynucleotide from the cell mass or the culture medium."** *Seed* teaches that Fc regions facilitate purification of the expressed proteins: "The fusion proteins and immunoglobulin-like molecules of the invention may be isolated and purified in accordance with conventional conditions, such as extraction, precipitation,... For example, the IgG1 fusion proteins may be purified by passing a solution through a column which contains immobilized protein A or protein G which selectively binds the Fc portion of the fusion protein. **Ex. 1006**, 8:50-58. *Capon* likewise discloses, "[t]he novel polypeptide is recovered and purified from recombinant cell cultures by known methods, including...immunoaffinity chromatography….Other known purification methods within the scope of this invention utilize…complement domains. Moreover, reverse-phase HPLC and chromatography using ligands for the hybrid immunoglobulin are useful for the purification of the hybrid." **Ex. 1002**, 30:26-37. *Smith* also teaches that hybrid IgG fusion proteins can be purified from recombinant cell cultures expressing polynucleotides ("reversed-phase high performance liquid chromatography (RP-HPLC) steps…can be employed to further purify a TNF-R composition.") **Ex. 1003**, 16:16-20; **Ex. 1004**, ¶103.

Purification methods mentioned in the '522 patent were standard ("the general methods of the state of the art used for the purification of proteins,

especially of membrane proteins, such as, for example, ion exchange chromatography, gel filtration, affinity chromatography, HPLC and SDS-PAGE can be used." **Ex. 1001**, 7:13-17). Thus *Seed*, *Smith*, *Capon* and the '522 patent all teach similar methods for "purifying an expression product of the polynucleotide from the cell mass or the culture medium" as claimed. In short, there is nothing novel or surprising about the purification methods in claim 7 of the '522 patent. **Ex. 1004**, ¶104.

In sum, a POSITA was motivated to: culture a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of (i) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor comprises the amino acid sequence of SEQ ID NO:27 and (ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region; then purify the expression product of the polynucleotide from the cell mass or the culture medium. **Ex. 1004**, ¶105. Thus, Claim 7 was obvious over *Seed* in view *Smith* and *Capon*.

Claim 8: The method of claim 7, wherein the human IgG immunoglobulin heavy chain is an IgG_1 heavy chain.

Claim 8 depends on claim 7 and incorporates all its limitations. Claim 8 further requires **"wherein the IgG heavy chain is an IgG_1 heavy chain."** *Seed* teaches, "the IgG1 fusion proteins may be purified…." **Ex. 1006**, 8:54-57. *Capon* specifically teaches IgG_1 as a preferred embodiment saying, "[s]uitable

immunoglobulin combining sites and fusion partners are obtained from IgG-1. -2. -3, or -4 subtypes, IgA, IgE, IgD or IgM, but preferably IgG-1." **Ex. 1002**, 14:65-68. Thus subtype IgG-1 (also known as IgG1 and IgG_1) is *Capon's* preferred fusion partner for ligand binding proteins. The POSITA would have selected IgG_1 because *Seed* and *Capon* described this subtype as the principal method. In sum, a POSITA would have been motivated to select the IgG_1 heavy chain of *Capon* in the method of claim 8. **Ex. 1004**, ¶106-107. Thus, claim 8 was obvious over *Seed* in view of *Capon* and *Smith.*

Claim 9: The method of claim 7, wherein the host cell is a CHO cell.

Claim 9 depends on claim 7 and incorporates all its limitations. Claim 9 requires, **"wherein the host cell is a CHO cell."** *Seed* discloses CHO cells suitable for expressing hybrids containing an IgG heavy chain: "Preferred hosts for fusion protein production are mammalian cells….Mammalian cells which may be useful as hosts include cells of fibroblast origins such as VERO or CHO-K1...." **Ex. 1006**, 7:29-35. *Capon* discloses CHO cells suitable for expression of hybrids containing an IgG heavy chain, "[t]wo examples [of mammalian host cells] are CHO DHFR-cells and mouse LTK cells." **Ex. 1002**, 29:1-2; **Ex. 1004**, ¶108. *Smith* also discloses CHO cells for expression of recombinant DNA containing TNF-R and an IgG heavy chain. **Ex. 1003**, 10:58-64, 15:46-48. Because *Seed*, *Capon* and *Smith* teach the use of CHO cells to express similar fusions, a POSITA would have been

motivated to use CHO cells to express the polynucleotide in claim 7. **Ex. 1004**, ¶108. Thus, claim 9 was obvious over *Seed* in view of *Smith* and *Capon.*

Claim 10: The method of claim 8, wherein the host cell is a CHO cell.

Claim 10 depends on claim 8 and incorporates all its limitations, including IgG_1. Claim 10 further requires, **"wherein the host cell is a CHO cell."** *Seed* discloses CHO cells suitable for expressing hybrids containing an IgG_1 heavy chain, as described in claim 9 above. **Ex. 1006**, 7:29-35. *Capon* discloses CHO cells suitable for expression of hybrids containing an IgG_1 heavy chain, "[t]wo examples [of mammalian host cells] are CHO DHFR-cells and mouse LTK cells." **Ex. 1002**, 29:1-2. Example 6 of *Seed* shows the stable expression of fusion construct pCD4Eγ1 in baby hamster kidney cells, i.e., an IgG_1 in a mammalian host cell. *Smith* also discloses CHO cells for expression of recombinant polynucleotides constructs containing TNF-R and an IgG heavy chain. **Ex. 1003**, 10:58-64, 15:46-48. Because *Seed*, *Capon* and *Smith* teach the use of CHO cells to express similar fusions, a POSITA would have been motivated to use CHO cells to express the DNA of claim 8. **Ex. 1004**, ¶109. Thus, claim 10 was obvious over *Seed*, *Smith* and *Capon.*

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42.6(e) CERTIFICATE OF SERVICE

I certify that this document was served or simultaneously is being served on each opposing party with the filing of this document. I certify that the following exhibits being filed along with this document, if any, have been or simultaneously are being served on each opposing party:

Exhibit Number	Description
1001	US Patent No. 8,163,522, titled "Human TNF Receptor" to Brockhaus et al.
1002	US Patent No. 5,116,964, titled "Hybrid Immunoglobulins" to Capon et al.
1003	US Patent No. 5,395,760, titled "DNA Encoding Tumor Necrosis Factor-α and –β Receptors" to Smith et al.
1004	Declaration of James J. Greene, PhD.
1005	CV of James J. Greene, PhD.
1006	US Patent No. 6,004,781 titled "Nucleic Acid Encoding Ig-CD4 Fusion Proteins" to Seed et al.
1007-1009	Unassigned.
1010	"Amino Acid Abbreviations (IUPAC)", Molecular Biology Review.
1011-1018	Unassigned.
1019	Non Final Rejection of 06/08/2010 for Application No. 08/444,791.
1020	Amendment and Request for Reconsideration of 09/08/2010 in Response to Non Final Office Action for Application No. 08/444,791.
1021	Unassigned.
1022	Amendment and Request for Reconsideration of 03/15/2011 in Response to Non Final Office Action for Application No. 08/444,791.
1023	Final Rejection of 06/24/2011 for Application No. 08/444,791.
1024	Amendment and Response of 11/23/2011 for Application No. 08/444,791.
1025	Unassigned.
1026	Notice of Allowance and Fee(s) Due of 02/15/2012 for Application No. 08/444,791.

1027	Swiss Application No. 3319/89 filed on 09/12/1989.
1028	Certified English translation of Swiss Application No. 3319/89 filed on 09/12/1989.
1029	Swiss Application No. 746/90 filed on 03/08/1990.
1030	Certified English translation of Swiss Application No. 746/90 filed on 03/08/1990.
1031	Swiss Application No. 1347/90 filed on 04/20/1990.
1032	Certified English Translation of Swiss Application No. 1347/90 filed on 04/20/1990.
1033	European Patent No. 0417563 filed on 08/31/1990.
1034	Certified English Translation of European Patent No. 0417563 filed on 08/31/1990.
1035-1036	Unassigned.
1037	Urlaub et al., "Isolation of Chinese hamster cell mutants deficient in dihydrofolate reductase activity", 07/1980, Proc. Natl. Acad. Set USA, Vol. 77, No. 7, pp. 4216-4220.
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1039	Smith et al., "The Active Form of Tumor Necrosis Factor is a Trimer*", 05/25/1987, The Journal of Biological Chemistry,Vol. 262, No. 15, pp 6951-6954.
1040	Capon et al., "Designing CD4 immunoadhesins for AIDS therapy", 02/9/1989, Nature Vol. 337.
1041	Traunecker et al., "Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules", 05/04/1989, Nature, Vol. 339.
1042	Patil et al., "TNF-α: A Potential Therapeutic Target for Inflammatory Bowel Disease", 2011, Asian Journal of Pharmaceutical and Clinical Research, Vol. 4, Suppl 1.
1043	Unassigned.
1044	Levinson, "Gene Expression Technology", 1990, Methods in Enzymology Volume 185.
1045	Watson et al., "A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules", June 1990, The Journal of Cell Biology, Vol. 110.

42.6(e)(4) (iii)(A) The date and manner of service:

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