UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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PALETTE LIFE SCIENCES, INC.,
Petitioner,

v.

INCEPT, LLC,
Patent Owner.

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Case IPR2020-00003
Patent No. 8,257,723

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**PETITION FOR *INTER PARTES* REVIEW**

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| 1009 | U.S. Provisional Application No.: 60/444,143, W.R. Noyes (filed: January 31, 2003) |
| 1010 | U.S. Patent No.: 6,624,245, D.G. Wallace et al., Issued: September 23, 2003 |
| 1011 | PCT Publication No.: WO 94/25080, L. Griffith-Cima et al. (published: November 10, 1994) |
| 1012 | A.B.S. Ball et al., "Silicone implant to prevent visceral damage during adjuvant radiotherapy for retroperitoneal sarcoma," *British Journal of Radiology* 63:346-348 (May 1990) |
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| 1060 | U.S. Patent No.: 6,723,709, D. Pressato et al., Issued: April 20, 2004 |
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# I. INTRODUCTION

Petitioner Palette Life Sciences, Inc. ("Palette") seeks *inter partes* review of claims 1-24 of U.S. Patent No. 8,257,723 ("the '723 patent," EX1001). 37 U.S.C. ch. 31. This petition shows a reasonable likelihood that the challenged claims are unpatentable.

# II. MANDATORY NOTICES

## A. Real Parties-In-Interest

The real parties-in-interest are Palette Life Sciences, Inc. and Pharmanest AB. Moreover, in an acquisition that closed on October 2, 2019, Nestlé S.A. sold Galderma S.A., Galderma Laboratories, Inc., Galderma Laboratories LP, Galderma Research & Development SNC, Nestlé Skin Health, Inc. (now SHDS, Inc.), and Nestlé Skin Health S.A. to an investment consortium of EQT Partners AB, Public Sector Pension Investment Board (PSP Investments), and Luxinva, a wholly owned subsidiary of Abu Dhabi Investment Authority. Galderma S.A., Galderma Laboratories, Inc., Galderma Laboratories LP, Galderma Research & Development SNC, Nestlé Skin Health, Inc., Nestlé Skin Health S.A., Nestlé S.A., EQT Partners AB, Public Sector Pension Investment Board (PSP Investments), Luxinva, and Abu Dhabi Investment Authority are identified as possible real-parties-in-interest.

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### B. Related Matters

A second petition for *inter partes* review of the ’723 patent is concurrently being filed, IPR2020-00002. In addition, two petitions for *inter partes* review, IPR2020-00004 and IPR2020-00005, are being filed concurrently against a related patent, U.S. Patent No. 7,744,913 (“the ’913 patent,” EX1002). The ’723 patent is a continuation of the ’913 patent.

## C. Identification of Counsel and Service Information

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## III. CERTIFICATIONS

Palette certifies the '723 patent is available for IPR, and that it is not barred or estopped from requesting IPR on these grounds.

## IV. IDENTIFICATION OF CHALLENGE; STATEMENT OF PRECISE RELIEF REQUESTED

Palette seeks cancellation of the challenged claims for the reasons stated below, supported with exhibits, including the Declaration of Dr. Adam Dicker (EX1003). The claims are unpatentable under pre-AIA 35 U.S.C. on these grounds:

| Ground | Claims | Basis |
|---|---|---|
| 1 | 1, 14-15, 23 | Anticipated under §102(b) over U.S. Patent No. 6,206,930 ("Burg," EX1041) |
| 2 | 1-7, 11, 14-18, 20, and 22-24 | Obvious under §103(a) over Burg |
| 3 | 8-10, 12, 19, 21 | Obvious under §103(a) over the combination of Burg and U.S. Patent No. 6,375,634 ("Carroll," EX1013) |
| 4 | 13 | Obvious under §103(a) over the combination of Burg and International Patent Application Publication No. WO94/25080 ("Griffith-Cima," EX1011) |

## V. STATEMENT OF REASONS FOR RELIEF REQUESTED

### A. Summary of Argument

The '723 patent broadly claims a method for delivering a therapeutic dose of radiation to a patient. At its core, the claimed invention aims to protect healthy tissues and organs from unsafe levels of exposure to radiation—a fundamental tenet that has been recognized by those in the art since the inception of radiation therapy. The '723 patent claims a means for accomplishing this aim through the injection of a biocompatible, biodegradable gel into a patient. The gel acts as a "filler," filling a space within the patient such that an organ is displaced from a

nearby tissue intended to be irradiated, allowing the organ to receive less of a radiation dose than what would have been received absent the gel. The gel is then left in place, and removed from the body through biodegradation.

Prior to the claimed invention, the use of filler devices to displace organs prior to subjecting a patient to radiation therapy had been well-known in the art. Moreover, the use of biocompatible, biodegradable gel materials for various medical treatments was common, and the benefits of using gels removed by biodegradation within the body was thoroughly appreciated. Indeed, the art had already recognized that such gels would be an appropriate and successful tool for organ displacement during radiation therapy. As this petition demonstrates, the claimed invention is nothing more than a predictable use of common, well-established materials for an already-recognized, beneficial purpose.

### B. The '723 Patent

#### 1.Background

The '723 patent is entitled "Fillers and Methods for Displacing Tissues to Improve Radiological Outcomes." EX1001, title. The patent aims "to provide a protocol to decrease the radiation dose to the rectum during radiotherapy for prostate cancer," while also "decreas[ing] radiation treatment-induced side effects on sensitive organs resulting from other therapies and applications directed to a target organ." *Id.*, 1:47-51. The patent discloses the use of a "filler" that is placed

between the radiation target tissue and other tissues to increase the distance between the tissues "so that the other tissues receive less radiation." *Id.*, 2:28-31. The filler may take many forms. It may be "a degradable material that is installed once prior to the course of radiation treatment." *Id.*, 2:32-35. It may also be an "inflatable device[] that [is] introduced" into the patient's body. *Id.*, 2:37-42. The '723 patent further discloses that many known materials may form the filler, which may, when introduced into the patient, form a gel. *See, e.g.*, *id.*, 6:26-33, 7:49-53. The '723 patent specifically describes the injection of human collagen into the space (*i.e.*, Denonvilliers' space) between the rectum and the prostate, such that the rectum is displaced during radiation treatment of the prostate. *See id.*, 11:36-42.

**2.Challenged Claims**

The '723 patent includes 24 claims. Claim 1 is independent, and claims 2-24 depend from claim 1. Claim 1 reads (formatting added):

> 1. A method of delivering a therapeutic dose of radiation to a patient comprising
>
> introducing a biocompatible, biodegradable filler between an organ and a nearby tissue to increase a distance between the organ and the tissue, and
>
> treating the tissue with the therapeutic dose of radiation so that the presence of the filler causes the organ to receive less of the dose of radiation compared to the amount of the dose of radiation the organ would receive in the absence of the filler,

wherein the filler is introduced as an injectable material and is a gel in the patient, and

wherein the filler is removable by biodegradation in the patient.

Claims 2-24 are directed to well-known materials that may form the filler, well-known agents that may be included within the filler, well-known properties that the filler may take, and well-known targets and applications of radiation therapy. EX1003, ¶¶46-47.

**3.Prosecution History**

The '723 patent issued from U.S. Patent Application No. 12/651,502 ("the '502 application"), which was filed on January 4, 2010. EX1001, cover. The '502 application was a continuation of U.S. Patent Application No. 10/602,526 ("the '526 application"), which issued as the '913 patent. *Id*.

During prosecution of the '526 application, applicant similarly claimed the use of various "biocompatible, biodegradable" materials as part of the claimed method. With regard to this limitation, the examiner made an enablement rejection under §112, stating "Applicant ha[d] only established ample support in the specification for the use of 'collagen' as a suitable filler material." EX1006, 193.[1]

[1] Citations to the prosecution histories of Exhibits 1005 and 1006 refer to the page numbering added by Petitioner.

Applicant ultimately overcame that rejection by submitting an expert declaration of Dr. Amarpreet Sawhney and several supporting references. *Id.*, 262-381. Based on that evidence, Applicant contended that the materials claimed were well-known and well-understood such that Applicant's specifically-disclosed use of collagen enabled the POSA to successfully use those materials for the purpose of displacing tissues during radiation therapy without undue experimentation. *Id.*, 251-252, 270-271.

During prosecution of the '502 application, the application that led to the '723 patent, the examiner did not issue a prior-art-based rejection of the claims that ultimately issued as claims 1-24. Instead, the examiner issued a rejection under §112, finding the specification had only enabled methods "for introducing a biocompatible, biodegradable filler between" the rectum and the prostate gland, but did not enable methods for introducing such a filler "between any first tissue location and any second tissue location" as had been claimed. EX1005, 155. After an examiner's interview, Applicant overcame the rejection by amending the claims to recite that the filler was introduced between "an organ and a nearby tissue." *Id.*, 184.

**C. Relevant Timeframe**

The '723 patent claims priority to three provisional applications: Nos. 60/391,027, filed June 24, 2002 ("the '027 provisional"; EX1007), 60/427,662,

filed November 19, 2002 ("the '662 provisional"; EX1008), and 60/444,143, filed January 31, 2003 ("the '143 provisional"; EX1009). *Id.* Claims 1-16 and 18-24, however, lack written description support under §112 in the '027 and the '662 provisionals, and thus are not entitled to a priority date earlier than the filing date of the '143 provisional: January 31, 2003. *See* pre-AIA §§119 and 120; *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989).

Specifically, both the '027 and '662 provisionals are limited to using collagen between the prostate and the rectum in order to reduce the radiation dose to the rectum. EX1007, 2[2]; EX1008, 2. Although both the '027 and '662 provisionals suggest using the method with any target organ and a critically-sensitive body organ, neither provisional describes the use of a filler material other than collagen. *See, e.g.*, *id.* It is not until the filing of the '143 provisional that other fillers, such as polysaccharides, alginates, polyethylene glycol, etc., were added. EX1009, 3. Thus, the earliest effective filing date to which the '723 patent

[2] Unless otherwise noted, the citation to a page number is to the original page number in the reference, and not the page number added by Petitioner.

is entitled is January 31, 2003, making this date the relevant timeframe for the '723 patent.[3]

### D. Level of Ordinary Skill

At the time of invention, a person of ordinary skill in the art ("POSA") would have held an M.D. with practical, academic, or industrial experience in radiation oncology. EX1003, ¶30. The POSA would further have knowledge of the side effects of radiation treatment, including, for example, tissue necrosis and formations of fibrotic plaques, and methods of counteracting the adverse side effects of radiation therapy. *Id*. The POSA would have experience in performing radiation treatments known at the time, as well as methods of shielding or protecting normal tissue or organs from the harmful effects of such treatments. *Id.*. This experience is consistent with the ongoing teaching that normal tissue and organs should be protected when delivering a therapeutic amount of radiation to a patient. *Id.,* ¶¶30-31. Such a teaching was especially important during the relative timeframe, where the development of improved radiation oncology treatments was

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[3] Nevertheless, the analysis provided in this petition applies equally even if the relevant timeframe were June 24, 2002, the filing date of the earliest-filed provisional.

occurring at a rapid pace, especially the use of increased and sustained radiation energy (*e.g.*, high-dose radiation therapies). *Id.* at 31.

### E. Claim Construction

Claims should be given their ordinary and customary meaning, consistent with the specification, as a POSA understood them. 37 C.F.R. §42.100(b) (as amended Nov. 13, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc). Except as discussed below, for purposes of this IPR, the claim terms should be given their plain and ordinary meaning.[4]

"Filler" as used in the claims of the '723 patent and "filler device" as used in the claims of the related '913 patent (EX1002) should be construed consistently with one another. The '723 patent is a continuation of the '913 patent, and the patents

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[4] Without taking a position here on whether the claims are sufficiently definite, even when the metes and bounds of a claim are indefinite, the Board nevertheless can determine whether embodiments plainly within the scope of the claim would have been obvious. *Ex parte Tanksley*, 26 U.S.P.Q.2d 1384, 1387 (B.P.A.I. 1991) (embodiment within scope despite indefiniteness); *Ex parte Sussman*, 8 U.S.P.Q.2d 1443, 1445 n.* (B.P.A.I. 1988) (affirming obviousness despite indefinite claim format).

share the same specification. In addition, the claims of the '913 patent use the terms "filler device" and "filler" interchangeably.

The specification of the '723 patent defined filler as:

> [A] substance that occupies a volume after its introduction into a body. Examples of fillers include but are not limited to polymers, gels, sols, hydrogels, sponges, bulking agents, and balloons.

EX1001, 4:34-37. Thus, as defined by the specification, a "filler" or "filler device" should be construed as "a substance that occupies a volume after its introduction into a body." *See also* EX1006, 9 (reiterating that a "filler is a substance that occupies a volume after its introduction into a body"). Neither the claim language nor the prosecution history excludes the use of multiple fillers, as long as the fillers are biocompatible and biodegradable. Thus, given the use of the transition term "comprises," the claims encompass the use of multiple fillers, so long as one of the fillers is "introduced [as] an injectable material and is a gel in the patient."

Claim 17 states that the "biocompatible, biodegradable material consists essentially of collagen." The transition phrase "consists essentially of" "limits the scope of a claim to the specified ingredients and those that do not *materially affect the basic* and *novel* characteristic(s) of a composition." *In re Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976) (emphasis added) (citation omitted); *see also PPG Indus., Inc. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998). The basic and novel characteristics of the collagen of claim 17 are its use as a filler that is

biocompatible and bioabsorbable. Thus, "consists essentially of" as used in claim 17 allows components other than collagen to be present so long as they do not prevent the collagen from being used as a biocompatible, bioabsorbable filler.

**F. State of the Art**

Cancer is one of the leading causes of death, and is also a difficult and costly disease to treat. EX1003, ¶48. At the time of invention, the POSA would have understood that there were a wide variety of options for the treatment of cancer. *Id.*, ¶¶49-52. The choice of one or more treatments would depend on the type of cancer, as well as the relative susceptibility of the cancer tissue to a given treatment. *Id.*, ¶51. Examples of treatments at the relevant time period typically included chemotherapy, surgical resection, radiotherapy, and cryotherapy. *See, e.g.*, EX1017, 197; EX1003, ¶49-51. In particular, radiotherapy would be applied preoperatively to reduce the size of a tumor prior to removal, as a standalone treatment for locally reducing or eliminating tumor tissue, or postoperatively to reduce local recurrence of excised cancer tissue. *See, e.g.*, EX1016, Abstract, 7-8; EX1003, ¶53.

Radiation was administered in one of two ways: internally or externally. EX1003, ¶53. External radiation treatments included both 3D-conformational radiation therapy and intensity-modulated radiation therapy ("IMRT"). *Id.*, ¶¶53-55. In 3D-conformational radiotherapy, a tumor is mapped through imaging, and

then beams of radiation are directed towards the tumor. *Id.*, ¶56. IMRT allowed the radiologist to more accurately deliver radiation to the tumor, which helped preserve the healthy tissue around the tumor. *Id.*, ¶56. In internal radiation therapy, or brachytherapy, an implant comprising a radioactive source is placed in or near a tumor. *Id.*, ¶¶57-59. Technical challenges associated with external and internal radiation therapy can affect surrounding normal tissues, leading to increased morbidity. *Id.*, ¶¶60-76.

One of the basic tenets of radiotherapy, whether external or internal, is to minimize the radiation's effect on nearby healthy tissue. EX1052, 504; EX1003, ¶¶47, 77-80. A POSA would have understood that the effect of radiation on the surrounding tissue decreases with distance from the source of radiation, with radiation exposure being inversely related to distance. EX1003, ¶¶77-78. For example, in brachytherapy the radiation at a distance from the source follows the relationship of $1/d^2$, wherein "d" is the distance from the source. *Id.* As a result, even small increases in distance between the tumor to be irradiated and the healthy tissue can minimize damage to the healthy tissue. *Id.* Thus, a POSA at the relevant time period would have understood the need to increase the space between the tumor and the surrounding healthy tissue in order to decrease the impact of the radiation on the healthy tissue. *Id.*.

For instance, treatment of abdominal or pelvic cancers with radiation can result in severe toxicity to abdominal organs due to incidental irradiation. EX1020, 51; EX1003, ¶64. Thus, at the time of invention, various techniques to protect the surrounding tissue were being employed, including advances in radiation field size and intensity (EX1053, Abstract), administration of antioxidants (EX1052, Abstract), and surgical insertion of a prosthesis capable of shielding the bowel from radiation damage (EX1039, 1212). EX1003, ¶¶80-88.

Moreover, the POSA would have understood at the relevant time that biocompatible and bioabsorbable polymers had been used and were being used as a means for protecting healthy tissue. EX1003, ¶¶96-100. For example, in the 1980s, absorbable polyglycolic acid mesh slings were developed, which could be surgically sewn above the pelvis site specifically to minimize radiation toxicity in the pelvic cavity. EX1039, 1216; EX1003, ¶89. Polyglycolic acid is a non-toxic material known to biodegrade in the body, and is often used in the production of biocompatible sutures. EX1054, Abstract; EX1003, ¶89. As such, the biocompatible mesh sling would be left in the body after surgery, thereby minimizing additional complications from surgical removal of the sling. EX1003, ¶89. In addition, biocompatible, bioabsorbable implants were used to displace cancer tissue from healthy tissue during radiation therapy. EX1055, 2:61-3:11; EX1003, ¶86-89. The use of biocompatible, bioabsorbable tissue expanders for

displacing healthy tissue from the radiation field was also known, in which the tissue expander may be filled with a biocompatible liquid or gel. EX1041, 2:62-3:6, 3:56-58; EX1003, ¶¶96-99. Moreover, the use of biocompatible, bioabsorbable gels to encapsulate a tumor to allow more aggressive therapy of tumors was known. EX1013, 3:55-65.

Additionally, a POSA would have known that surgical prosthetics had been used to exclude healthy abdominal tissue from radiation-induced toxicity through insertion into the pelvic cavity to separate the tumor from the healthy tissue. EX1003, ¶¶89-95. For example, silicone prostheses typically used for breast implants were found to afford protection from radiation toxicity when secured in the pelvic cavity prior to post-operative radiation. EX1012, 346; EX1003, ¶¶93-94. However, the static nature of the implant within the body after surgery could result in perforation of the bowel due to the additional space occupied by the silicone implant. EX1012, 348; EX1003, ¶94. Another approach involved the use of saline-filled tissue expanders. EX1020, Abstract; EX1003, ¶¶91-92. However, such devices are not bioabsorbable and require eventual removal, thus increasing surgically-related complications, such as infection. EX1003, ¶92. A POSA would have understood that use of a biodegradable implant would ameliorate both risks due to the gradual degradation of the prosthesis, which would limit the mass-effect

risk associated with silicone implants, and would also eliminate the need for additional surgery to remove the prosthesis. EX1012, 348; EX1003, ¶¶96-97.

At the time of invention, a POSA would have been aware of a wide variety of biocompatible, bioabsorbable materials. EX1003, ¶¶96-101. As discussed above, materials such as a polyglycolic acid were already employed as biodegradable sutures that could be absorbed in the body without production of toxic byproducts. EX1054, Abstract; EX1003, ¶89. Other naturally-occurring polymers, such as gelatin, hyaluronic acid ("HA"), and collagen, were additionally in use in surgical and medical applications prior to June 2002. EX1003, ¶¶96-101.

For example, a POSA would have understood collagen to be a widely-used biocompatible material. EX1003, ¶100. Collagen was commonly used as a soft tissue implant, for example, in plastic surgery, and to prevent surgical adhesions. EX1056, 1:18-24; EX1057, 2:37-55; EX1003, ¶100. Collagen had also been used as an absorbable delivery system for brachytherapy. EX1058, 3:35-42, 4:3-6; EX1003, ¶100. As collagen is a naturally-occurring polymer present in animal tissue, a POSA would have understood collagen to have low immunogenicity and toxicity when placed in the body. EX1003, ¶100. Thus, a POSA would have recognized collagen as a viable space-filler for separating tumor tissue from surrounding healthy tissue. *See, e.g.*, EX1013, 7:45-50; EX1003, ¶100.

Another known natural polymer, HA, is present in connective tissues in mammals, and is a biocompatible polymer capable of being formulated as an injectable sol-gel solution. EX1059, Abstract, 1:18-20; EX1003, ¶100. For instance, HA was developed as an injectable treatment for arthritis by placing high molecular weight HA into the synovial space. EX1059, 1:38-57. HA had also been used as a biodegradable carrier to deliver drugs. EX1013, 8:38-59, 14:64-15:9. Further, HA viscous gels had been used to protect against surgical adhesions post-surgery by acting as a space-filler between adjacent healing tissue. EX1060, 1:46-50; EX1003, ¶100. To prevent surgical adhesions, injective formulations of HA were injected into the abdomen to cover injured areas, which allowed the injected material to conform to the surface of the tissue and act as a barrier to prevent adhesion of injurious tissue before eventually degrading. EX1060, 43:30-39; EX1003, ¶100. A POSA would thus understand HA to have low immunogenicity and toxicity when placed in the body. EX1003, ¶100. Moreover, a POSA at the relevant time would have also recognized that HA gels may be used as a viable space-filler for separating tumor tissue from the healthy tissue surrounding it. EX1013, 2:18-22; EX1003, ¶100.

Accordingly, prior to June 2002, compositions containing biocompatible, biodegradable polymers, which are capable of forming gels *in vivo*, such as HA and collagen, had been proposed for use in preventing radiation-induced toxicity in

abdominal tissue. EX1003, ¶100. For example, Wallace taught that these compositions could be used as a "large space-filling device" when injected into a body cavity to, for example, displace and "protect the intestines during a planned course of radiation to the pelvis" during surgery and radiation procedures. EX1010, 33:64-67; EX1003, ¶100. Thus, at the time of invention, a POSA would have understood that biocompatible compositions, such as collagen and HA, may be used as a superior replacement for non-biodegradable devices, such as saline-filled devices, which require removal. EX1003, ¶¶100-101.

The prior art applied to the claims challenged in this petition is described briefly below.

**1. Burg**

Burg discloses bioabsorbable tissue expanders that are useful for various medical procedures, including the displacement of organs, such as the intestines during radiation therapy.[5] EX1041, 2:62-3:6, 9:17-46; EX1003, ¶¶107-110. The tissue expander includes an envelope, which is formed of a biocompatible,

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[5] Burg published March 27, 2001, making it prior art under §102(b). Burg was cited in an Information Disclosure Statement during prosecution of the '502 application, but it was not applied substantively by the examiner.

bioabsorbable material. EX1041, Abstract; EX1003, ¶108. The envelope includes a chamber that is filled with a biocompatible, bioabsorbable liquid or gel to displace tissue during a medical treatment. EX1041, Abstract; EX1003, ¶¶108-109. Such a configuration allows the expander to be left in place, as it slowly degrades within the patient's body over time. EX1041, 3:2-6, 9:37-41; EX1003, ¶109.

### 2. Carroll

Carroll discloses biocompatible hydrogel compositions that may be used to encapsulate tissue, thereby providing a protective barrier for surrounding healthy tissue during medical procedures, such as radiation therapy.[6] EX1013, Abstract;

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[6] Carroll was filed on April 6, 1999, making it prior art under §102(e). Carroll was not before the examiner during prosecution of the '502 application. To swear behind Carroll, Incept must prove conception of the claimed invention before Carroll's filing date and diligence in reducing the invention to practice after that date. *Apator Miitors APS v. Kamstrup A/S*, 887 F.3d 1293, 1295 (Fed. Cir. 2018) (citing *Perfect Surgical Techniques, Inc. v. Olympus Am., Inc.*, 841 F.3d 1004, 1007 (Fed. Cir. 2016)). Thus, Incept must show diligence over a time period of nearly thirty-nine months for the '723 patent's collagen-specific claim and nearly

EX1003, ¶¶116-118. The compositions may be formed from a variety of known, biocompatible materials that may be configured to degrade within the patient's body over a predetermined amount of time. EX1013, 5:2-6, 7:62-8:59, 14:64-15:4; EX1003, ¶¶117-118. Thus, Carroll evidences that the use of biocompatible, biodegradable polymers to separate tumors from surrounding healthy tissue was known. EX1003, ¶¶117-118.

**3. Griffith-Cima**

Griffith-Cima discloses a variety of biocompatible, polysaccharide hydrogels useful for medical treatments within the body.[7] *See, e.g.*, EX1011, Abstract, 9:32-10:18, 15:27-34; EX1003, ¶¶111-113. Applicant relied on Griffith-Cima during prosecution of the '526 application to establish that polysaccharide hydrogels for human use was well-known and well-understood at the time of invention. EX1006, 199, 254.

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forty-six months for all other claims. Moreover, with respect to the latter, Incept's failure to suggest the use of filler materials other than collagen in the '027 and '662 provisionals is evidence of lack of diligence on Incept's part. *See supra*, section V.C.

[7] Griffith-Cima published November 10, 1994, making it prior art under §102(b).

## G. Ground 1: Claims 1, 14-15, and 23 Are Anticipated by Burg

As described more below, Burg discloses each and every element of independent claim 1 and dependent claims 14-15 and 23, and thus anticipates those claims.

### 1. Independent Claim 1

#### *a. [1.Preamble] A method of delivering a therapeutic dose of radiation to a patient comprising*

Burg discloses "an absorbable implantable tissue expander device that can be used in surgeries as a gradually diminishing space filler." EX1041, Abstract; EX1003, ¶108. Burg further discloses that the expander "may be used in positioning a particular organ or tissue inside the body." EX1041, 9:21-22; EX1003, ¶¶189-190. By positioning the organ using the filler, Burg further discloses that a dose of radiation may be applied to tissue intended to be treated without adversely affecting the displaced organ or tissue. *See* EX1041, 9:25-37; EX1003, ¶¶190. Thus, to the extent the preamble is limiting, Burg discloses it.

#### *b. [1.1] introducing a biocompatible, biodegradable filler between an organ and a nearby tissue to increase a distance between the organ and the tissue, and*

Burg discloses that the tissue expander includes an envelope made from biocompatible and biodegradable materials. EX1041, 3:45-50; EX1003, ¶191.

Burg further discloses that the envelope itself is filled with a filler,[8] which may be a gel that is biocompatible. *See, e.g.*, EX1041, 2:54-3:6, 6:37-41, 9:25-41; EX1003, ¶191. Burg discloses that, as the envelope degrades within the patient's body, the gel is "gradually released" into the patient's body. EX1041, 4:29-31, 6:37-41, 9:25-41 (disclosing that the expander "will gradually degrade and eventually be absorbed by the surrounding tissue"); EX1003, ¶195. A POSA would have understood this to mean that the gel is made from a material that is biodegradable. EX1003, ¶195. When the envelope is filled with the gel filler, a distance between an organ and a nearby tissue may be increased. EX1041, 2:54-3:6, 9:25-41; EX1003, ¶191. Burg thus discloses this element.

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[8] The claim's "comprising" language does not preclude embodiments that use multiple fillers—*i.e.*, it does not preclude embodiments where a filler, in the form of a balloon or envelope, contains a second filler, in the form of a liquid or gel. Thus, Burg's disclosure of a method for treating a patient with radiation therapy using two types of fillers in conjunction (an envelope injected with a gel) that are both biocompatible and biodegradable falls within the scope of the claim.

***c. [1.2] treating the tissue with the therapeutic dose of radiation so that the presence of the filler causes the organ to receive less of the dose of radiation compared to the amount of the dose of radiation the organ would receive in the absence of the filler***

As explained above, Burg discloses introducing a tissue expander having a biodegradable, biocompatible envelope containing a biodegradable, biocompatible gel filler into a patient to displace organs, such as the small bowel, during radiation therapy. *See, e.g.*, EX1041, 2:54-3:6, 9:25-41; EX1003, ¶190. At the time of invention, it was well-understood that the strength of an applied radiative field decreases as a function of distance, and a tissue spaced a given distance relative to the field's maximum strength would receive a dose of radiation that is less than the field's maximum strength. EX1003, ¶¶192-193; *see also supra*, section V.F. As such, the POSA would have understood Burg as disclosing that, when a treatment site was subjected to a therapeutic dose of radiation, the displaced organ would "receive less of the dose of radiation" compared to the amount that would have been received absent the tissue expander. *Id*. Accordingly, Burg discloses this element.

***d. [1.3] wherein the filler is introduced as an injectable material and***

Burg discloses that the gels are injected into a patient's body through injection into the biodegradable envelope, and are thus "introduced as an injectable material." *See, e.g.*, EX1041, 2:27-34, 6:9-15, 6:50-52, 9:7-10; EX1003, ¶194.

***e. [1.4] [the filler] is a gel in the patient, and wherein the filler is removable by biodegradation in the patient.***

As explained above, Burg discloses a filler that is a gel with biocompatible and biodegradable properties, and thus "is removable by biodegradation in the patient." *See, e.g.*, EX1041, 4:29-31, 6:37-41, 9:25-41; EX1003, ¶¶194-196. Accordingly, Burg discloses this element.

**2. Dependent Claims**

Claims 14-15 recite that the filler includes at least one therapeutic agent, which may be "a member of the group consisting of an anti-inflammatory drug, an antibiotic, an antimycotic, a hemostat, a steroid, and an analgesic." EX1001, 17:18-23. Burg discloses that the gel may include therapeutic materials, such as antibiotics and growth factors. *See, e.g.*, EX1041, 3:7-10, 4:29-34, 7:21-36, 8:23-44, 9:41-46; EX1003, ¶¶198-199.

Claim 23 recites that "the filler occupies a volume in the range of about 10 to about 200 cubic centimeters in the patient." EX1001, 18:16-18. Burg discloses that the tissue expander, containing the gel filler, may occupy a volume that "depend[s] on the defect area," including, for example, "from about 1 $cm^3$ to about 1000 $cm^3$." EX1041, 5:32-35; EX1003, ¶¶201-202; *see also* EX1001, 10:39-41 (noting that "[f]iller volumes for separating tissues are dependent on the configuration of the tissues to be treated and the tissues to be separated from each other.").

### H. Ground 2: Claims 1-7, 11, 14-18, 20, and 22-24 Are Obvious over Burg

#### 1. Independent claim 1

As explained above, Burg discloses a method of introducing a biocompatible, biodegradable gel into a patient's body in order to increase a distance between an organ and a tissue during a planned course of radiation treatment, and thus anticipates claim 1. Nevertheless, to the extent Burg does not explicitly disclose the use of a gel that is both biocompatible and biodegradable, Burg renders use of such a gel obvious. *See* EX1003, ¶¶204-209.

Burg generally discloses the use of a gel filler that is injected into an envelope to increase the distance between an organ and surrounding tissue. *See* EX1041, 2:54-3:6, 9:25-41; EX1003, ¶¶207. Burg also discloses that the gel filler is biocompatible, and may be "gradually released" into the patient's body as the outer envelope degrades, such that the gel is "eventually … absorbed by the surrounding tissue." *See* EX1041, 4:29-31, 6:37-41, 9:25-41; EX1003, ¶207.

Burg further provides a number of materials that may form the absorbable tissue expander device and were known to be biodegradable. *See, e.g.*, EX1041, 4:58-5:10; EX1003, ¶¶206-209. To the extent Burg does not explicitly disclose that the gel itself may comprise these biodegradable materials, a POSA would have understood that such materials would be appropriate to form a gel that would biodegrade within the patient's body so that it would be "eventually … absorbed

by the surrounding tissue" after completion of radiation therapy. EX1003, ¶¶204-209; *see also supra*, section V.F. Thus, to the extent Burg does not anticipate the method of claim 1, it nevertheless renders the method obvious.

### 2. Dependent Claims

#### *a. Claims 2-5*

Claims 2-5 recite that the organ is an ovary, at least part of a nerve, a bone, and located in a brain, respectively. EX1001, 16:60-67.

Burg generally teaches the use of a tissue expander to displace organs during radiation therapy, but does not specifically disclose that the organ may be an ovary, at least part of a nerve, a bone, or located in the brain. *See* EX1041, 9:21-46 (disclosing organ displacement generally, using displacement of the bowel as an example); EX1003, ¶211.

Based on the above teachings of Burg, a POSA would have had reason to displace those organs relative to a tissue to be treated with radiation using the biodegradable tissue expanders taught by Burg, and would have had a reasonable expectation of success in doing so. *See* EX1003, ¶¶210-213.

Burg recognizes the benefits of displacing an organ away from a site intended to be irradiated, as doing so would protect the organ from the harmful effects of radiation. EX1041, 9:25-30; EX1003, ¶¶211-212. Burg expressly teaches biocompatible and biodegradable tissue expanders that can be used to

displace organs for this purpose. EX1003, ¶211. Thus, understanding the benefits of displacing a healthy organ, such as those recited in claims 2-5, relative to tissue to be irradiated, the POSA would have reasonably expected that the biocompatible, biodegradable tissue expanders of Burg would successfully displace the organs recited in claims 2-5 relative to the treated tissue. EX1003, ¶212.

This understanding of the knowledge and skill of those in the art is similarly acknowledged and relied upon by the '723 patent. Specifically, the '723 patent describes methods for displacing the rectum relative to the prostate gland using collagen for radiation therapy. *See, e.g.*, EX1001, Abstract, 11:26-14:26; EX1003, ¶213. The '723 patent relies on that specific disclosure to provide the POSA with a reasonable expectation that using fillers of a variety of materials would successfully displace any organ during radiation therapy. Indeed, during prosecution of the '502 application, applicant amended the claims to specify that the filler displaced "an organ" from surrounding tissues to overcome an enablement rejection. *See* EX1005, 184. The skill of those in the art as understood by Burg is consistent with that relied upon by the '723 patent. EX1003, ¶213. Thus, Burg teaches these claims.

***b. Claims 6-7, 11, 17-18, and 20***

Claims 6-7, 11, 17-18, and 20 recite specific materials that may form the filler. In that regard, as to the state of the art at the time of invention, the

specification of the '723 patent specifically states that "[t]he successful use of collagen as a filler shows that other materials may also be used." EX1001, 3:46-47. Moreover, as explained above, to the extent Burg does not specifically disclose that the gel filler may be formed from a biodegradable material, a POSA would have found it obvious to do so. *See supra*, V.H.1.

Claim 6 recites that the filler "comprises a member of the group consisting of polylactide, polyglycolide, polycaprolactone, and poly(alpha-hydroxy acid)." EX1001, 17:1-3. Burg expressly teaches that the tissue expanders can include polylactide, polyglycolide, and polycaprolactone. EX1041, 4:58-62; EX1003, ¶¶216-217.

Claims 7, 11, 18, and 20 recite that the filler comprises alginate, polyethylene glycol, at least one polysaccharide, and a synthetic polymer, respectively. EX1001, 17:4-5, 17:12-13, 18:3-4, 18:7-8. Burg discloses that the tissue expanders may include those materials. *See* EX1041, 4:58-5:10; EX1003, ¶¶216-217.

Claim 17 recites that the filler "consists essentially of collagen." EX1001, 18:1-2. Burg discloses that the tissue expanders may include collagen. *See* EX1041, 5:5-7; EX1003, ¶216. A POSA would have understood that this would include expanders having gel fillers that "consisted essentially of" collagen. EX1003, ¶216, n.15; *cf.* EX1001 (providing no lower bound limit to the term

"essentially of"). Moreover, as discussed above, the transition phrase "consisting essentially of" allows components other than collagen to be present so long as they do not prevent the collagen from being used as a biocompatible, bioabsorbable filler. *See* supra, section V.E. Burg teaches that the disclosed materials, such as those including collagen, may be used as a filler material during radiation therapy.

***c. Claims 16, 22, and 24***

Claim 16 recites that "the filler is biodegradable in vivo in between three months and twelve months." EX1001, 17:24-25. Burg discloses that the speed of absorption of the tissue expanders can be chosen to suit different needs. EX1041, 5:52-63; EX1003, ¶219. As an example, Burg further discloses that the period of degradation of the tissue expander may occur "from about 1 month to about 2 years, more preferably from about 3 months to about 1 year after the device is implanted." EX1041, 4:35-49; EX1003, ¶220. A POSA would have understood that such degradation time would encompass the degradation time of a biocompatible, biodegradable gel filler that has been injected into the outer envelope. EX1003, ¶220. Thus, a POSA would have known and readily understood how to configure the gel filler to biodegrade within a predetermined time, including between three and twelve months, to suit the given need. EX1003, ¶220.

Claim 22 recites that the filler includes a pH buffering agent. EX1001, 18:14-15. Burg does not expressly disclose the use of pH buffering agents in the tissue expanders. Nevertheless, a POSA would have understood that buffering agents were a common, well-understood, and predictable material that would prevent rapid changes in the pH of the gel fillers during use, thereby maintaining the filler's stability. EX1003, ¶221. A POSA thus would have readily understood the benefit of incorporating buffering agents into filler devices like those taught by Burg, and would have had a reasonable expectation of success in doing so. *Id*.

Claim 24 recites that "the therapeutic dose of radiation is between 70 to 300 Gy," and the filler causes the organ "to receive less than 50% of the dose of radiation[.]" EX1001, 18:19-23. As noted above, it was well-known that the strength of an applied radiative field decreases as a function of distance, and tissues spaced apart from the maximum strength of the field received less of the applied dose of radiation. EX1003, ¶222. The POSA also would have understood the amount of dose of radioactivity that would be acceptably safe for a given organ or tissue. *Id*. The POSA would have further understood that, by displacing an organ away from a treated tissue, a higher dose of radiation, such as 70 to 300 Gy, could be applied, with the organ receiving less of that dose, thus making the radiation treatment more effective. EX1003, ¶223. A POSA also would have

readily appreciated the distance the organ should be displaced to receive less than 50% of that dose such that the organ received an acceptably-safe dose. *Id*.

#### *d. Claims 14-15 and 23*

As explained above, Burg discloses each of the elements recited in claims 14-15 and 23, and thus renders those claims obvious for the reasons discussed above. *See supra*, V.L.2; EX1003, ¶225.

### I. Ground 3: Claims 8-10, 12, 19, and 21 Are Obvious over Burg and Carroll

Claims 8-10, 12, and 19 recite specific materials that may form the filler.

Claims 8-10 recite that the filler comprises gelatin, fibrin or fibrinogen, and albumin, respectively. EX1001, 17:6-11. Burg does not explicitly disclose that the gel filler may include these materials, but Burg does disclose that the tissue expander may be formed from protein materials. *See* EX1041, 5:5-7; EX1003, ¶227. Carroll discloses biocompatible, biodegradable hydrogel compositions that may be inserted into a patient's body and used for medical treatment, such as radiation therapy. EX1013, Abstract; EX1003, ¶228. Carroll similarly discloses that proteins, such as gelatin, fibrin or fibrinogen, and albumin, may be used as part of the hydrogel compositions. EX1013, 8:46, 7:47, 25:67; EX1003, ¶228. A POSA would have understood that proteins, such as gelatin, fibrin or fibrinogen, and albumin, would be materials appropriate for successfully forming the gel

fillers taught by Burg, and thus would have found it obvious to include such materials in the gel fillers taught by Burg. EX1003, ¶228.

Claim 12 recites that the filler comprises a thixotropic polymer, and claim 19 recites that the filler comprises hyaluronic acid. EX1001, 17:14-15, 18:5-6. Burg generally discloses the use of polysaccharides, a material that was known to include polymers that could be configured to be thixotropic. EX1041, 4:63-66; EX1003, ¶229; EX1061,[9] 8:35-39; *cf.* EX1006, 200, 211, 216-218. Carroll similarly discloses the use of polysaccharides as a polymer appropriate for forming biocompatible, biodegradable hydrogel compositions, including hyaluronic acid, which a POSA would have understood to be a polysaccharide that is thixotropic. *See* EX1013, 8:52-62; EX1061, 8:35-39; EX1003, ¶229. A POSA would have understood that thixotropic polymers, such as hyaluronic acid, would be materials appropriate for successfully forming the gel fillers taught by Burg, and thus would have found it obvious to include such materials in the gel fillers taught by Burg. EX1003, ¶229.

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[9] Note that this teaching by Hubbell was added by amendment to the specification of the ’913 patent during prosecution. EX1006, 200, 211, 216-218.

Claim 21 recites that the filler includes "a member of the group consisting of ... a radio opaque marker [.]" EX1001, 18:9-13. Carroll teaches the use of markers so that the gel fillers can be readily evaluated by imaging techniques, including x-ray. EX1013, 10:28-34; EX1003, ¶230. A POSA would have understood that, for x-ray imaging techniques, radio opaque markers should be utilized. EX1003, ¶230. A POSA also would have readily appreciated the benefit of incorporating such markers into the gel fillers taught by Burg in order to better visualize placement of the filler within the patient's body.

### J. Ground 4: Claim 13 Is Obvious over Burg and Griffith-Cima

Claim 13 recites that the filler includes a thermoreversible polymer. EX1001, 17:16-17.

Burg generally teaches the use of gel fillers that can be injected into an envelope within a patient's body to displace organs. EX1041, 2:37-38, 2:54-61, 3:2-6, 4:18-32; EX1003, ¶230. Burg expressly contemplates that the tissue expanders may be formed of a variety of polymer materials. EX1041, 4:58-5:10; EX1003, ¶231.

Thermoreversible polymer compositions were well-known and well-understood prior to the filing date of the '913 patent. EX1003, ¶¶232-234. For instance, as noted above, Dr. Sawhney cited Pluronics™ as an example of a well-known thermoreversible polymer that can form a gel. *See* EX1006, 256, 273;

EX1003, ¶233. Griffith-Cima similarly teaches the use of Pluronics™ to form a biocompatible hydrogel that may be crosslinked by temperature. *See, e.g.*, EX1011, 15:20-34. Thus, a POSA would have found the use of thermoreversible polymers in the gel fillers of Burg to be well-known, well-understood, and predictable.

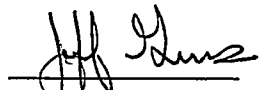
## VI. SECONDARY CONSIDERATIONS

Any evidence of secondary considerations is irrelevant to the extent the claims of the '723 patent are anticipated. Moreover, Palette is also unaware of any objective evidence of nonobviousness that would outweigh a conclusion of obviousness of the claims.

## VII. CONCLUSION

The challenged claims are unpatentable. Palette respectfully requests that IPR be instituted.

Respectfully submitted,



Jeff Guise, Reg. No. 34,613
Lead Counsel for Petitioner Palette

## CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for Inter Partes Review totals 6,850, which is less than the 14,000 allowed under 37 C.F.R. 42.24(a)(i). In accordance with 37 C.F.R. 42.24(a), this word count does not include table of contents, table of authorities, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: 14 October 2019

Jeff Guise, Reg. No. 34,613

## CERTIFICATE OF SERVICE

I certify that today I caused to be served a true and correct copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,257,723 and Exhibits 1001-1062** by *Federal Express Next Business Day Delivery* to the Patent Owner's correspondence address of record:

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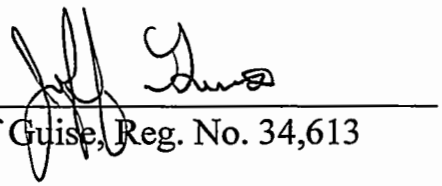
Dated: 14 October 2019



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