39. BMS's recombinant, human monoclonal antibody Yervoy® (ipilimumab) is approved for the treatment of unresectable or metastatic myeloma. December 2013 Yervoy® Labeling. A phase I/II study evaluating ipilimumab alone or in combination with radiotherapy in patients with mCRPC "suggested clinical antitumor activity with disease control and manageable AEs [adverse events]." Slovin *et al., Ipilimumab Alone or in Combination with Radiotherapy in Metastatic Castration-Resistant Prostate Cancer: Results from an Open-Label, Multicenter Phase I/II Study*, 24 Annals of Oncol. 1813-21, 1813 (2013). Eight patients receiving ipilimumab and radiotherapy had PSA declines greater than or equal to 50%, and one had a complete response with a duration of over 11.3 months. *Id.* Another phase II study comparing ipilimumab as a single agent to combination therapy with docetaxel in CRPC patients reported three patients in each arm with a PSA decrease of more than 50%. Small *et al., Randomized Phase II Study Comparing 4 Monthly Doses of Ipilimumab (MDX-010) as a Single Agent or in Combination with a Single Dose of Docetaxel in Patients with Hormone-Refractory Prostate Cancer*, 24(18S) J. Clin. Oncol. (Meeting Abstracts) S4609 (June 2006). The authors concluded that further studies in prostate cancer were warranted. *Id.* In September 2013 BMS reported that a phase III, double-blind study comparing ipilimumab to placebo following radiation in patients with advanced mCRPC who had previously received treatment with docetaxel showed no statistically significant improvement in overall survival, the primary endpoint. *Bristol-Myers Squibb Reports Results for Phase 3 Trial of Yervoy® (Ipilimumab) in Previously-Treated Castration Resistant Prostate Cancer*, Business Wire NewsHQ Press Release (September 12, 2013), http://news.bms.com/press-release/rd-news/bristol-myers-squibb-reports-results-phase-3-trial-yervoy-ipilimumab-previousl. The phase II data did not translate into phase III success.

40. In April 2014 OncoGenex announced that custirsen plus docetaxel and prednisone in first line therapy did not provide a statistically significant improvement in overall survival in men with mCRPC compared to docetaxel plus prednisone alone. *OncoGenex Announces Top-Line Survival Results of Phase 3 SYNERGY Trial Evaluating Custirsen for Metastatic Castrate-Resistant Prostate Cancer,* Acquire Media Press Release (April 28, 2014), http://ir.oncogenex.com/releasedetail.cfm?ReleaseID=842949. A phase II trial evaluating custirsen plus docetaxel and prednisone compared to docetaxel plus prednisone in patients with chemotherapy-naïve mCRPC had indicated an increase in overall survival with custirsen, and 19% of patients had a partial response. Zielinski & Chi, *Custirsen (OGX-011): A Second-Generation Antisense Inhibitor of Clusterin in Development for the Treatment of Prostate Cancer*, 8(1) Future Oncol. 1239-51, 1245-46 (2012). A phase II trial evaluating custirsen plus docetaxel in mCRPC patients previously treated with docetaxel also reported 15% of patients as having a partial response and 40% of patients as having a PSA response. *Id.* at 1246.

41. In June 2014 Takeda announced that it was terminating development of orteronel, an inhibitor of 17,20 -lyase, after two disappointing phase III trials in mCRPC. *Takeda Announces Termination of Orteronel (TAK-700) Development for Prostate Cancer in Japan, U.S.A. and Europe*, Takeda Latest News Release (June 19, 2014), http://www.takeda.com/news/2014/20140619_6615.html. The first reported phase III trial was in men with mCRPC that had progressed during or following chemotherapy. *Id.* An interim analysis indicated that orteronel plus prednisone would not likely meet the primary endpoint of overall survival. *Id.* The second phase III failure was in men with mCRPC who had not previously received chemotherapy. *Id.* There was no statistically significant improvement in overall survival, one of the primary endpoints. *Id.* These failures came after at least six phase I

and II studies in patients with CRPC. Van Hook *et al., Orteronel for the Treatment of Prostate Cancer*, 10(5) Future Oncol. 803-11, 807 (2014). A phase II study of orteronel plus docetaxel and prednisone in mCRPC patients reported an overall objective response rate of 56%, with 72% of men experiencing a PSA decline of more than or equal to 50%. *Id.* at 805-06. A phase I/II study of orteronel in chemotherapy naïve mCRPC patients with or without prednisone reported an objective response rate of 19% with 41-63% of patients experiencing a PSA decline of more than or equal to 50% depending on dose and the addition of prednisone. *Id.* at 807.

42. Antonarakis and Eisenberger report on the failure of eight phase III clinical trials in patients with mCRPC. These trials were of eight different combination therapies with docetaxel: bevacizumab, aflibercept, atrasentan, zibotentan, dasatinib, GVAX, lenalidomide, and calcitriol. Antonarakis & Eisenberger at 1709-10. The authors suggest that these late stage failures could be reduced if more stringent standards were required in phase II before proceeding to phase III. *Id.* at 1711 ("[P]hase III trials should not be pursued without the prior conduct of at least one phase II study that has met a prespecified rationally selected primary end point and its predefined metric for success . . . .").

43. A person of ordinary skill would have understood, as can be seen from the above mentioned studies, that it would have been extremely difficult to predict whether a compound would provide a clinically meaningful benefit such as prolongation of survival in mCRPC patients while providing a reasonable side effect profile, even after positive phase II results in the same indication. This understanding was true in 2009 and remains true today.

II. Disclosure of Cited Art

A. Beardsley

44. Beardsley is a review article describing research developments on a wide variety of different approaches to treating mCRPC. Of the eleven compounds discussed, only one is a taxane: cabazitaxel.

45. Beardsley states that XRP6258 (cabazitaxel) "is a semi-synthetic taxoid compound with low affinity for the P-glycoprotein ("P-gp") drug efflux transporter and cytotoxic in cell lines with acquired resistance to paclitaxel or docetaxel." Beardsley at 163. The P-gp drug efflux transporter is a protein that removes toxins, such as drugs, from cells. *See, e.g.*, Cabral, *Factors Determining Cellular Mechanisms of Resistance to Antimitotic Drugs*, 4 Drug Resistance Updates 3-8, 3 (2001) ("Cabral"). It was hypothesized that one cause of taxane resistance was a proliferation of P-gp in resistant cells, which pumped the drug out of the cell before it could have an effect. *See id.*

46. Beardsley discloses that a phase II study of cabazitaxel was conducted in patients with docetaxel-refractory metastatic breast cancer, with an objective response rate of 14%. Beardsley at 163. Two patients reportedly achieved a complete response with a median response duration of 7.6 months. *Id.*

47. Beardsley notes that "given its activity in the docetaxel refractory setting" of the phase II study in breast cancer, cabazitaxel was being investigated in a phase III trial "comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment." *Id.* The doses of cabazitaxel and prednisone are not disclosed.

48. Beardsley does not report any results from a phase III study on cabazitaxel or any clinical data from administration of cabazitaxel to patients with prostate cancer. In fact, this article simply catalogues the various approaches being used or studied at that time.

B. Mita

49. Mita describes the results of a phase I and pharmacokinetic study of cabazitaxel administered as a 1-hour infusion every three weeks in patients with advanced solid tumors. The objectives of the study were to characterize the toxicities of cabazitaxel without premedication, determine the maximum tolerated dose and recommended dose for phase II studies, characterize the pharmacokinetic profile of cabazitaxel, and to document preliminary evidence of antitumor activity. Mita at 724. Phase I studies are not designed for, and therefore cannot provide a person of ordinary skill with a reasonable expectation of, efficacy in a treatment population.

50. Mita discloses that cabazitaxel was more potent than docetaxel in a broad array of cancer cell lines with acquired resistance to docetaxel. *Id.* at 723-24. Although a substrate for the ATP-dependent drug efflux pump P-gp, cabazitaxel is described as a weaker substrate than docetaxel. *Id.* at 723.

51. Mita states that cabazitaxel has "shown a broad spectrum of antitumor activity in mice." *Id.* at 724. However, cabazitaxel did not retain activity against Calc18/TXT and P388/VCR tumors, which Mita describes as expressing higher levels of *ABCB1* mRNA, the mRNA coding for P-gp. *Id.* This finding casts doubt on the role of P-gp in cabazitaxel's ability to overcome resistance to docetaxel.

52. Twenty-five patients received cabazitaxel in four dose levels: 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, and 25 mg/m^2. *Id.* at 726. The patients had a variety of documented

advanced solid malignancies "refractory to conventional treatment." *Id.* at 724. Twenty-two patients (88%) had previously received chemotherapy with eight patients having received prior taxane-based therapy. *Id.* at 726. Prior anticancer therapy had to be completed at least 28 days before study enrollment, 42 days for nitrosureas and mitomycin C. *Id.* at 724. Eight of the twenty-five patients had prostate cancer. *Id.* at 725.

53. Mita reports that neutropenia was the principal toxicity of cabazitaxel. *Id.* at 726. Severe neutropenia was reported at the 25 mg/m^2 level, with grade 4 events occurring in 8 of the 19 (42%) evaluable courses. *Id.* Diarrhea was reported in 52% of patients, nausea in 40%, and vomiting in 16%. *Id.* Mita suggests that the gastric toxicities may be caused by accumulation of cabazitaxel in enterocytes that constitutively express P-gp because cabazitaxel is a poorer substrate for the transporter pump than docetaxel. *Id.* at 728.

54. Evidence of anti-cancer activity due to cabazitaxel was noted in two prostate cancer patients with confirmed partial responses. *Id.* at 727. The first patient was an 80 year old male with prostate cancer metastatic to the liver and bones whose disease had progressed through castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone. *Id.* He declined further treatment after his sixth course. *Id.* I note that he had never received docetaxel, thus cabazitaxel was his first taxane.

55. The second patient was a 50 year old male with hormone and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes. *Id.* Progressive disease was noted after eight courses. *Id.*

56. Mita states that the "preliminary antitumor activity reported" still "needs to be confirmed." *Id.* at 729.

C. **Tannock**

57. Tannock reports the results of a phase III study comparing docetaxel plus prednisone with mitoxantrone plus prednisone in metastatic hormone-refractory prostate cancer, also commonly referred to as mCRPC. Treatment with 75 mg/m^2 of docetaxel every three weeks plus 10 mg daily prednisone led to superior survival and improved rates of response "in terms of pain, serum PSA level, and quality of life" as compared to 12 mg/m^2 of mitoxantrone every three weeks plus 10 mg daily prednisone. Tannock at 1502. Cabazitaxel is not mentioned in this publication.

58. Eligible patients had histologically or cytological confirmed adenocarcinoma of the prostate with clinical or radiologic evidence of metastatic disease, had disease progression during hormonal therapy, and were receiving primary androgen-ablation as a maintenance therapy. *Id.* at 1503. At least four weeks had to have elapsed between withdrawal of the antiandrogens, six weeks in the case of bicalutamide, and enrollment, so as to "avoid the possibility of confounding as a result of the response to antiandrogen withdrawal." *Id.*

59. The primary endpoint was overall survival. Secondary endpoints included reductions in pain, improvement in the quality of life, reduction in serum PSA levels of at least 50% and objective tumor responses. *Id.* at 1504. In the discussion section, Tannock states, "[m]ore important, we found a significant improvement in overall survival for docetaxel as compared with mitoxantrone." *Id.* at 1511.

III. Prior Art Treatment of Prostate Cancer

60. mCRPC is an incurable condition. The goals of treatment emphasize symptom control and overall survival. Beardsley at 161. Docetaxel plus prednisone became the standard of care in large part because two phase-III trials demonstrated a survival advantage over

mitoxantrone plus prednisone. *See, e.g., id.* Mitoxantrone plus prednisone had been previously shown not to improve survival over prednisone alone. Berry *et al., Phase III Study of Mitoxantrone Plus Low Dose Prednisone Versus Low Dose Prednisone Alone in Patients with Asymptomatic Hormone Refractory Prostate Cancer*, 168 J. Urol. 2439-43, 2439, 2442 (2002).

61. Unfortunately, as the '720 application explains, it was known that patients' cancer will eventually progress after docetaxel treatment because their cancer develops resistance to docetaxel therapy. Several mechanisms of resistance have been described in the literature. Cabral at 3-8; Dumontet & Sikic, *Mechanisms of Action of and Resistance to Antitubulin Agents: Microtubule Dynamics, Drug Transport, and Cell Death*, 17(3) J. Clin. Oncol. 1061-1070 (1999). Even today, the mechanisms of taxane resistance are not well understood, and it may be a combination of changes to cancer cells exposed to docetaxel that gives rise to the resistance.

62. Beardsley noted in 2008 that there was an "urgent need for systemic treatment options for patients with castration-resistant prostate cancer who have progressed after receiving first-line docetaxel chemotherapy." Beardsley at 161. Beardsley describes a variety of treatments proposed for mCRPC in 2008, including satraplatin, four epothilones, custirsen, sorafenib, sunitinib, abiraterone, and MDV3100 (enzalutamide). None of these treatments succeeded in meeting that clinical need before the earliest filing date of the '720 application.

IV. The Treatment of mCRPC with Cabazitaxel

63. The urgent need described by Beardsley was not met until the FDA approval of Jevtana (cabazitaxel) in 2010, based on a phase III clinical trial (the TROPIC study) that demonstrated a statistically significant improvement in overall survival compared to mitoxantrone plus prednisone.

64. As co-PI on the TROPIC study, I presented to the ASCO Genitourinary Cancers Symposium as the first public presentation of the mature phase III data. The response to the data was very positive. The results were unexpected, and many physicians expressed surprise given that there was virtually no data available prior to that time in mCRPC. For the first time, patients with mCRPC progressing on or after docetaxel treatment had an opportunity to prolong life.

65. Prior to these results, the person of ordinary skill in the art could not reasonably predict whether cabazitaxel would provide a clinically meaningful benefit in palliation or survival in mCRPC patients, particularly not for those patients progressing after docetaxel treatment, based on the results reported in Mita or Beardsley. In fact, the typical response was one of surprise at the positive results.

66. As the '720 application describes, metastatic prostate cancer is particularly difficult to evaluate because of the heterogeneity of the disease and the lack of consensus regarding the treatment response criteria. '425 Publication at [0007]; Mackinnon *et al.*, *Molecular Biology Underlying the Clinical Heterogeneity of Prostate Cancer: An Update*, 133 Arch. Pathol. Lab. Med. 1033-40, 1033 (2009) ("Mackinnon"); Armstrong & George, *New Drug Development in Metastatic Prostate Cancer*, 26 Urologic Oncol.: Seminars & Original Investigations 430-37, 430 (2008) ("Armstrong & George"). There are currently no biomarkers indicating which prostate cancer patients will respond to particular therapies. Many patients do not have measurable disease, and therefore alternative markers such as PSA are needed to evaluate response. '425 Publication at [0007]. However, even PSA is notorious for not being able to predict survival.

67. A skilled artisan would have known that changes in PSA are not necessarily indicative of efficacy. Beardsley at 164 (noting that PSA may not be reflective of disease progression with vascular endothelial growth factor receptor targeting agents); *see* Berry at 2439 (reporting a significantly greater decrease in PSA levels without a statistically significant increase in overall survival for mitoxantrone); Tannock at 1502 (reporting statistically significant improvements in rates of PSA response in patients taking docetaxel weekly compared to mitoxantrone, but no difference in overall survival). Susan Halabi, myself, and others found that "the benefits of cabazitaxel in mediating a survival benefit are not fully captured by early PSA changes." Halabi *et al.*, *Prostate-Specific Antigen Changes as Surrogate for Overall Survival in Men with Metastatic Castration-Resistant Prostate Cancer Treated with Second-Line Chemotherapy*, 31(31) J. Clin. Oncol. 3944-50, 3944 (2013).

68. The primary endpoint leading to FDA approval of docetaxel for the treatment of mCRPC,[2] and all post-docetaxel treatments has been overall survival. D'Amico, *US Food and Drug Administration Approval of Drugs for the Treatment of Prostate Cancer: A New Era Has Begun*, 32(4) J. Clin. Oncol. 362-64 (2014). "[T]he only validated phase III endpoint in advanced prostate cancer, particularly CRPC, is overall survival." Ramiah *et al., Clinical Endpoints for Drug Development in Prostate Cancer*, 18 Curr. Opin. Urol. 303-08, 307 (2008). Accordingly, the person of ordinary skill was seeking a therapy that prolonged overall survival in a patient population with an acceptable side effect profile.

69. But, as Ramiah *et al.* have emphasized, "[i]n phase II trials, however, it remains a challenge to select the ideal intermediate endpoint to gauge the efficacy of novel

[2] The exception is denosumab, also approved for osteoporosis, which is used to decrease the rate of skeletal-related events in bone-metastatic CRPC patients. This is a palliative benefit and does not influence survival.

agents. The lack of proven surrogates, the heterogeneity of PFS definitions, the unknown effects of novel agents on PSA production, and the variability in patient-reported outcomes make many of these endpoints problematic." *Id.* Indeed, Armstrong and George report that one of the challenges to drug development in mCRPC is "the lack of established surrogates for overall survival." Armstrong & George at 430-31. Seeking to explain the high rate of phase III failures in mCRPC continuing in 2013, Antonarakis and Eisenberger also recognized that "there are currently no established surrogate end points for overall survival in men with mCRPC, [and] new efforts should focus on identification and validation of alternative intermediate biomarkers of clinical benefit . . . ." Antonarakis & Eisenberger at 1711.

70. It follows that phase I and II data, including responses in PSA levels and measurable lesions, would not have allowed a person of ordinary skill in the art to predict whether a patient would have ultimately lived longer or tolerated the medication long enough to see such a survival benefit.

V. Interpretation of Cited Art

71. As noted above, I have reviewed the references cited in the Office Action. In my opinion, these references, alone or in combination, would not give a person of ordinary skill at the relevant time a reasonable expectation that cabazitaxel could successfully treat mCRPC. Indeed, based on the evidence and experience in the field, such a skilled person would more reasonably expect failure than success.

A. Phase I Data in Mita

72. Mita evaluated twenty-five patients, eight of which had prostate cancer. This trial was not powered sufficiently to detect a survival or palliative benefit in prostate cancer. Nor did it report statistically significant results.

73. The 80 year old man with a partial response had previously been treated with bicalutamide, an antiandrogen, in addition to other therapies. Prior treatment needed to have ceased 28 days prior to enrollment in this phase I study, but it was known that bicalutamide withdrawal could cause a response. Wirth & Froschermaier, *The Antiandrogen Withdrawal Syndrome*, 25 (Suppl. 2) Urol. Res. S67-71, S67-68 (1997). This is why the phase III trial with docetaxel described in Tannock required at least six weeks to have elapsed after bicalutamide treatment before enrollment. Tannock at 1503 ("so as to avoid the possibility of confounding . . . the response to antiandrogen withdrawal").

74. The 80 year old man had not been previously treated with docetaxel and was therefore not docetaxel-refractory. In addition, he declined further treatment after his sixth course, indicating that the side effects might not have been acceptable.

75. The 50 year old man with a partial response is the **only** docetaxel-refractory patient in Mita to have a partial response after cabazitaxel treatment. Progressive disease was noted after eight courses. A person of ordinary skill would not have found this result in a single patient sufficient to predict whether cabazitaxel would have provided a clinical benefit in palliation or survival for a population of mCRPC patients progressing after docetaxel therapy, or whether cabazitaxel would have had a risk-benefit ratio such that it would have been considered a treatment for the disease.

76. These two patients are essentially a case study with cabazitaxel. The responses could be an anomaly, reflecting certain qualities in each patient's particular cancer. A person of ordinary skill would not take partial responses in two patients and extrapolate to predict the ability of cabazitaxel to provide a meaningful clinical benefit, e.g., prolongation of survival, for a patient population with mCRPC. In light of the voluminous phase III failures in

this indication, a person of ordinary skill would not expect success in a phase III trial given this data, and indeed would predict that such a trial would more likely fail than succeed.

77. Indeed, when I was on the faculty at Harvard in 2007 I had difficulty opening the TROPIC phase III study of cabazitaxel in mCRPC patients progressing after docetaxel therapy at the Lank Center for Genitourinary Oncology because the evidence of activity was considered too preliminary by those at the institution.

B. Phase II Data in Beardsley

78. Beardsley reports data from a phase II clinical trial of cabazitaxel in docetaxel-refractory breast cancer patients. A person of ordinary skill in the art would not assume that data in breast cancer patients would translate to prostate cancer patients. They are distinct tissue types, and even within each type of cancer there is substantial heterogeneity. Mackinnon at 1033; Wiechec & Hansen, *The Effect of Genetic Variability on Drug Response in Conventional Breast Cancer Treatment*, 625 Eur. J. Pharmacol. 122-30 (2009). A person of ordinary skill would not have given weight to these phase II results in evaluating the use of cabazitaxel for mCRPC.

C. Use of Prednisone in Tannock

79. Tannock does not indicate whether the use of prednisone contributes to any palliative or survival benefit because docetaxel alone is not compared to docetaxel plus prednisone. Therefore it would not have suggested that prednisone improved therapy with docetaxel or that prednisone would have improved therapy with cabazitaxel. Consequently, a person of ordinary skill would not add prednisone to an oncologic agent, including a taxane, based on this article.

VI. Conclusion

80. A person of ordinary skill would not have had a reasonable expectation of success in using cabazitaxel to provide a clinically meaningful benefit, e.g., prolongation of life with acceptable toxicity, in patients with mCRPC in light of the phase I data or phase II data in breast cancer described above for several reasons:

- Anecdotal responses in particular patients can be, and often are, due to factors peculiar to those patients and do not represent a generalizable finding in a heterogeneous population of patients. As noted above, there are innumerable examples of patients in phase I or phase II studies showing significant responses with drugs that go on to fail completely in phase III clinical studies.
- As the FDA has recognized, a meaningfully beneficial clinical endpoint (e.g., improving survival in mCRPC patients refractory to docetaxel) is not typically predefined in phase I or phase II clinical studies. Consequently, as a matter of statistics and good clinical practice, a person of ordinary skill would draw no definite conclusions regarding the efficacy of a drug after a phase I or II trial unless those trials were exceptionally large or conducted in cancers where phase III trials are not feasible. Moreover, phase II studies are generally not sufficiently powered to determine whether the risk-benefit ratio justifies the use of a compound. Many drugs showing significant activity fail because the risks to patients outweigh the benefits of the drug (*see, e.g.*, the discussion of the taxane Larotaxel above). This last point cannot be emphasized enough: **a treatment that is too toxic to the patient is no treatment at all.** Finally, as phase II studies

are not usually designed to evaluate alternative therapies, one cannot conclude that an experimental drug is superior to conventional therapy.

- Finally, cancers are biologically distinct. A drug that works for one tumor type will usually not work for another. A phase III study in the target tumor type (in this case prostate cancer) is typically required before any conclusion can be drawn regarding a compound's efficacy against that tumor.

81. Indeed, prediction of a positive phase III study in mCRPC has been described as "an impossible endeavor." Antonarakis & Eisenberger at 1711. A person of ordinary skill in the art would have understood that clinical development in oncology is inherently unpredictable. In particular, they would have also understood that amongst the high level of late stage failures in oncology, mCRPC has proven to be a particularly difficult indication to predict success. That understanding is as true today as it was when the patent application was filed.

82. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, Under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Alton Oliver Sartor, M.D.

Date: July 14, 2014

EXHIBIT 1

CURRICULUM VITAE

PART I: General Information

DATE PREPARED: June 30, 2014

Name: A. Oliver Sartor, M.D

Home Address: 1511 Dufossat Street, New Orleans, LA 70115

Work E-Mail: osartor@tulane.edu

Place of Birth: Shreveport, LA

Education:

1977 B.A.	Colorado College, Colorado Springs, CO
1982 M.D.	Tulane University School of Medicine, New Orleans, LA

Postdoctoral Training:

1982-1983	Intern in Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Pediatrics Program, Philadelphia, PA
1983-1984	Intern in Medicine, Tulane University School of Medicine
1984-1985	Junior Resident, Internal Medicine, Tulane University School of Medicine
1985-1986	Senior Resident, Internal Medicine, Tulane University School of Medicine
1986-1989	Fellow in Medical Oncology, National Cancer Institute, Bethesda, MD
1989-1990	Senior Staff Fellow, Laboratory of Cellular Development and Oncology, National Institutes of Dental Research, Bethesda, MD

Licensure and Certification:

1985-	Louisiana Medical Licensure
1986-lifetime	American Board of Internal Medicine Certificate
1989-lifetime	American Board of Internal Medicine, Medical Oncology Certificate
1986-1993	Maryland Medical Licensures
1988-1990	Virginia Medical Licensures
2006-2008	Massachusetts Medical Licensure

Academic Appointments:

1990-1993	Senior Investigator, Clinical Pharmacology Branch, National Cancer Institute, Bethesda, MD
1993-1998	Associate Professor of Medicine (with tenure), Section of Hematology/Oncology, Departments of Medicine and Urology, Louisiana State University School of Medicine, Shreveport, LA
1998-2006	Patricia Powers Strong Professor of Oncology (with tenure), Louisiana State University School of Medicine, New Orleans, LA

2002-2006	Adjunct Clinical Professor of Medicine, Tulane University School of Medicine, New Orleans, LA
2006-2007	Associate Professor of Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2007-2008	Lecturer, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2008-2010	Piltz Endowed Professor of Cancer Research in Depts. of Medicine and Urology), Professor of Medicine and Urology, Tulane Medical School, New Orleans, LA
2010-	C.E. and Bernadine Laborde Professor of Cancer Research and Medical Director, Tulane Cancer Center

Hospital Appointments:

1990-1993	Attending Physician, NIH Clinical Center, Bethesda, MD
1993-1998	Attending Physician, Louisiana State University Hospital, Shreveport, LA
1993-1998	Attending Physician, Willis-Knighton Hospital, Shreveport, LA
1998-2006	Attending Physician, Medical Center of Louisiana at New Orleans, New Orleans, LA
1998-2006	Attending Physician, Memorial Medical Center, New Orleans, LA
2006-2007	Attending Physician, Dana Farber Cancer Institute, Boston, MA
2006-2007	Attending Physician, Brigham and Women's Hospital, Boston, MA
2008-	Attending Physician, Tulane University Hospital, New Orleans, LA

Hospital and Health Care Organization Service Responsibilities:

1998-2006	Head, LSU Oncology Services, Medical Center Louisiana, New Orleans

Major Administrative Responsibilities:

1998-2006	Chief, Hematology/Oncology Section, Department of Medicine, Louisiana State University School of Medicine
1998-2006	Director, Stanley S. Scott Cancer Center, Louisiana State University Health Sciences Center
2002-2006	Co-Director, Louisiana Cancer Research Consortium (comprised of both Louisiana State University Health Sciences Center in New Orleans and Tulane Health Sciences Center, New Orleans, LA)
2006-2007	Director, Clinical Trials Unit, Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute
2010-	Medical Director, Tulane Cancer Center

Major Committee Assignments:

1993-1998	Genitourinary Cancer Committee, Member, Southwestern Oncology Group
1995-1998	Institutional Review Board, Member, Louisiana State University School of Medicine
1996-1998	Medical School Admissions Committee, Member, Louisiana State University School of Medicine

1997-1998	Institutional Review Board, Chairman, Louisiana State University School of Medicine
1998-2006	Louisiana Cancer and Lung Trust Fund Board, Member, (Board Appointed by the Governor of Louisiana)
1999-2002	Promotion and Tenure Committee, Member, Department of Medicine, Louisiana State University Health Sciences Center
2000-2002	Promotion and Tenure Committee, Chairman, Department of Medicine, Louisiana State University Health Sciences Center
2001-2005	Clinical Faculty Advisory Committee to the LSU Health Care Network, member, Louisiana State University Health Sciences Center
2003-2009	The Comprehensive Multicenter Prostate Adenocarcinoma Registry (COMPARE), Co-Chairman, sponsored by *sanofi-aventis*.
2003-2005	Louisiana Cancer and Lung Trust Fund Board, Chairman, 2004 (Board Appointed by the Governor of Louisiana)
2003-2006	Executive Committee, Member, Louisiana Cancer Control Partnership
2003-2006	Finance Committee, Member, LSU Health Care Network (organization responsible for overall billing and collections at the LSU Medical School, New Orleans)
2003-2006	Contracts Committee, Member, LSU Health Care Network (responsible for insurance/managed care contracting at the LSU Medical School, New Orleans)
2005-2006	Investment Strategic Planning Committee, *ad hoc* Member, LSU Health Sciences Center Foundation (LSU endowment investments)
2006-	Medical Oncology, Co-Chairman, Genitourinary Cancer Committee, Radiation Therapy Oncology Group (RTOG)
2006-	Medical Oncology Committee, Radiation Therapy Oncology Group (RTOG)
2008-	Louisiana Cancer and Lung Trust Fund Board, (Board Appointed by the Governor of Louisiana)
2008-2010	Institutional Review Board member, Tulane Medical School
2009-	LCRC Tissue Utilization Committee
2010-	Tulane Cancer Center Executive Committee
2010-	Chairman, Tulane Cancer Center Strategic Planning Committee
2013	FDA Public Workshop Panelist: Clinical Trial Design Issues - Drug & Device Development for Localized Prostate Cancer
2013-	MEDCAC (Medicare Evidence Development & Coverage Advisory Committee) Panel Member

Teaching leadership

1990-1993	Medical Oncology Attending, National Cancer Institute, Bethesda, MD, inpatient oncology service ~2 months/year (fellows)
1990-1993	Medical Oncology Attending, National Cancer Institute, Bethesda, MD, outpatient oncology clinics, 12 months/year (fellows)
1993-1998	Medical Oncology Attending, LSU Medical School and VA Medical Center, Shreveport, LA, inpatient oncology service ~2 months/year (fellows, residents, students)

1993-1998	Medical Oncology Attending, outpatient oncology attending, LSU Medical School and VA Medical Center, Shreveport, LA, outpatient oncology service, 12 months/year (fellows, residents a portion of the time)
1998-2005	Medical Oncology Attending, LSU Medical School, New Orleans, LA, inpatient oncology service ~2 months/year (fellows, residents, students)
1998-2005	Medical Oncology Attending, outpatient oncology attending, LSU Medical School, New Orleans, LA, outpatient oncology service, 12 months/year (fellows, residents a portion of the time)
2006-2007	Medical Oncology Attending, Solid Tumor Service, Brigham & Women's Hospital, Boston, MA, 4-6 weeks/year (residents)
2006-2007	Medical Oncology Attending, outpatient GU oncology clinics, Dana-Farber Cancer Institute, Boston, MA, 12 months/year (fellows, a portion of the time)
2008-	Tulane Cancer Center Attending, Inpatient and outpatient services

Scientific Advisory Boards:

1999-	Center for Prostate Disease Research-Walter Reed Hospital & US Department of Defense, Washington, DC
2000-2004	Atrix Laboratories, Ft. Collins, CO
2000-2006	Metastatin Pharmaceuticals, Washington, DC
2004-2006	Patient Advocates Against Advanced Cancer (PAACT), Grand Rapids, MI
2004-2011	Theralogix, Rockville, MD
2006-2011	Prostate Cancer Prevention Trial P01
2010-	Bellicum
2013-	Biscayne Pharmaceuticals

Miscellaneous ad hoc Advisory Boards and Consultant Agreements

1993	Henri-Beaufour Institute (France)
1993-1995	Immunex (USA)
1995	DuPont (USA)
1996	Schering (USA)
1996-2008	Cytogen (USA)
1996	Debiopharm (Swiss)
1996	Janssen (USA)
1996-1998	Berlex (German)
2003-2009	GPC Biotech (German)
2003-2004	Atrix Laboratories (USA)
2003-2005	Bracco (Italy)
2004-2007	Negma-Lerads (France)
2004-2005	Abbott (USA)
2004-	*sanofi* (France)
2004-	Dendreon
2005	Novacea (USA)
2005	Astella (Japan)

2005	Novartis (Swiss)
2005-2006	Spectrum Pharmaceuticals (USA)
2006-2007	QLT, Inc. (Canada)
2006	Roche (Swiss)
2006-2007	Sermo (USA)
2006	TEVA (Israel)
2006-2010	GlaxoSmithKline (UK)
2006	General Electric (USA)
2007	Cleveland Biolabs (USA)
2007-	Pfizer (USA)
2007-2008	Ausio Pharmaceuticals, LLC (USA)
2007-	OncoGenex (Canada)
2007	Bind Biosciences (USA)
2007-	Algeta (Norway)
2008	EUSA (USA)
2008-	Tolmar (Argentina)
2009	Ascenta (USA)
2009	Takeda (Japan)
2009-2011	Celgene
2009-2011	BMS
2009-	Medivation
2009-2011	Amgen
2009-	Bellicum
2010	ExonHit
2010-	Exelixis
2011-	Bayer
2010-2011	Centocor (JNJ)

Independent Data Safety and Monitoring Committees:

2004-2009	Chairman, IDMC, Dendreon, Provenge Vaccine Trial 9902B phase III IMPACT study
2007-2009	Chairman, Dendreon, Provenge Vaccine Trial PO-7 Study
2006-2012	IDMC (sole member), OncoGenex, OGX-427-01 Trial
2008-2010	Chairman, IDMC, Pfizer, A6181120 (Phase III study in hormone-refractory prostate cancer with sunitinib/prednisone versus prednisone
2008-2013	IDMC, Pfizer, A4061032 (Phase III Trial of axitinib in metastatic renal cancer). Chairman, 2010-
2009-2012	IDMC member, Celgene, Phase III MAINSAIL Study (Evaluation of efficacy and safety of docetaxel and prednisone with or without lenalidomide in subjects with castrate-resistant prostate cancer)
2009-2011	Chairman, IDMC, Medivation, Affirm Phase III trial in castrate-refractory Prostate Cancer with MDV3100 versus Placebo
2010-	Chairman, IDMC, OncoGenex/TEVA, OGX-011 and Docetaxel Trial
2010-	Chairman, IDMC, Medivation Affirm Trial in Prostate Cancer
2011-	Chairman, IDMC, Bavarian-Nordic, PROSTVAC-VF TRICOM Phase III trial

2012-	Chairman, IDMC, OncoGenex/TEVA. OGX-011 and Cabazitaxel Trial
2013-	Chairman, IDMC, Aragon phase III trial with ARN-509

Special NCI Service:

2005 and 2008	Site Reviewer/Advisor: National Cancer Institute Intramural Medical Oncology Prostate Cancer Program

Community Service Related to Professional Work:

1998, 2002-2005	Executive Committee, "Key to the Cure" Fundraiser, Saks Fifth Avenue, New Orleans, LA
1998-2006, 2008	Komen Foundation, New Orleans Chapter, Board of Directors
1999	Louisiana Legislative Act 1357: Provides for health insurance coverage of certain cancer patients participating in federally sponsored clinical trials. Worked with Rep. Clarkson and testified for Legislative Committees, co-wrote legislation
2001	Louisiana Legislative Act 1116: Access to Mammography Act. Worked with Rep. Clarkson and testified for Legislative Committees, co-wrote legislation
2002	Louisiana Legislative Act 41 (2002 Special Session): Louisiana Cancer Research Consortium. Co-wrote legislation: Worked with Senate President, John Hainkel and Representative Mitch Landrieu; testified for various Legislative Committees.
2002	Louisiana Legislative Act 19: Tobacco Tax: Increased tax on cigarettes: Funds from three cents per pack of each cigarette sold in the state directed to support the Louisiana Cancer Research Consortium. Worked with Senate President, John Hainkel and Representative Mitch Landrieu; testified for various Legislative Committees and co-wrote legislation with Dr. Roy Weiner of Tulane.
2004-2006	Operations Co-Chair, Hope Lodge New Orleans, American Cancer Society Project
2005-2008	Advisory Board to the Honorary Consul from Louisiana to Canada
2005-	PER Continuing Medical Education Advisory Board, Dallas, TX
2006-2008	Medical Advisory Committee, Massachusetts Prostate Cancer Coalition
2008-2011	Komen Foundation, New Orleans, Board Member
2011-	Tulane CME Advisory Committee

Professional Societies:

~1987-	American Society for Clinical Oncology
~1990-2010	American Association for Cancer Research
~1994-	American Urological Association
~1998-	Society of Urologic Oncology
~2002-2010	Society of Basic Urological Research

Editorial Boards:

1999-2001	The Prostate Journal
2002-2009	Clinical Prostate Cancer/Clinical Genitourinary Oncology

2002-	CURE (Periodical for cancer patients: CURE has won multiple awards including Top 10 magazine launches in the USA, 2002; silver and gold Eddies Award for editorial excellence for consumer health magazine category, circulation between 250,000-500,000) .
2003-2006	Urology
2011-	Asian Journal of Andrology
2011-	Journal of the Louisiana State Medical Society
2012-	Personalized Medicine in Oncology (PMO)
2012-	International Journal of Targeted Therapies (IJTT)

Editor-in-Chief:

1997-1999	Advances in Prostate Cancer, PER Publications, Dallas, TX (CME)
2002-2005	Clinical Prostate Cancer (peer-reviewed, MEDLINE listed). Note: name change in 2006 to Clinical Genitourinary Cancer.
2003-2004	New Urology (CME)
2006-	Clinical Genitourinary Cancer (Co-Chief Editor, peer-reviewed and MEDLINE listed)

Reviewer:

~1993-	Journal of the National Cancer Institute
~1995-	Journal of Clinical Oncology
~1998-	Journal of Urology
~1998-	Urology
~1999-	The Prostate
~2000-	Cancer
~2004-	International Journal of Cancer
2006-	Asian Journal of Andrology
2006-	Clinical Cancer Research
2007-	New England Journal of Medicine
2008-	Cancer Investigation
2008-	British Journal of Urology International
2008	Molecular Cancer Therapeutics
2009-	Lancet Oncology
2009-	Prostate Cancer and Prostatic Disease
2013-	Journal of Clinical investigation
2013-	The Oncologist

National Study Sections (CDC, NIH, DOD)

1996-1998	Centers for Disease Control, Chronic Disease Program, member
1998-2004	Department of Defense-Prostate Cancer Study Section in Epidemiology/Behavioral Sciences, member
1998-2005	*Ad hoc* member of various PO1s, P20s, U54s, U56s, and P30s study sections. Reviewer of NCI designated cancer center grants-P30s at Fred Hutchinson-University of Washington, Seattle, WA and University of Pennsylvania, Philadelphia, PA

2006-	Prostate Cancer Integration Panel, US Department of Defense (DOD): Oversees all peer-reviewed DOD funding for prostate cancer research in the United States
2006-2010	Elected to Executive Committee of the Prostate Cancer Integration Panel, US Department of Defense (DOD)
2008-2009	Chairman for 2008-2009, Prostate Cancer Integration Panel, US Department of Defense (DOD)

Awards and Honors:

1981	Alpha Omega Alpha (Springtime selectee and President of Tulane AOA Chapter)
1982	New Orleans Pediatric Society Award for outstanding ability in Pediatrics
1982	Hymen S. Mayerson Award for exceptional academic and/or research achievement in physiology as a medical student
1982	C.V. Mosby Book Award for outstanding scholarship as a medical student
1985	Outstanding teaching resident, Department of Medicine, Tulane Medical School
1985	First place prize for scientific presentation at the La. Chapter of the American College of Physicians
2002-2005	New Orleans "Best Doctors", by local New Orleans magazine
2004	Spirit Award Recipient, American Cancer Society, New Orleans, LA
2005-	Best Doctors in America
2008-	New Orleans "Best Doctors", by local New Orleans magazine

PART II: Research, Teaching, and Clinical Contributions

A. Narrative Report

In 1998 I was appointed as the Patricia Powers Strong Professor of Oncology, Chief of Hematology-Oncology, and Director of the Stanley S. Scott Cancer Center at Louisiana State University (LSU) Health Sciences Center in New Orleans. As a consequence of these positions and their attached responsibilities, I had broad purview over the development and coordination of basic, clinical, and epidemiologic cancer research at the largest Health Sciences Center in the State of Louisiana. From 1998-2005, the Stanley S. Scott Cancer Center grew considerably by every metric (grants/philanthropy/clinical). Growth was a consequence of increased resources that enabled investments in both faculty recruitment and equipment. These resources (approximately $10 million per year net to LSU) were primarily derived from 1) The Tobacco Settlement Funds from the Attorneys General settlement against tobacco companies and 2) A new state-wide Tobacco Tax dedicated to the establishment of the Louisiana Cancer Research Consortium (a legislatively established collaborative effort between the LSU and Tulane Health Sciences Centers). The tobacco tax and the collaborative effort between LSU and Tulane were the result of an intense and successful lobbying effort that Roy Weiner (Tulane) and I helped to lead in 2002. Full credit for these efforts must be given to the (now deceased) Senate President John Hainkel, Representative Mitch Landrieu, and Tulane Cancer Center Director Roy Weiner who were also critical leaders of this process.

Management of the aforementioned activities had essentially been a full time job, however I continued to see patients in the clinic, teach, attend in the hospital, and focus my research efforts predominantly on clinical and translational aspects of advanced prostate cancer. Over the past several years, as a consequence of collaborative arrangements, I have been a principal investigator or co-principal investigator (and author on the peer-reviewed manuscripts) on four pivotal multi-institutional trials that have lead to FDA approvals. This includes samarium-153 lexidronam (Quadramet), two formulations of leuprolide acetate (Eligard) and cabazitaxel (Jevtana). I anticipate that radium-223 will be approved in 2013. I was the North American PI on this trial.

I have chaired and continue to chair and participate in various independent data monitoring committees (IDMC). These are critical aspects of large clinical trials. Three of the pivotal trials have lead to FDA approvals including sipuleucel-T, axitinib, and enzalutamide.

Direct teaching and mentoring of hematology-oncology fellows, medical residents, and medical students at LSU, Harvard, and Tulane have also occurred on a regular basis. In 2004, I mentored the fellow winning the top research prize in the LSU Dept. of Medicine research day.

As part of the Cancer Center's outreach programs in Louisiana, I was instrumental in establishing, promoting, and funding both community- and hospital-based educational programs promoting early detection of cancer. These programs have particularly targeted low income and minority populations in the state of Louisiana. Federal, Foundation, and State Legislative grants were obtained for the establishment of cancer-focused early detection programs, not only in New Orleans, bit also throughout the state. As Chairman of the Governor-appointed Louisiana Cancer and Lung Trust Fund Board, I was instrumental in establishing and funding new state-wide collaborations between CDC funded programs, Komen Foundation funded programs, and multiple practice sites.

I returned to New Orleans after serving at the Dana-Farber/Harvard Cancer Center from March, 2006-November, 2007. At Dana-Farber I served as head of the clinical trials group in the Lank Genitourinary Oncology Program. I also served as co-Chair of the Registry in PSA Rising after Local Therapy in Prostate Cancer (COMPARE Registry). I have served as co-PI (with Dr. Mathew Freedman) on a project in the Harvard SPORE submission in prostate cancer (Kantoff-PI). This was favorably scored and funding occurred but because of the change in location to Tulane, I have relinquished this grant to a Harvard investigator. I currently serve as the North American PI on the ALYSYMPCA trial using radium-223 in advanced prostate cancer and National co-PI on a trial comparing bicalutamide plus or minus dutasteride in advanced prostate cancer. I am also International Co-PI on the FIRSTANA trial with cabazitaxel and doectaxel.

I serve as the Medical Oncology Co-Chairman of the GU Committee of RTOG. I serve as national co-PI on RTOG 0521, RTOG 0622, and also on RTOG trial 0621.

B. **Selected Funding Information**

1993-1994	NIH contract Serum Sample and Patient Demographic Data on Elderly Males Without Prostate Cancer	PI

1993-1998	Parke-Davis Study of Suramin vs. Placebo in Patients with Metastatic Hormone Refractory Disease	Site-PI
1994-1995	Louisiana Cancer & Lung Trust Fund A Pilot Study for the Early Detection of Prostate in African Americans with a Familial Risk of the Disease	PI
1995-1996	Louisiana Cancer & Lung Trust Fund Developing Prevention Programs for African American Men	PI
1995-1996	Matrix A Pilot Study to Evaluate the Histologic Response to CDDF-e Therapeutic Implant (MPI 5010) Administered Prior to Radical Prostatectomy in Patients with Stage A, B, or C Prostatic Carcinoma	Site-PI
1995-1997	CDC-Demonstration Project Developing Prostate Cancer Early Detection Demonstration Program	PI
1995-1998	SWOG Prostate Cancer Prevention Trial	Site-PI
1995-1998	Cytogen Study of Intravenously Administered ^{111}In-Capromab Pendetide in the Evaluation of Patients with Prostate Cancer	Site-PI
1995-1998	Cytogen Open-Label Study of Intravenously Administered ^{153}Sm-EDTMP (CYT-424) for the Treatment of Patients with Bone Pain- Secondary Metastatic Carcinoma	Site-PI
1995-1998	Schering-Plough Comparative Study of the Clinical Efficacy of Two Dosing Regimens of EULEXIN	Site PI
1996-1998	Janssen A Phase III Trial to compare the efficacy and the tolerability of Liarozole Versus prednisone in Patients with Relapsed Hormone-Resistant Prostate Cancer	Site-PI
1996-1998	Zeneca A Randomized Double-Blind Comparative Trial of Bicalutamide versus Placebo in Patients with Early Prostate Cancer	Site-PI
1996-1998	Janssen & Kyowa Protocol for a Phase II Study of KW2189 for the Treatment of Advanced Renal Cell carcinoma	Site-PI
1996-1998	Ligand Pharmaceuticals A Multicenter Phase 2 Evaluation of a Combination Therapy of TARGRETIN oral capsules (LGD1069) and INTRON A (Interferon-alfa-2b) in Patients with Advanced Renal Cell Carcinoma	Site-PI
1996-1998	Cytogen Phase II Study of Ascending Multiple Dose ^{153}Sm-lexidronam (Quadramet) in Combination with Total Androgen Blockade for the Treatment of Patients with Stage D2 Prostate Carcinoma	Site-PI
1997-1998	CaPCURE Foundation Award Clinical Utility of Determining the Androgen Receptor Polymorphism.	Site PI
1997-1998	Lilly Phase I Clinical and Pharmacological Evaluation of Escalating Doses of LY320236 Administered in Patients with Metastatic Prostate Cancer	Site-PI

1997-1998	Abbott	Site-PI
	A Phase II, Double-Blind Comparison of the Safety and Efficacy of ABT-627 versus Placebo in Subjects with Symptomatic Hormone Refractory Prostate Cancer	
1998-2002	NCI/ P20	PI
	Cancer Center Planning Grant	
1998-2000	Pharmacia & Upjohn	Site-PI
	Estramustine Phosphate in Advanced Prostate Cancer	
2000-2002	Baptist Community Ministries/Daughters of Charity	PI
	Partners in Health: The Breast and Cervical Health Cooperative	
2000-2003	ASPH/CDC	Co-PI
	Geographic Information Systems and Prostate Cancer	
2000-2004	Atrix	Site-PI
	LA-2575 for hormonally Sensitive Prostate Cancer	
2001-2004	Medarex	Site-PI
	MDX-010 With and Without Docetaxel in Hormone-Refractory Prostate Cancer	
2002-2006	GPC-Biotech	Site-PI
	JM-216 in Hormone Refractory Prostate Cancer	
2002-2006	HRSA	PI
	Design and Construction of a Cancer Prevention and Research Facility	
2002-2005	Atrix	Site-PI
	LA-2580 in Hormonally Sensitive Prostate Cancer	
2003-2006	Louisiana Cancer Research Consortium	Co-PI
2003-2006	Department of Energy	PI
	Funding for Cancer Control Personnel	
2004-2006	GlaxoSmithKline	Site-PI
	Dutasteride in Recurrent Prostate Cancer	
2004-2006	*sanofi*	Site-PI
	COMPARE – Registry for Recurrent Prostate Cancer	
2004-2006	CDC	Site PI
	Cancer Prevention and Control in High Risk Families	
2008-	GlaxoSmithKline (GSK)	Site PI
	TARP randomized clinical trial	
2007-2009	S*anofi*	Site PI
	TROPIC randomized clinical trial (XRP-6258)	
2007-2008	Prostate SPORE project 2 co-PI	co-PI
	Genetic and Clinical characterization of the 8q24 risk locus	
2008-	Cougar Biotechnology	Site-PI
	Randomized Abiraterone post-docetaxel (Cougar 301)	
2008-	AstraZeneca	Site-PI
	ENTHUSE study (ZD4054 versus placebo in M0 prostatate)	
2009-	Cougar Biotechnology	Site-PI
	Randomized Abiraterone pre-docetaxel (Cougar 302)	
2009-	Algeta	Site PI
	ALSYMPCA (Alpharadin randomized study in prostate cancer)	

C. Report of Clinical Activities

In terms of clinical services, for the past 22 years I attended on the inpatient oncology services, typically 2-3 months per year. These attending services have occurred in the context of teams that included fellows alone (at the NCI), or a combination of medical students, house officers,

and fellows for oncology services at Louisiana State University affiliated hospitals. In addition, I have regularly had oncology fellows participate in my clinics. At the NCI, I supervised the fellows in the prostate cancer clinic from 1990-1993 and this clinic consistently had approximately 8 fellows per clinic. At LSU, the clinics were configured differently and fellows electively rotated through my clinic focusing on genitourinary oncology. Each year several fellows would rotate through for a total of 3-6 fellows per year while on the faculty at LSU and at Tulane this is an option as well. I never ceased seeing patients and attending on the inpatient services despite numerous administrative responsibilities. While in Boston, I was integrated into the teaching and attending rotations at Dana Farber Cancer Institute and the Brigham and Women's hospital both in the attending and conference schedules. At Tulane, I am rotating on the general oncology service three-four months per year and attending in clinics twice weekly.

1. Description of clinical practice

My current clinical practice has been based at Tulane Cancer Center and the Tulane urology multi-disciplinary clinic. I focus on urologic malignancies and have nearly 90% of my patients with prostate cancer. I am now involved with a wide variety of protocols covering both translational issues and advanced treatments.

2. Patient Load

I see 25-50 patients per week with urologic malignancies, about 3-5 new patients per week. Currently about 1000 patients, mostly prostate cancer, are under my care.

3. Clinical Contributions

My clinical contributions are documented within the overall context of my publications. Particularly noteworthy in my mind is having been a lead author on two studies that have been pivotal in terms of FDA approvals for new drug applications (NDAs). These studies included a new radio-isotopic treatment for bone metastases in prostate cancer (Quadramet), as well as a new formulation for hormonal treatment of prostate cancer (4 month Eligard). I was co-PI on the TROPIC trial which was positive for survival and lead to an FDA approval. I've been involved in a wide variety of clinical and translational investigations over the last 22 years, as detailed within my publications and abstracts. At this time I am a national PI or Co-PI on 4 separate prostate cancer studies.

4. Other relevant information about clinical role

I have been recognized with several clinical awards while in Boston and New Orleans for my patient care including the Spirit Award by the American Cancer Society and named to "Best Doctors" by various publications. In 2005-2013, I was named as one the "Best Doctors in America" by Best Doctors, Inc. This is based upon a peer survey (according to that organization).

Publications:

1. Spirtes MA, Gerber AR, Wood KS, **Sartor AO**, and Christenson CW. The effect of MIF-I on in vitro cGMP production in a particulate rat brain fraction. Neuropharmacology 1980; 19:687-89
2. Spirtes MA, Woods KS, **Sartor AO**, Gerber AR, and Wheeler WF. The in vitro effects of L-Prolyl L-Leucyl glycinamide (MIF-I) on the guanylate cyclase system of a rat brain mitochondrial fraction. Neuropeptides 1981; 1:391-400
3. **Sartor O** and Bowers CY. Hypothalamic hypophysiotropic hormones: Generalizations, concepts, and mechanisms. Rational Drug Therapy 1983; 17(7):1-6.
4. **Sartor O**, Bowers CY, and Chang D. Parallel studies of His-D-Trp-Ala-Trp-D-Phe-Lys-NH2 and hpGRF-44-NH2 in rat primary pituitary cell monolayer culture. Endocrinology 1985; 116:952-57
5. **Sartor O**, Bowers CY, Reynolds GA, and Momany FA. Variables determining the GH response of His-D-Trp-Ala-Trp-D-Phe-Lys-NH2 in the rat. Endocrinology 1985: 117:1441-47
6. **Sartor O** and Sander GE. Unusual variant of eosinophilic fascitis. Southern Med J 1985; 78:1387-89
7. **Sartor O** and Anday E. Campylobacter jejuni enteritis in a premature neonate. Southern Med J 1987; 80:1593-94
8. Lebacq-Verheyden AM, Krystal G, **Sartor O**, Way J, and Battey JF. The rat prepro-gastrin releasing peptide gene is transcribed from two initiation sites in the brain. Mol Endocrinol 1988; 2:556-63
9. Battey JF, Lebacq-Verheyden AM, Krystal G, Markowitz S, **Sartor O**, and Way J. Expression, regulation, and post-translational processing of the human prepro-gastrin releasing peptide gene. Annals of the New York Academy of Sciences 1988; 547:30-40.
10. **Sartor O**, Gregory FS, Templeton NS, Pawar S, Perlmutter RM, and Rosen N. Selective expression of alternative lck mRNAs in human malignant cell lines. Mol Cell Biol 1989; 9:2983-88
11. Rosen N, **Sartor O**, Foss F, and Bolen JB. Altered expression of src-related tyrosine kinases in human colon cancer. Cold Spring Harbor Symposia (Cancer Cells 7) 1989; 161-66.
12. Foss FM, Veillette A, **Sartor O**, Rosen N, and Bolen JB. Alterations in the expression of $pp60^{c\text{-}src}$ and $p56^{lck}$ associated with butyrate-induced differentiation of human colon carcinoma cells. Oncogene Research 1989; 5:13-23.
13. **Sartor O**, Sameshima JH, and Robbins KC. Differential association of cellular proteins with src-family protein-tyrosine kinases. J Biol Chem 1991; 266:6462-66.
14. **Sartor O**. Book review for: molecular genetics in cancer diagnosis, edited by J. Cossman. J Natl Cancer Inst 1991; 83:877.
15. Grem JL, McAtee N, Murphy RF, Balis FM, Steinberg SM, Hamilton JM, Sorenson JM, **Sartor O**, Kramer BS, Goldstein LJ, Gay LM, Caubo KM, Goldspiel B, and Allegra CJ. A pilot study of interferon alpha-2a in combination with 5-fluorouracil plus high-dose leucovorin in metastatic gastrointestinal carcinoma. J Clin Oncology 1991; 9:1811-20.
16. Bowers CY, **Sartor AO**, Reynolds GA, and Badger TM. On the actions of the growth hormone-releasing hexapeptide, GHRP. Endocrinology 1991; 128:2027-35.
17. **Sartor O**, Moriuchi R, Sameshima J, Severino M, Gutkind JS, and Robbins KR. Diverse biologic properties imparted by the c-fgr proto-oncogene. J Biol Chem 1992; 267:3460-65.

18. Cardinali M, **Sartor O**, and Robbins KR. Suramin, an experimental chemotherapeutic drug, activates the receptor for epidermal growth factor and promotes growth of certain malignant Cells. J Clin Invest 1992; 89:1242-47.
19. **Sartor O**, McLellan CA, Myers CE, and Borner MM. Suramin rapidly alters tyrosine phosphorylation in prostate cancer cell lines. J Clin Invest 1992; 90:2166-74.
20. **Sartor O**, McLellan CA, and Chiueh T. Comparison of src family cDNAs reveals distinct mechanisms underlying focus formation in transfected fibroblasts. J Biol Chem 1992; 267:21044-051.
21. Shlaifer D, Cooper MR, Attal M, **Sartor O**, Trepel JB, Laurent G, and Myers CE. Myeloperoxidase: An enzyme involved in vincristine resistance in human myeloblastic leukemia. Blood 1993; 81:482-89.
22. Thibault A, Figg WD, Cooper MR, Prindiville S, **Sartor O**, and Myers CE. Anaphylactoid reaction with suramin. Pharmacotherapy 1993; 13:656-57.
23. **Sartor O**, and Robbins KC. Substrate specificity for normal but not mutationally activated variants of src family kinases. J Biol Chem 1993; 268:21014-020.
24. Worland PJ, Kaur G, Stetler-Stevenson M, Sebers S, **Sartor O**, and Sausville EA. Alteration of the phosphorylation state of $p34^{cdc2}$ kinase by the flavone L86-8275 in breast carcinoma cells. Correlation with decreased H1 kinase activity. Biochemical Pharmacology 1993; 46:1831-40.
25. Myers CE, Cooper M, Ranson M, **Sartor O**, and Sausville E. Antitumor activity of polyanions. In Holland and Frei's, Cancer Medicine. 1993; 806-14.
26. Borner M, and **Sartor O**. More is not always better: a case for low-dose leucovorin. J Clin Oncology 1993; 11:382-83.
27. Myers C, Trepel J, **Sartor O**, Cooper M, Ranson M, Toko T, Linehan MW. Antigrowth Factor Strategies. Cancer. 1993; 71(3Suppl):1172-8.
28. Myers CE, Cooper M, Ranson M, **Sartor O**, and Sausville E. Antitumor Activity of Polyanions. In Holland and Frei's, Cancer Medicine, pgs 806-814, 1993.
29. Myers C, Trepel J, **Sartor O**, Cooper M, Ranson M, Toko T, and Linehan MW. Antigrowth factor strategies. Cancer (Supplement) 1993; 71:1172-78.
30. **Sartor O**, Cooper M, Weinberger M, Headlee D, Thibault A, Tomkins A, Steinberg S, Figg WD, Linehan WM, and Myers CE. Surprising activity of flutamide withdrawal, when combined with aminoglutethimide, in treatment of "Hormone-Refractory" prostate cancer. J Natl Cancer Institute 1994; 86:222-27.
31. **Sartor O**, Cooper M, Khleif S, and Myers CE. Suramin decreases circulating levels of insulin-like growth factor-I. Am J Med 1994; 96:390.
32. Thibault A, Cooper MR, Figg WD, Venzon DJ, **Sartor AO**, Tomkins AC, Weinberger MS, Headlee DJ, McCall NA, Samid D, Myers CE. A phase I and pharmacokinetic study of intravenous phenylacetate in patients with cancer. Cancer Res 1994; 54:1690-94.
33. Figg WD, Thibault A, **Sartor AO**, Mays D, Headlee D, Calis KA, and Cooper MR. Hypothyroidism associated with aminoglutethimide in patients with prostate cancer. Arch of Internal Med 1994; 154:1023-25.
34. Figg WD, Thibault A, **Sartor O**, Cooper MR, Headlee D, Tompkins A, Humphrey J, Dawson N, and Myers CE. Acute renal toxicity associated with suramin in the treatment of prostate cancer. Cancer 1994; 74:1612-14.
35. Figg WD, Walls RG, Cooper MR, Thibault A, **Sartor O**, McCall NA, Myers CE, and Samid D. In vitro antitumor effects of hydroxyuruea on hormone-refractory prostate cancer cells and its potentiation with phenylbutyrate. Anti-Cancer Drugs 1994; 5:336-42.

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38. Figg WD, Thibault A, Cooper MR, Reid R, Headlee D, Dawson N, Kohler DR, Reed E, and **Sartor O**. A phase I study of the somatostatin analogue somatuline in patients with metastatic hormone-refractory prostate cancer. Cancer 1995; 74: 2159-64.
39. Figg WD, **Sartor O**, Cooper MR, Thibault A, Bergan RC, and Myers CE. Prostate specific antigen decline following the discontinuation of flutamide in patients with stage D2 prostate cancer. Am J Med 1995; 98:412-14.
40. Figg WD, McCall NA, and **Sartor O**. The in vitro response of four antisteroid receptor agents on the hormone-responsive prostate cancer cell line LNCaP. Oncology Reports 1995; 2:295-98.
41. Sartor BM, **Sartor O**, and Flanders KC. Analogous tamoxifen and estrogen effects on transforming growth factor-betas 1 and 2 in the rat uterus. J. Reprod Toxicol 1995; 9:225-31
42. Dawson NA, Cooper MR, Figg WD, Headlee DJ, Thibault A, Bergan RC, Steinberg SM, Sausville EA, Myers CE, and **Sartor O**. Antitumor activity of suramin in hormone-refractory prostate cancer controlling for hydrocortisone treatment and flutamide withdrawal as potentially confounding variables. Cancer 1995; 76:453-62.
43. **Sartor O**. Prostate-specific antigen changes before and after administration of an angiogenesis inhibitor. Oncol Reports 1995; 2:1101-02.
44. Middleman MN, Lush RM, **Sartor O**, Reed E, and Figg WD. Prolonged response to flutamide withdrawal and initiation of aminoglutethimide in a patient with metastatic prostate cancer. J Oncol Pharm Practice 1995; 1:45-47
45. Borner MM, Myers CE, **Sartor O**, Sei V, Toko T, Trepel JB, Schneider E. Drug-induced apoptosis is not necessarily dependent on macromolecular synthesis in the p53-negative human prostate cancer cell line PC-3. Cancer Res 1995; 2122-2128
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Patents:

1. Koochekpour, **Sartor AO**, inventors. Saposin C and receptors as targets for treatment of benign and malignant disorders. US patent awarded January 23, 2007 (patent no. 7,166,691).

7/3/2014

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 5

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Antonarakis & Eisenberger, Phase III Trials with Docetaxel-Based Combinations for Metastatic Castration-Resistant Prostate Cancer: Time to Learn From Past Experiences, 31(14) J. Clin. Oncol., 1709-12 (2013)	
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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 5

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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		Diéras et al., Larotaxel in Combination with Trastuzumab in Patients with HER2+ Metastatic Breast Cancer: Interim Analysis of an Open Phase II Label Study, 26 (15S) J. Clin. Oncol. (Meeting Abstracts) Suppl. 1070 (May 2008)	
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		Mita et al., Phase I and Pharmacokinetic Study of XRP6258 (RPR 116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors, 15(2) Clinical Cancer Research, 723-30 (2009) (previously cited)	

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Sheet 3 of 5

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Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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		Mulcahy, Phase 3 Trial of Immunotherapy for Metastatic Prostate Cancer Terminated, Medscape Medical News (October 17, 2009), [retrieved on June 26, 2014] from: http://www.medscape.com/viewarticle/582220	
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		Van Hook et al., Orteronel for the Treatment of Prostate Cancer, 10(5) Future Oncol., 803-811 (2014)	

Examiner Signature		Date Considered	

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Sheet 4 of 5

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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		Wiechec & Hanson, The Effect of Genetic Variability on Drug response in Convention Breast Cancer Treatment, 625 Eur. J. Pharmacol., 122-130 (2009)	
		Williams, Discontinued Drugs in 2008: Oncology Drugs, 18(11) Expert. Opin. Investig. Drugs 1581-1594 (2009)	
		Wirth & Froschermaier, The Antiandrogen Withdrawal Syndrome, 25 (Suppl. 2) Urol. Res., S67-71 (1997)	
		Zatloukal et al., Randomized Multicenter Phase II Study of Larotaxel (XRP9881) in Combination with Cisplatin or Gemcitabine as First-Line Chemotherapy in Nonirradiable Stage IIIB or Stage IV Non-Small Cell Lung Cancer, 3 J. Thorac. Oncol. 894-901 (2008)	
		Zielinski & Chi, Custirsen (OGX-011): A Second-Generation Antisense Inhibitor of Clusterin in Development for the Treatment of Prostate Cancer, 8(1) Future Oncol., 1239-1251 (2012)	
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		Avastin (bevacizumab), Prescribing Information (Label) July 2009	
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Sheet 5 of 5

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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		Bristol-Myers Squibb Reports Results for Phase 3 Trial of Yervoy® (Ipilimumab) in Previously-Treated Castration Resistant Prostate Cancer, Press Release September 12, 2013 [retrieved on June 27, 2014] from: http://news.bms.com/press-release/rd-news/bristol-myers-squibb-reports-results-phase-3-trial-yervoy-ipilimumab-previousl	
		Clinical Trials.gov, Satraplatin in Hormone Refractory Prostate Cancer Patients Previously Treated with one Cytotoxic Chemotherapy Regimen [retrieved on June 27, 2014] from: https://clinicaltrials.gov/ct2/show/NCT00069745?term=SPARC&cond=prostate&rank=3	
		Clinical Trials.gov, Larotaxel every 3 weeks vs. capecitabine in patients with metastatic breast cancer progressing after taxanes and anthracycline therapy [retrieved on June 24, 2014] from: https://clinicaltrials.gov/ct2/show/NCT00081796?term=larotaxel&rank=7	
		Clinical Trials.gov, Larotaxel plus cisplatin vs. gemcitabine plus cisplatin in first line treatment of patients with locally advanced/metastatic bladder cancer [retrieved on June 24, 2014] from: https://clinicaltrials.gov/ct2/show/NCT00625664?term=larotaxel&rank=4	
		Clinical Trials.gov, Larotaxel vs. 5-FU or capecitabine in patients with pancreatic cancer previously treated with gemcitabine [retrieved on June 24, 2014] from: https://clinicaltrials.gov/ct2/show/NCT00417209?term=larotaxel&rank=2	
		Press Release: OncoGenex Announces Top-Line Survival results of Phase 3 SYNERGY Trial Evaluating Custirsen for Metastatic Castration-Resistant Prostate Cancer, PRNewswire April 28, 2014	
		Press Release: Roche Provides Update on Phase III study of Avastin in Men with Late Stage Prostate Cancer, Media Release March 12, 2010 [retrieved on June 27, 2014] from: http://www.roche.com/media/media_releases/med-cor-2010-03-12.htm	
		Press Release: Takeda Announces Termination of Orteronel (TAK-700) Development for Prostate Cancer in Japan, U.S.A. and Europe, June 19, 2014 [retrieved on June 27, 2014] from: http://www.takeda.com/news/2014/20140619_6615.html	
		Jevtana NDA Clinical Overview, excerpt, (2014), pp.12-13	

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/456,720	Filing Date 04/26/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**380**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**380**

APPLICATION AS AMENDED – PART II

AMENDMENT **07/16/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 30	Minus	** 33	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***10	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/KIMBERLY D. JONES/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/456,720	04/26/2012	Sunil GUPTA	FR2009/121 US CNT	1083

5487 7590 07/15/2014

ANDREA Q. RYAN
SANOFI
55 Corporate Drive
MAIL CODE: 55A-505A
BRIDGEWATER, NJ 08807

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
07/15/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi.com
andrea.ryan@sanofi.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/456,720	GUPTA, SUNIL	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1629	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JAMES D. ANDERSON*.

(2) *Kelly Bender & Aude Gaslonde (Sanofi)*.

(3) *Raymond Mandra*.

(4) *Oliver Sartor*.

Date of Interview: *10 July 2014*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☒102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *Pending claims*.

Identification of prior art discussed: *Prior art of record*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussion focused on the rejections set forth in the Non-Final Office Action mailed 4/16/2014. Applicants presented a draft 1.132 Declaration for discussion purposes, which was provided to demonstrate prior art knowledge regarding treatment of the claimed patient population and the unpredictability and failure of other taxanes in Phase III clinical trials despite demonstrating efficacy in Phase I and Phase II clinical trials. The Examiner agreed that amending the independent claims to recite 1) treatment of prostate cancer in patients who had progressed during or after docetaxel treatment and 2) administering a dose of 20 to 25 mg/m2 cabazitaxel or a hydrate or solvate thereof in combination with a corticoid would be allowable. Applicants will file a response, claim amendments, and the aforementioned 1.132 Declaration.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES D ANDERSON/ Primary Examiner, Art Unit 1629	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Please type a plus sign (+) inside this box → ☑

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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		7,772,274		PALEPU	08-10-2010	
		2012/0077845		DALTON, et al.	03-29-2012	
		2012/0115806		MAGHERINI	05-10-2012	
		2011/0237540		CRAWFORD, et al.	09-29-2011	
		5,889,043		BOUCHARD, et al.	03-30-1999	
		2011/0105598		GURJAR, et al.	05-05-2011	
		6,160,135		BOUCHARD, et al.	12-12-2000	
		5,962,705		DIDIER, et al.	10-05-1999	
		6,346,543		BISSERY, et al.	02-12-2002	
		6,403,634		BISSERY	06-11-2002	
		2004/0126379		ADOLF, et al.	07-01-2004	
		2005/0070496		BOROVAC, et al.	03-31-2005	
		2011/0160159		RYAN	06-30-2011	
		2008/0279923		BRADKE, et al.	11-13-2008	
		2010/0311825		RORTAIS, et al.	12-09-2010	
		2011/0144362		BILLOT, et al.	06-16-2011	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	Kind Code[5] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		WO	2011/063421		WOLFGANG, et al.	05-26-2011		
		WO	94/18164		OJIMA	08-18-1994		
		FR	2732340		BOUCHARD, et al.	10-04-1996		
		WO	96/30356		BOUCHARD, et al.	10-03-1996		
		WO	00/10547		BISSERY, et al.	03-02-2000		
		WO	2006/062811		GRUENEBERG, et al.	06-15-2006		
		WO	2010/117668		ELIASOF, et al.	10-14-2010		
		WO	2010/128258		MAGHERINI	11-11-2010		
		WO	2011/051894		GUPTA	05-05-2011		
		WO	2011/124689		CHAUCHEREAU, et al.	10-13-2011		

Examiner Signature		Date Considered	

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[1] Unique citation designation number. [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 6

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	Kind Code[5] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		WO	2011/130317		MUTZ, et al.	10-20-2011		
		WO	2011/130566		SLAWIN, et al.	10-20-2011		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 6

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		CISTERNINO, et al., Nonlinear Accumulation in the Brain of the New Taxoid TXD258 Following Saturation of P-Glycoprotein at the Blood-Brain Barrier in Mice and Rats, British Journal of Pharmacology, (2003), Vol. 138, pp. 1367-1375	
		PIVOT, et al., Multicenter Phase 2 Study of XRP6258 in Taxane- Resistant Metastatic Breast Cancer (MBC) Patients (pts), Breast Cancer Research and Treatment, (2005), Vol. 94, No. Suppl. 1, p. S68, Abst. 1084	
		ATTARD, et al., Update on Tubulin-Binding Agents, Pathologie Biologie, Vol. 54, (2006), pp. 72-84	
		BEARDSLEY, et al., Systemic Therapy After First-Line Docetaxel in Metastic Castration-Resistant Prostate Cancer, Current Opinion in Supportive and Palliative Care, (2008), Vol. 2, No. 3, pp.161-166,	
		PIVOT, et al., A Multicenter Phase II Study of XRP6258 Administered as a 1-h i.v. Infusion Every 3 Weeks in Taxane-Resistant Metastatic Breast Cancer Patients, Annals of Oncology, Vol. 19, No.9, pp. 1547-1552, (2008)	
		The National Horizon Scanning Centre of National Institute for Health Research, Cabazitaxel (XRP-6258) For Hormone Refractory, Metastatic Prostate Cancer - Second Line After Docetaxel, University of Birmingham, pp. 1-6, (2009)	
		Sanofi-Aventis Press Release: 2006: In a Difficult Environment, Another Year of Growth in Adjusted EPS Excluding Selected Items, (February 13, 2007), pp. 1-31	
		BUONERBA, et al., Docetaxel Rechallenge in Castration-Resistant Prostate Cancer: Scientific Legitimacy of Common Clinical Practice, European Urology, (2010), Vol. 58, No. 4, pp. 636-637	
		Di LORENZO, et al., Castration-Resistant Prostate Cancer: Current and Emerging Treatment Strategies, Drugs, (2010), Vol. 70, No. 8, pp. 983-1000	
		YOO, et al., XRP6258-Induced Gene Expression Patterns in Head and Neck Cancer Carcinoma, Laryngoscope, (2010), Vol. 120, No. 6, pp.1114-1119	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 6

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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		SHABAFROUZ, et al., New Drugs at the Horizon for Men With Prostate Cancer, Revue Medicale Suisse, (2010), Vol. 6, No. 250, pp. 1057-1058 & 1060-1061	
		DORFF, Cabazitaxel in Prostate Cancer: Stretching a String, Lancet, (2010), Vol. 376, No. 9747, pp. 1119-1120	
		BOUCHET, et al., Cabazitaxel, a New Taxane With Flavorable Properties, Drugs of Today, (2010), Vol. 46, No. 10, pp.735-742	
		PAL, et al., Critical Appraisel of Cabazitaxel in the Management of Advanced Prostate Cancer, Clinical Interventions in Aging, (2010), Vol. 5, pp.395-402	
		FIGG, et al., Cabazitaxel : Filling One of the Gaps in the Treatment of Prostate Cancer, Cancer Biology & Therapy, Vol. 10, No. 12, pp.1233-1234	
		SARTOR, et al., Improving Outcomes With Recent Advances in Chemotherapy for Castrate-Resistant Prostate Cancer, Clinical Genitourinary Cancer, (2010), Vol. 8, No. 1, pp.23-28	
		POUESSEL, et al., Actualities in Prostate Cancer in ASCO Annual Meeting 2010, Bulletin du Cancer. (2010), Vol. 97, No. 12, pp. 1563-1572	
		RICHARDS, Improved Survival in Second-Line Advanced Prostate Cancer Treated With Cabazitaxel, Nature Reviews Clinical Oncology, (2010), Vol. 7, No. 12, p. 671	
		DE BONO, et al., Cabazitaxel or Mitoxantrone With Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated With Docetaxel: Final Results of a Multinational Phase III Trial (TROPIC)., 46th Annu Meet Am Soc Clin Oncol (ASCO), J. Clin. Oncology, (2010) 28:15S (Suppl), Abst 4508	
		DENIS, et al., Phase I and Pharmacokinetic Study of RPR116258A, A Novel Taxane Derivative, Administered Intravenously over 1 hour every 3 weeks, Clinical Cancer Research, Vol. 6, (2000), (Supplement), Abstract 568, p.4579s	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 6

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		LORTHOLARY, et al., Phase I and Pharmacokinetics (PK) Study of RPR 116258A Given as 1-hour Infusion in Patients (pts) With Advanced Solid Tumors, Clinical Cancer Research, Vol. 6, (2000), (Supplement), Abstract 569, pp.4579s-4580s	
		OUDARD, et al., Cabazitaxel Plus Prednisone/Prednisolone Significantly Increases Overall Survival Compared to Mitoxantrone Plus Prednisone/Prednisolone in Patients With Metastatic Castration-Resistant Prostate Cancer (MCRPC) Previously Treated With Docetaxel: Final Results With Updated Overall Survival of a Multinational Phase III Trial (TROPIC), Ann. of Oncology, Vol. 21, (Suppl. 8), p. viii272, (2010), Abstract 871PD	
		KRIS, et al., Clinical Cancer Advances 2010: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology, J Clin Oncology, (2010), Vol. 28, No. 36, pp. 5327-5347, 947	
		Drug Data Report, Antimitotic Drugs, (2003), Vol. 25, No. 6, p. 550, (2003)	
		Drug Data Report, Cabazitaxel, (2010), Vol. 32, No. 10, pp. 999-1017 at p.1012	
		Sanofi-Aventis Press Release: Resilient Sales and Business EPS in Q3 2010, (October 28, 2010), pp. 1-24	
		Sanofi-Aventis Press Release: EPS Growth in Q2 2010, (July 29, 2010), pp. 1-27	
		ClinicalTrials.gov, Safety and Pharmacokintic Study of Cabazitaxel in Patients With Advanced Solid Tumors and Liver Impairment, Web site, (2010), pp. 1-7 [retrieved on January 6, 2014]	
		Sanofi-Aventis Press Release: Q1 2010: A Good First Quarter, (April 29, 2010), pp. 1-19	
		ClinicalTrials.gov, Effect of Cabazitaxel on the QTc Interval in Cancer Patients (QT-Cab), Web site, (2010) March 24, pp. 1-7 [retrieved on January 6, 2014]	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 6 of 6

Complete if Known	
Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Group Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 - US - CNT

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		Sanofi-Aventis Press Release: Sanofi-Aventis Delivers Double-Digit EPS Growth in 2009 as the Transformation Program Progresses, (February 10, 2010), pp. 1-26	
		ClinicalTrials.gov, A Study to Evaluate the Effects of Combining Cabazitaxel With Cisplatin Given Every 3 Weeks in Patients With Advanced Solid Cancer, Web Site, (July 22, 2009), pp. 1-7 [retrieved on January 6, 2014]	
		Sanofi-Aventis Press Release: Sanofi-Aventis Delivers 2008 Results Above Guidance, (2009), February 11, pp. 1-27	
		NUMATA, et al., The Preliminary Results of Docetaxel-Prednisolone Combination Therapy for the Japanese Pateients With Hormone-Refractory Prostate Cancer, Acta Urol. Jpn., Vol. 53, pp. 93-97, (2007)	
		MIURA, et al., A Case of Hormone-Refractory Prostate Cancer (HRPC) With Tumor Fever Responding to Docetaxel Plus Prednisolone Therapy, Jpn J Cancer Chemother, Vol. 33, No. 6, pp.841-844, (2006)	
		SHIMAZUI, et al., Three-Weekly Docetaxel With Prednisone is Feasible for Japanese Patients With Hormone-Refractory Prostate Cancer: A Retrospective Comparative Study With Weekly Docetaxel Alone, Jpn J Clin Oncol, (2007), Vol. 37, No. 8, pp.603-608	
		KOLA, et al., Can the Pharmaceutical Industry Reduce Attrition Rates?, Nature Reviews Drug Discovery, Vol. 3, (2004), pp. 711-715	
		DIMASI, et al., Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs, Nature, Vol. 87, No. 3, pp. 272-277, (2010)	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
GUPTA, et al.

Examiner:
James D. Anderson

Application No.:
13/456,720

Art Unit:
1629

Filed:
April 26, 2012

Title: **NOVEL ANTITUMORAL USE OF CABAZITAXEL**

CERTIFICATE OF EFS-WEB TRANSMISSION
I hereby certify that the correspondence below is being transmitted via the USPTO's electronic filing system in accordance with 1.6(a)(4), on

April 28, 2014
Date of Deposit

/Brian Pritchett/
Signature

TO: Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Attached are the following documents:

			Number of Pages
☐	Application Data Sheet		
☐	Declaration		
☐	Drawings		
☐	Extension of Time		
☒	Information Disclosure Statement and Form 1449		10
☐	Response to		
☐	Specification, Claims and Abstract	Specification	
		Claims	
		Abstract	
☐	Transmittal Letter:		
☐	Other *(specify):*		
☐	Other *(specify):*		
☐	Other *(specify):*		

Electronic Patent Application Fee Transmittal

Application Number:	13456720
Filing Date:	26-Apr-2012
Title of Invention:	NOVEL ANTITUMORAL USE OF CABAZITAXEL
First Named Inventor/Applicant Name:	Sunil GUPTA
Filer:	Kelly L. Bender/Brian Pritchett
Attorney Docket Number:	FR2009/121 US CNT

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	18876043
Application Number:	13456720
International Application Number:	
Confirmation Number:	1083
Title of Invention:	NOVEL ANTITUMORAL USE OF CABAZITAXEL
First Named Inventor/Applicant Name:	Sunil GUPTA
Customer Number:	5487
Filer:	Kelly L. Bender/Brian Pritchett
Filer Authorized By:	Kelly L. Bender
Attorney Docket Number:	FR2009/121 US CNT
Receipt Date:	28-APR-2014
Filing Date:	26-APR-2012
Time Stamp:	16:11:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal Letter	FR2009-121USCNT_20140428_IDS_RESUBMISSION_LETTER.pdf	119211 855a7a7749ef2862cd36a854a5ca576981412589	no	4
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	FR2009-121USCNT_20140316_SUPP_IDS_SB08.pdf	248588 bc0e88d378202c3dc3c9345f26d88842913bae36	no	6
Warnings:					
Information:					
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3	Miscellaneous Incoming Letter	FR2009-121USCNT_20140428_COT.pdf	111507 3bd18a4969c38a228b6d763d8934c19087cc4de1	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30674 ecd2f6dc69379e025c43f2841e102d7c7cff48b4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	509980		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **GUPTA, et al.**		Examiner:	**James D. Anderson**
		Art Unit:	**1629**
Application No.:	**13/456,720**		
Filed:	**April 26, 2012**	Conf. No.	**1083**
Title:	**NOVEL ANTITUMORAL USE OF CABAZITAXEL**		

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §1.56

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicant's duty of disclosure pursuant to 37 C.F.R. §1.56.

Applicants note that an Information Disclosure Statement and the documents listed in the Form PTO/SB/08 filed herewith, other than the U.S. Patent Documents, were submitted on March 17, 2014. Through error, the corresponding FORM PTO/SB/08 was not submitted with the Information Disclosure Statement. Applicants respectfully request consideration of the FORM PTO/SB/08 being submitted herewith, together with the Information Disclosure Statement and documents previously submitted on March 17, 2014.

The submission of the Form PTO/SB/08, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 C.F.R. §1.56(b). Applicants do not waive any right to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

A concise explanation of the relevance of some or all of the items listed on the attached Form PTO/SB/08 is as follows:

Listed references FR2732340 and WO96/30356 are in the French language. U.S. Patent No. 5,889,043 (also listed) is an English language family member of FR2732340

and WO96/30356, and is believed to have similar content as FR2732340 and WO96/30356.

Shabafrouz et al. is in a non-English language. An English language abstract of Shabafrouz et al. is as follows: "Despite major progress in the understanding of biological mechanisms underlying metastatic prostate cancer, the treatment of men with advanced prostate cancer remains challenging. Several randomized controlled trials with promising or positive results are underway or just released. Here we discuss new treatments which might be used in clinic in the near future: hormonal treatments (Abiraterone and MDV3100), a new chemotherapy (Cabazitaxel), a cellular vaccine (Sipuleucel-T), anti-angiogenic drugs (Bevacizumab, Aflibercept), a new radioactive treatment (Alpharadin) and a new bone-protective agent (Deno-sumab)."

Pouessel et al. is in a non-English language. An English language abstract of Pouessel et al. is as follows: "In urologic oncology, prostate cancer represented, even this year, a wide part during the ASCO 2010 meeting. In the non metastatic diseases, two phase III trials confirmed the benefit of radiotherapy combined with hormonotherapy in locally advanced stage. For patients with metastatic hormonoresistan cancer, two randomized trials will probably change the daily practice in the next months. On the one hand, denosumab versus zoledronate decreased significantly the risk of skeletal-related events in bone metastases. On the other hand, compared with mitoxantrone, cabazitaxel in docetaxel pretreated patients improved overall survival. On the contrary, docetaxel in monotherapy remains the standard of care in first line chemotherapy in castration refractory metastatic prostate cancer. Indeed, in two trials, combination of bevacizumab or calcitriol with docetaxel showed no benefit for patients with more toxicities. Finally, docetaxel-based chemotherapy was again evaluated in two other situations: biological recurrence, and hormono-sensitive metastatic stage. Preliminary results of tolerance were presented this year. No doubt that communications during future ASCO meetings would reporte In urologic oncology, prostate cancer represented, even this year, a wide part during the ASCO 2010 meeting. In the non metastatic diseases, two phase III trials confirmed the benefit of radiotherapy combined with hormonotherapy in locally advanced stage. For patients with metastatic hormonoresistant cancer, two randomized trials will probably change the daily practice in the next months. On the one hand, denosumab versus zoledronate decreased significantly the risk of skeletal-related events in bone metastases. On the other hand, compared with mitoxantrone, cabazitaxel in docetaxel pretreated patients improved overall survival. On the contrary, docetaxel in monotherapy

remains the standard of care in first line chemotherapy in castration refractory metastatic prostate cancer. Indeed, in two trials, combination of bevacizumab or calcitriol with docetaxel showed no benefit for patients with more toxicities. Finally, docetaxel-based chemotherapy was again evaluated in two other situations: biological recurrence, and hormono-sensitive metastatic stage. Preliminary results of tolerance were presented this year. No doubt that communications during future ASCO meetings would reported definitive results of efficiency of these phase III studies."

Miura et al. is in a non-English language. An English language title and abstract of Miura et al. are as follows: "A case of Hormone-Refractory Prostate Cancer (HRPC) with Tumor Fever Responding to Docetaxel Plus Prednisolone Therapy," and "We have experienced a patient with tumor fever from hormone-refractory prostate cancer (HRPC) who was treated successfully using docetaxel plus prednisolone therapy. A 65-year-old male was diagnosed with prostate cancer (T4 N1 M1b). He received androgen-ablation therapy. But six months later he was confirmed to show failure of the previous hormone therapy and disease progression even after anti-androgen withdrawal. Then docetaxel plus prednisolone therapy was started. After two courses of this therapy, the PSA level decreased by 50% or more, and after ten courses an improvement was seen on the bone scan. The patient has survived for twelve months after starting docetaxel plus prednisolone therapy, without serious adverse effects."

TIMING OF THE DISCLOSURE

The Form PTO/SB/08 is being submitted in compliance with 37 C.F.R. §1.97(c), as the submission is filed after the period specified in §1.97(b) but before the mailing date of any of a final action under §1.113, a notice of allowance under §1.311, or an action that otherwise closes prosecution in the application. Applicants respectfully submit that a bona fide attempt was made to comply with §1.98 prior to the mailing of a first office action after the filing of a request for continued examination under §1.114, but part of the content (FORM PTO/SB/08) was inadvertently omitted.

Applicants hereby authorize the Director to charge any fees required under 37 C.F.R. §1.17(p) or any additional fees required by this submission, or credit any overpayment, to Deposit Account No. 18-1982.

Respectfully submitted,

/Kelly L. Bender/
Kelly Bender, Reg. No. 52,610
Attorney for Applicant

Sanofi US
U.S. Patent Operations
55 Corporate Drive
Mail Code: 55A-505A
Bridgewater, New Jersey 08807
email: **uspatent.e-filing@sanofi.com**
Telephone: (908) 981-**6782**
Telefax: (908) 981-7830
Sanofi US Ref. FR2009/121 US CNT

Date: April 28, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/456,720	04/26/2012	Sunil GUPTA	FR2009/121 US CNT	1083

5487 7590 04/16/2014

ANDREA Q. RYAN
SANOFI
55 Corporate Drive
MAIL CODE: 55A-505A
BRIDGEWATER, NJ 08807

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
04/16/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi.com
andrea.ryan@sanofi.com

Office Action Summary	Application No. 13/456,720	Applicant(s) GUPTA, SUNIL	
	Examiner JAMES D. ANDERSON	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/17/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,2,4,6-11,13-19,24 and 34-44* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,2,4,6-11,13-19,24 and 34-44* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 3/17/2014, are acknowledged and entered. Claims 34-44 are newly added. Claims 1-2, 4, 6-11, 13-19, 24, and 34-44 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/2014 has been entered.

TrackOne Request

Applicants' request for prioritized examination under 37 CFR 1.102(e), filed 3/17/2014, has been received and **APPROVED**.

The instant application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. **filing a petition for extension of time** to extend the time period for filing a reply;

B. **filing an amendment to amend the application to contain more than four independent claims**, more than thirty total claims, or a multiple dependent claim;

C. **filing a request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application

Response to Arguments

Applicants' arguments, filed 3/17/2014, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or

objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

It appears that Applicants intended to file an Information Disclosure Statement with the reply filed 3/17/2014 as numerous NPL and foreign references were supplied and the transmittal letter states "Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicant in order to comply with Applicant's duty of disclosure pursuant to 37 C.F.R. §1.56".

However, the Office did not receive a PTO-SB-08 listing the supplied references and no IDS is listed as being submitted on the EFS Acknowledgement Receipt.

Accordingly, unless a supplied reference has been cited by the Examiner, it has not been considered by the Office.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 2 recites that the method of claim 1, where said patient "is not catered for by a taxane-based treatment". However, claim 1 requires administration of cabazitaxel, which is a taxane. As such, it is unclear how the patients of claim 1 cannot be catered for by a taxane-based treatment when claim 1 requires administration of a taxane.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 10, 13, 24, 35-36, 38-39, 41-42, and 44 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by **Beardsley *et al***. (Current Opinions in Supportive and Palliative Care, September 2008, vol. 2, pages 161-166).

Beardsley et al. teach that there is an urgent need for systemic treatment options for patients with castration-resistant prostate cancer who have progressed after receiving first-line docetaxel chemotherapy. See Abstract.

Beardsley et al. teach that XRP6258, i.e., cabazitaxel, is a semi-synthetic taxoid compound with low affinity for the P-glycoprotein drug efflux transporter and cytotoxic in cell lines with acquired resistance to paclitaxel or docetaxel. Beardsley et al. teach that a phase II study of XRP6258 was conducted in patients with docetaxel refractory metastatic breast cancer and an objective response rate of 14% was observed. See page 163, right column, "Taxanes".

Beardsley et al. teach that given its activity in the docetaxel refractory setting described above (docetaxel refractory metastatic breast cancer), this agent [XRP6258] is **"currently being investigated in a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment."** *Id.*

Beardsley et al. thus anticipate administering cabazitaxel in combination with prednisone to patients with castration-resistant metastatic prostate cancer previously treated with docetaxel-containing treatment as presently claimed as they teach that a Phase III trial of such treatment is "currently being invenstigated".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4, 8-11, 13-19, 24, and 34-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mita *et al.*** (Clinical Cancer Research, 2009, vol. 15, pages 723-730) (Published Online January 15, 2009) in view of **Tannock *et al.*** (N. Engl. J. Med., 2004, vol. 351, pages 1502-1512) and **Beardsley *et al.*** (Current Opinions in Supportive and Palliative Care, September 2008, vol. 2, pages 161-166).

Claimed Invention

The amended claims are drawn to treating prostate cancer in a patient comprising administering to said patient an effective amount of cabazitaxel (XRP6258) in combination with a corticoid (e.g., prednisone or prednisolone). Dependent claims recite the limitations wherein the patient has hormone refractory prostate cancer and/or wherein the patient has been previously treated with a docetaxel containing regimen.

Teachings of Mita et al.

Mita *et al.* disclose a Phase I and pharmacokinetic study of cabazitaxel (XRP6258), administered as a **1-hour intravenous infusion every 3 weeks** in patients with advanced solid tumors, thus expressly teaching a 3 week cycle as recited in claims 10, 38, 41, and 44. *See* Abstract.

Mita *et al.* disclose that cabazitaxel (XRP6258) has shown broad spectrum antitumor activity in mice bearing s.c. implanted human xenografts, including Du-145 prostate cancers. *See* page 724, left column, first full paragraph.

Mita *et al.* disclose that the encouraging spectrum of antitumor activity of XRP6258 in experimental tumor models, **particularly its notable activity against docetaxel-resistant, Pgp-expressing malignancies**, served as a rationale to clinical evaluations. *See* page 724, left column, second full paragraph.

Regarding claims 8-9, 34, 37, 40, and 43, Mita *et al.* disclose that XRP6258 was administered as a 1-hour i.v. infusion every 3 weeks at a starting dose of 10 mg/m2, with subsequent incremental increases to 15, 20, and **25 mg/m² dose levels**. *See* page 724, right column, "Drug administration" and "Dose escalation".

Regarding claims 14-16, Mita *et al.* disclose pharmacokinetic variables observed in patients at all tested dose levels, including AUC, Cmax, and clearance falling within the scope of the instant claims. *See* Table 5.

Regarding claims 17-19, Mita *et al.* disclose monitoring blood neutrophil counts, *i.e.*, absolute neutrophil counts (ADC), and that at the highest dose level (**25 mg/m²**), the ADC was ≤ 1,500 cells/mm3 (990) and at that dose level there were cases of Grade 3 and Grade 4 neutropenia. Mita *et al.* disclose that the rate of dose limiting toxicity (DLT) exceeded the predefined limits of tolerability at the 25 mg/m2 dose level. *See* Table 3; page 726, left column, second full paragraph.

Regarding anticancer activity, Mita et al. disclose that evidence of anticancer activity was observed in a patient with **prostate cancer metastatic to liver and bones** whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone. Further evidence of anticancer activity was observed in a patient with **hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes**. *See* page 727, left column, "Anticancer activity".

Mita *et al.* differ from the instant claims in that while Mita *et al.* unequivocally teach, suggest, and motivate the administration of carbazitaxel to treat prostate cancer, including metastatic, hormone- and docetaxel-refractory prostate cancer, Mita *et al.* does not disclose combining carbazitaxel with a corticoid such as prednisone.

Teachings of Tannock et al.

Tannock *et al.* disclose that mitoxantrone plus prednisone reduces pain and improves quality of life in men with advanced, hormone-refractory prostate cancer, but it does not improve survival. Tannock *et al.* disclose a study comparing the effects of docetaxel combined with prednisone to mitoxantrone combined with prednisone. *See* Title; Abstract.

Regarding claim 8, Tannock *et al.* disclose that **prednisone was administered at a dose of 5 mg twice daily**, thus teaching administration of prednisone at a dose of 10 mg/day. *See* Abstract; page 1504, left column, "Randomization and Treatment".

Regarding claims 17-19, Tannock *et al.* disclose that a dose reduction or treatment delay was stipulated for patient who had an absolute neutrophil count of less than 1500 per cubic millimeter (for those receiving weekly docetaxel). See page 1504, right column, first full paragraph.

Tannock *et al.* disclose that when given with prednisone, treatment with docetaxel every 3 weeks led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared to mitoxantrone plus prednisone, and conclude that **docetaxel plus prednisone is the preferred option for most patients with hormone-refractory prostate cancer**. *See* Abstract; page 1511, right column, last paragraph.

Teachings of Beardsley et al.

Beardsley et al. disclose that there is an urgent need for systemic treatment options for patients with castration-resistant prostate cancer who have progressed after receiving first-line docetaxel chemotherapy. See Abstract.

Beardsley et al. disclose that XRP2658, i.e., cabazitaxel, is a semi-synthetic taxoid compound with low affinity for the P-glycoprotein drug efflux transporter and cytotoxic in cell lines with acquired resistance to paclitaxel or docetaxel. Beardsley et al. disclose that a phase II study of XRP6258 was conducted in patients with docetaxel refractory metastatic breast cancer and an objective response rate of 14% was observed. See page 163, right column, "Taxanes".

Beardsley et al. disclose that given its activity in the docetaxel refractory setting described above (docetaxel refractory metastatic breast cancer), this agent [XRP6258] is **"currently being investigated in a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with**

prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment." *Id.*

Principles of Law

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "In determining whether obviousness is established by combining the teachings of the prior art, 'the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.'" *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995).

"[I]in a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976).)

Analysis & Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer cabazitaxel in combination with prednisone as taught by Mita et al. in view of the teachings of Tannock et al. to patients with hormone-refractory prostate cancer previously treated with docetaxel.

One would have been motivated to do so because Mita et al. teach that cabazitaxel is effective in treating prostate cancer metastatic to liver and bones whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone and **hormone- and docetaxel-refractory prostate cancer** metastatic to bone and iliac lymph nodes when administered as a single agent. The motivation to add prednisone to such treatment is clearly seen in Tannock *et al.*, who teach that administration of the taxane, docetaxel, in combination with prednisone is effective in treating hormone-refractory prostate cancer. As such, the skilled artisan would predict that addition

of prednisone to the treatment regimen of Mita *et al.* would also be effective in treating hormone-refractory prostate cancer, including prostate cancers refractory to docetaxel therapy. In fact, Beardsley et al. disclose that as early as September 2008, XRP6258 (cabazitaxel) is **"currently being investigated in a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment."**

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mita *et al.*** (Clinical Cancer Research, 2009, vol. 15, pages 723-730) (Published Online January 15, 2009) in view of **Tannock *et al.*** (N. Engl. J. Med., 2004, vol. 351, pages 1502-1512) and and **Beardsley *et al.*** (Current Opinions in Supportive and Palliative Care, September 2008, vol. 2, pages 161-166) as applied to claims 1-2, 4, 8-11, 13-19, 24, and 34-44 above, and further in view of **Didier *et al.*** (US 2005/0065138 A1; Published Mar. 24, 2005).

Mita et al. and Tannock et al. teach as applied to claims 1-2, 4, 8-11, 13-19, 24, and 34-44, supra, which teachings are herein incorporated by reference in their entirety. Claims 6-7 differ from Mita et al. and Tannock et al. in that the references do not disclose an acetone solvate of carbazitaxel.

Teachings of Didier et al.

Didier et al. disclose acetone solvates of carbazitaxel. *See* Abstract; Claims.

Didier et al. disclose acetone solvates containing between 5% and 8% of acetone. *See* page 1, [0020].

Analysis & Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer the acetone solvate of cabazitaxel in combination with prednisone as taught by Mita et al. in view of the teachings of Tannock et al., Beardsley et al., and Dinier et al.

The skilled artisan would expect that the acetone solvate of carbazitaxel would possess the same anticancer properties as the free base compound. As both carbazitaxel and the acetone solvate thereof were known in the art, selection of either one for use in treating prostate cancer would have been prima facie obvious to the skilled artisan.

Response to Arguments

Applicant again submits that the claimed elements of the present invention were not known in the prior art and the combination of Mita and Tannock would not have provided a reasonable expectation of predictable results. Accordingly,

Applicant respectfully submits that any presumption of obviousness based on the combination of these references is not warranted. In support of the above, Applicants present the following arguments.

Applicant argues that the primary Mita reference describes Phase I and pharmacokinetic studies of cabazitaxel in a limited number of patients with a variety of solid tumors. The studies were designed to evaluate the safety and dosage of cabazitaxel, but "preliminary evidence of antitumor activity" was to be documented. (Mita at 724, left column). While eight of the twenty-five patients had prostate tumors (Id. at 725, Table 1), Mita indicated that evidence of anticancer activity was noted in two patients, including one patient with "hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes." (Id. at 727). Applicant asserts that the evidence of anticancer activity in a single patient does not provide an expectation that the claimed method would successfully treat prostate cancer. In support of this assertion, Applicant argues that the antitumor activity observed in Mita could have been entirely due to chance (i.e., the patient's tumor regressed spontaneously), rather than an effect of cabazitaxel, because that study was not statistically powered to determine whether the observed efficacy was due to the drug. Moreover, Applicant argues that it is important to note that Mita nowhere suggests that one skilled in the art should use cabazitaxel for the treatment of prostate cancer based on these results, as the efficacy data provided is only "preliminary" evidence.

In response, the Examiner respectfully submits that Mita et al. clearly and unequivocally suggests that one skilled in the art should in fact use cabizitaxel for the treatment of taxane-refractory prostate cancer.

Conclusion: The recommended phase II dose of XRP6258 on this schedule is 20 mg/m^2. The general tolerability and encouraging antitumor activity in taxane-refractory patients warrant further evaluations of XRP6258.

In conclusion, XRP6258 is a new taxane characterized by convenient administration with less premedication, linear PKs, and a favorable safety profile for hematologic toxicity and hypersensitivity reaction. XRP6258 is a weak P-gp substrate in preclinical models, which seems to correlate with a greater potency and possibly an extended spectrum of antitumor activity in the clinic, including those patients who have shown taxane resistance. Therefore, the results of this study support broad disease-directed evaluations of XRP6258 on this administration schedule, which are ongoing.

Thus, Mita et al. not only explicitly state that further evaluations of cabazitaxel are warranted (and in fact "ongoing") but even provide a recommended Phase II dose for cabizitaxel. Further, Beardsley et al. disclose that a phase II study of XRP6258, i.e., cabazitaxel, was conducted in patients with docetaxel refractory metastatic breast cancer and an objective response rate of 14% was observed. See page 163, right column, "Taxanes". Beardsley et al. also disclose that given its activity in the docetaxel refractory setting described above (docetaxel refractory metastatic breast cancer), this agent [XRP6258] is **"currently being investigated in a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment."**

Applicant next argues that cancer research, and in particular clinical trials of antitumor drugs, is highly unpredictable. (See e.g., Kola et al. stating "[a]pproximately 62% of all compounds that enter Phase II trials undergo attrition, and again the highest rate of attrition at this phase is in the oncology field: more than 70% of oncology compounds fail in this phase," Nature Reviews Drug Discovery, 2004, Vol 3., pp. 711-715 at 712, cited in attached IDS). Accordingly, given the extremely limited nature of the patients described in Mita and the unpredictability and complexity of treatment of cancer, Applicant asserts that one skilled in the art would not have the requisite reasonable expectation that patients with hormone refractory metastatic prostate cancer, who were previously treated with a docetaxel-containing regimen, could be successfully treated by the claimed method.

Applicant argues that as noted by the Examiner, the abstract of Mita states that "the general tolerability and encouraging antitumor activity in taxane-refractory patients warrant further evaluations of XRP6258 [cabiztaxel]." Even assuming, arguendo, that this statement gives a general incentive to evaluate cabazitaxel in these taxane-refractory patients, Applicants argue that none of the cited references provide the requisite evidence of predictability in the treatment of such cancer patients. Absent evidence of predictability, Applicant asserts that Mita cannot provide a reasonable expectation of success in the treatment of prostate cancer in taxane-refractory patients. Therefore, Applicant submits that, based on

Mita's preliminary and limited nature of description of effectiveness with respect to cabazitaxel in patients and the lack of evidence of a reasonable correlation between docetaxel and cabazitaxel-based prednisone combinations, the present claims would be non- obvious to one skilled in art over the combination of Mita and Tannock.

In response, the Examiner respectfully submits that a guarantee of success is not the standard of obviousness. Rather, all that is required is at least a "reasonable expectation of success". Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart,* 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). In this case, given the fact that Mita et al. demonstrate activity of cabazitaxel against taxane-resistant prostate cancer and unequivocally teach, suggest, and motivate treating taxane-resistant prostate cancer with cabazitaxel, the claimed invention is clearly prima facie obvious. The "evidence" Applicant relies on (Nature Reviews Drug Discovery, 2004, Vol 3., pp. 711-715 at 712) regarding there being no reasonable expectation of success says nothing whatsoever about cabazitaxel and is therefore not persuasive. As the structurally related docetaxel is used clinically for the treatment of prostate cancer, the skilled artisan would have clearly been imbued with a reasonable expectation that cabazitaxel, which has demonstrated activity in treating taxane-resistant prostate cancer in a Phase I trial, would be effective in treating prostate cancer as presently claimed. In fact, Beardsley et al.

disclose that a phase II study of XRP6258, i.e., cabazitaxel, was conducted in patients with docetaxel refractory metastatic breast cancer and an objective response rate of 14% was observed. See page 163, right column, "Taxanes". Beardsley et al. also disclose that given its activity in the docetaxel refractory setting described above (docetaxel refractory metastatic breast cancer), this agent [XRP6258] is **"currently being investigated in a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment."** Here, all Applicant has done is take the next logical step in the development of cabazitaxel for the treatment of taxane-resistant prostate cancers that is expressly suggested by Mita et al. and in fact stated by Beardsley et al. as "currently being investigated" in September 2008. In other words, Applicant is basing the patentability of the claimed invention solely on the results obtained from carrying out the Phase III trial that Beardsley et al. states was "currently being investigated" more than 1 year before Applicant's invention. It is well established in the art that Phase I clinical trials are used as a basis for continuing Phase II and Phase III clinical trials. Given the documented evidence of anti-cancer activity in the Phase I trial taught by Mita against hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes, the documented evidence of objective response in patients with docetaxel refractory

metastatic breast cancer in a Phase II trial, and the express teaching that a Phase III trial in patients with **castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment,** the skilled artisan would have clearly been imbued with at least a reasonable expectation of success in treating such prostate cancer with cabazitaxel. This is clearly evidenced by Mita who in fact demonstrate that carbazitaxel is clinically effective in treating hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes and Beardsley et al. who document evidence of objective response in patients with docetaxel refractory metastatic breast cancer in a Phase II trial.

Conclusion

If applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in *ipsis verbis*, clarification on the record may be helpful). Should applicants present new claims, applicants should clearly identify where support can be found in the disclosure

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES ANDERSON whose telephone number is

(571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D. Anderson/

James D. Anderson, Ph.D.
Primary Patent Examiner, Art Unit 1629
UNITED STATES PATENT AND TRADEMARK OFFICE
400 Dulany Street
Alexandria, VA 22314-5774
Tel. No.: (571) 272-9038

Notice of References Cited	Application/Control No. 13/456,720	Applicant(s)/Patent Under Reexamination GUPTA, SUNIL	
	Examiner JAMES D. ANDERSON	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Beardsley et al. Current Opinions in Supportive and Palliative Care, September 2008, vol. 2, pages 161-166
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13456720	GUPTA, SUNIL
	Examiner	Art Unit
	JAMES D ANDERSON	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search	1/11/2013	JDA
EAST Search (see attached)	1/11/2013	JDA
STN Structure Search (see attached)	1/11/2013	JDA
Inventor Name Search	9/10/2013	JDA
EAST Search (see attached)	9/10/2013	JDA
STN Structure Search (see attached)	9/10/2013	JDA
Inventor Name Search	4/10/2014	JDA
EAST Search (see attached)	4/10/2014	JDA
Medline NPL Search	4/10/2014	JDA

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	42	((SUNIL) near2 (GUPTA)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2014/04/10 10:50
L2	42	L1	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L3	1	L2 and (cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L4	5421	Sanofi-aventis.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L5	4073	"Aventis Pharma".as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L6	9021	L4 or L5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L7	13	L6 and (cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L8	13	L3 or L7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:50
L9	311	(cabazitaxel or XRP6258 or (XRP adj2 "6258"))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:51
L10	33	L9 and (@ad<"20101027" or @pd<"20101027")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:51
L11	7	l10 and (cabazitaxel or XRP6258 or (XRP adj2 "6258")).clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/04/10 10:51
S1	14	"5847170"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 12:37
S2	102	cabazitaxel	US-PGPUB; USPAT; USOCR;	OR	ON	2013/01/11 12:40

			EPO; JPO; DERWENT			
S3	21	cabazitaxel.clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 12:40
S4	12	XRP6258	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 12:42
S5	38	((SUNIL) near2 (GUPTA)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2013/01/11 12:43
S6	4725	Sanofi-aventis.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:15
S7	38	S6 and taxane	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:15
S8	9	("5229526" | "5319112" | "5486601" | "5739362").PN. OR ("5847170").URPN.	US-PGPUB; USPAT; USOCR	OR	ON	2013/01/11 14:18
S9	4016	"Aventis Pharma".as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:21
S10	67	S9 and taxane	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:21
S11	6	"2005065138"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:31
S12	3	"20050065138"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:31
S13	11	("20020038038" | "6372780" | "6331635" | "6387946" | "20050065138" | "5438072" | "7241907" | "5847170").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 09:58
S14	39	((SUNIL) near2 (GUPTA)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2013/09/10 09:59
S15	39	S14	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 09:59
S16	1	S15 and (cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
S17	5090	Sanofi-aventis.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
S18	4061	"Aventis Pharma".as.	US-PGPUB;	OR	ON	2013/09/10

			USPAT; USOCR; EPO; JPO; DERWENT			10:00
S19	8681	S17 or S18	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
S20	11	S19 and (cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
S21	197	(cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:01
S22	29	S21 and (@ad<"20101027" or @pd<"20101027")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:01

EAST Search History (Interference)

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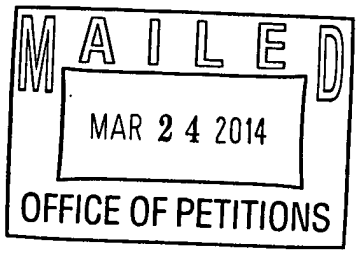


Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/456,720

1. THE REQUEST FILED March 17, 2014 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	13/456,720
Filing Date	April 26, 2012
First Named Inventor	GUPTA, et al.
Art Unit	1629
Examiner Name	James D. Anderson
Attorney Docket Number	FR2009/121 US CNT

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 18-1982.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Kelly L. Bender/	Date	March 17, 2014
Name (Print/Type)	Kelly L. Bender	Registration No.	52,610

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

Instruction Sheet for RCEs

(not to be submitted to the USPTO)

NOTES:

An RCE is not a new application, and filing an RCE will not result in an application being accorded a new filing date.

Filing Qualifications:

The application must be a utility or plant application filed on or after June 8, 1995. The application cannot be a provisional application, a utility or plant application filed before June 8, 1995, a design application, or a patent under reexamination. See 37 CFR 1.114(e).

Filing Requirements:

Prosecution in the application must be closed. Prosecution is closed if the application is under appeal, or the last Office action is a final action, a notice of allowance, or an action that otherwise closes prosecution in the application (e.g., an Office action under *Ex parte Quayle*). See 37 CFR 1.114(b).

A submission and a fee are required at the time the RCE is filed. If reply to an Office action under 35 U.S.C. 132 is outstanding (e.g., the application is under final rejection), the submission must meet the reply requirements of 37 CFR 1.111. If there is no outstanding Office action, the submission can be an information disclosure statement, an amendment, new arguments, or new evidence. See 37 CFR 1.114(c). The submission may be a previously filed amendment (e.g., an amendment after final rejection).

WARNINGS:

Request for Suspension of Action:

All RCE filing requirements must be met before suspension of action is granted. A request for a suspension of action under 37 CFR 1.103(c) does not satisfy the submission requirement and does not permit the filing of the required submission to be suspended.

Improper RCE will NOT toll Any Time Period:

Before Appeal - If the RCE is improper (e.g., prosecution in the application is not closed or the submission or fee has not been filed) and the application is not under appeal, the time period set forth in the last Office action will continue to run and the application will be abandoned after the statutory time period has expired if a reply to the Office action is not timely filed. No additional time will be given to correct the improper RCE.

Under Appeal - If the RCE is improper (e.g., the submission or the fee has not been filed) and the application is under appeal, the improper RCE is effective to withdraw the appeal. Withdrawal of the appeal results in the allowance or abandonment of the application depending on the status of the claims. If there are no allowed claims, the application is abandoned. If there is at least one allowed claim, the application will be passed to issue on the allowed claim(s). See MPEP 1215.01.

See MPEP 706.07(h) for further information on the RCE practice.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	**Gupta et al.**	Examiner:	**James ANDERSON**
		Art Unit:	**1629**
Application No.:	**13/456,720**	Conf No.	**1083**
Filed:	**April 26, 2012**		
Title:	**NOVEL ANTITUMORAL USE OF CABAZITAXEL**		

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE ACCOMPANYING REQUEST FOR CONTINUED EXAMINATION PURSUANT TO 37 C.F.R. 1.114

Dear Sir:

This paper and the accompanying Request for Continued Examination ("RCE") are in response to the Final Office Action issued September 16, 2013, by the United States Patent and Trademark Office setting a three-month period for response set to expire on December 16, 2013. The period for response is extended three months to expire Monday, March 17, 2014, pursuant to the Petition for Extension of Time under 37 C.F.R. 1.136(a) submitted herewith. This response is timely filed.

Entry of the following amendments and consideration of the following remarks are respectfully requested.

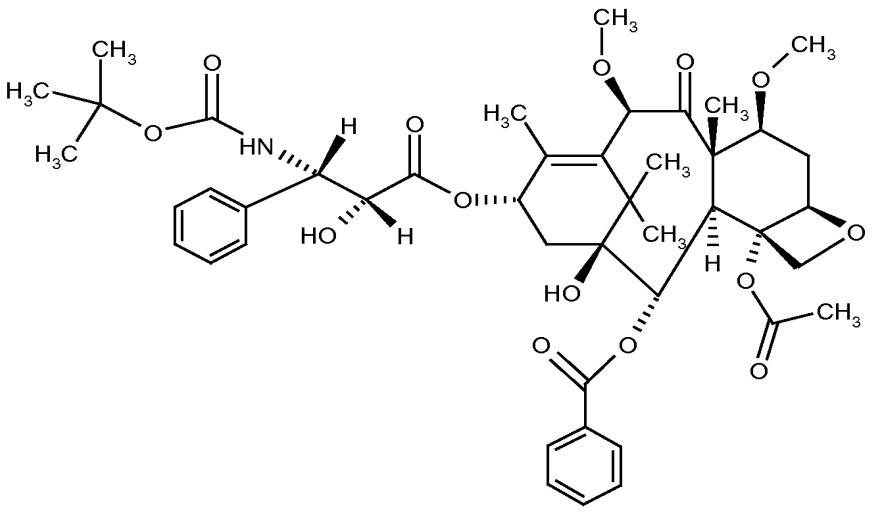
Amendments to the claims start on page 2.

Remarks to amendments and the outstanding office action begin on page 6.

Amendment Pursuant to 37 C.F.R. § 1.121

In the Claims:

1. (Currently amended) A method for treating prostate cancer in a patient in need thereof comprising administering to said patient an effective amount of a compound of formula



which may be in base form or in the form of a hydrate or a solvate,

in combination with a corticoid~~prednisone or prednisolone, wherein said patient has hormone refractory metastatic prostate cancer and wherein said patient has been previously treated with a docetaxel containing regimen~~.

2. (Currently amended) The method according to claim 1, where ~~the treated patients are~~ said patient is not catered for by a taxane-based treatment.

3. (Cancelled)

4. (Original) The method according to claim 1, where the prostate cancer is an advanced metastatic disease.

5. (Cancelled)

6. (Original) The method according to claim 1, where the compound is in the form of an acetone solvate.

7. (Original) The method according to claim 6, in which the acetone solvate contains between 5% and 8% by weight of acetone.

8. (Currently amended) The method according to claim 35~~claim 1~~, where the compound is administered at a dose of between 15 and 25 mg/m^2, and the prednisone or prednisolone ~~being~~ is administered at a dose of 10 mg/day.

9. (Original) The method according to claim 8, where the compound is administered at a dose of 25 mg/m^2.

10. (Original) The method according to claim 1, comprising repeating the administration of such compound as a new cycle every 3 weeks.

11. (Original) The method according to claim 10, wherein the median number of cycles is 6.

12. (Cancelled)

13. (Previously presented) The method according to claim 1, where the compound is cabazitaxel.

14. (Original) The method according to claim 1, wherein said compound is administered in an amount to provide an AUC of about 991 ng•h/mL (CV 34%).

15. (Original) The method according to claim 1, wherein said compound is administered in an amount to provide an C_{max} of about 226 ng•h/mL (CV 107%).

16. (Original) The method according to claim 1 wherein said compound is administered in an amount to provide a plasma clearance of 48.5 L/h (CV 39%).

17. (Original) The method according to claim 1, further comprising monitoring blood counts and measuring neutrophil levels in the patient.

18. (Original) The method according to Claim 17, wherein said monitoring comprises taking a blood sample from the patient.

19. (Original) The method according to Claim 18, further comprising discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500 cells/mm^3.

20. - 23. (Cancelled)

24. (Original) A method of increasing the survival of a patient with hormone refractory metastatic prostate cancer, comprising administering a clinically proven effective amount of a compound as defined in claim 1 to the patient in combination with prednisone or prednisolone.

25. – 33. (Cancelled)

34. (New) The method according to claim 1, where the compound is administered at a dose of 25 mg/m^2.

35. (New) The method according to claim 1, wherein the corticoid is selected from the group consisting of prednisone and prednisolone.

36. (New) The method according to claim 1, wherein said patient has been previously treated with a docetaxel-based regimen.

37. (New) The method according to claim 36, where the compound is administered at a dose of 25 mg/m^2.

38. (New) The method according to claim 36, comprising repeating the administration of said compound as a new cycle every 3 weeks.

39. (New) The method according to claim 1, where the prostate cancer is a castration resistant prostate cancer or hormone-refractory prostate cancer.

40. (New) The method according to claim 39, where the compound is administered at a dose of 25 mg/m^2.

41. (New) The method according to claim 39, comprising repeating the administration of said compound as a new cycle every 3 weeks.

42. (New) The method according to claim 1, wherein said patient has been previously treated with a docetaxel-based regimen and where the prostate cancer is a castration resistant prostate cancer or hormone-refractory prostate cancer.

43. (New) The method according to claim 42, where the compound is administered at a dose of 25 mg/m^2.

44. (New) The method according to claim 42, comprising repeating the administration of said compound as a new cycle every 3 weeks.

Remarks

In the Office Action, the Examiner noted that claims 1, 2, 4, 6 to 11, 13 to 19 and 24 are pending in the application, and that claims 1, 2, 4, 6 to 11, 13 to 19 and 24 are rejected.

Support for the amendments to claim 1 can be found throughout the specification, for example on page 8, lines 14 to 16 (second full paragraph).

Claim 2 is amended to place said claim in conventional US claim format.

Claim 8 is amended to place said claim in conventional US claim format and to change the dependency of said claim in view of the amendments to claim 1,

Support for new claims 34 to 44 can be found throughout the specification and in the original claims, for example on page 4, and in original claims 1 to 12.

No new matter is added by these amendments.

Applicant reserves the right to file one or more continuation, continuation-in-part, or divisional applications on the deleted subject matter.

As presently amended, claims 1, 2, 4, 6 to 11, 13 to 19, 24 and 34 to 44 are pending in this application.

Discussion of Rejection under 35 U.S.C. § 103(a)

The rejection of claims 1, 2, 4, 8 to 12, 13 to 19 and 24 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Mita et al. (Clin Cancer Res, 2009, 15(2) pp. 723-730, hereinafter "Mita") in view of Tannock et al. (N Eng J Med, 2004, 351, pp. 1502-1512, hereinafter "Tannock") has been maintained. This rejection is traversed.

It is the Examiner's position that one would have been motivated to "combine the teachings of the references so as to administer cabazitaxel in combination with prednisone" because "Mita et al. teach that cabazitaxel is effective in treating prostate cancer metastatic to liver and bones whose disease has progressed through surgical castration, bicalutamide, diethery stilbestrol, and mitoxantrone and predisone and hormone- and docetaxel-refractory prostate caner metastatic to bone and iliac lymph nodes when administered as a single agent." (Office Action, page 8). Further, it is the Examiner position that the "motivation to add prednisone to such treatment is clearly seen in Tannock et al., who teach that administration of the

taxane, docetaxel, in combination with prednisone is effective in treating hormone-refractory prostate cancer." (Office Action, page 9).

To render a claimed invention obvious under 35 U.S.C. § 103, the cited reference themselves, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to combine or modify them in the manner necessary to arrive at the claimed invention (*See,* MPEP § 2143.01). In addition, the proposed combination or modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. (*See,* MPEP § 2143.02). Finally, the prior art references must teach or suggest all limitations of the claims; i.e., each of the limitations must "be found in the prior art, and not be based on applicant's disclosure." (MPEP § 2143).

Applicant submits that the claimed elements of the present invention were not known in the prior art and the combination of Mita and Tannock would not have provided a reasonable expectation of predictable results. Accordingly, Applicant respectfully submits that any presumption of obviousness based on the combination of these references is not warranted.

The present application, which describes the results from a Phase III clinical trial, demonstrates that administration of cabazitaxel in combination with prednisone to patients with hormone refractory metastatic prostate cancer, who were previously treated with a docetaxel-containing regimen resulted in a statistically significant longer overall survival compared to patients receiving a mitoxantrone plus prednisone. (*See*, Specification, p. 18).

The primary Mita reference describes Phase I and pharmacokinetic studies of cabazitaxel in a limited number of patients with a variety of solid tumors. The studies were designed to evaluate the safety and dosage of cabazitaxel, but "preliminary evidence of antitumor activity" was to be documented. (Mita at 724, left column). While eight of the twenty-five patients had prostate tumors (Id. at 725, Table 1), Mita indicated that evidence of anticancer activity was noted in two patients, including one patient with "hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes." (Id. at 727).

The evidence of anticancer activity in a single patient does not provide an expectation that the claimed method would successfully treat prostate cancer. First, the antitumor activity observed in Mita could have been entirely due to chance (i.e.

the patient's tumor regressed spontaneously), rather than an effect of cabazitaxel, because that study was not statistically powered to determine whether the observed efficacy was due to the drug. Indeed, no antitumor activity was seen in the majority of the patients treated. Moreover, it is important to note that Mita nowhere suggests that one skilled in the art should use cabazitaxel for the treatment of prostate cancer based on these results, as the efficacy data provided is only "preliminary" evidence.

Second, cancer research, and in particular clinical trials of antitumor drugs, is highly unpredictable. (See e.g., Kola et al. stating "[a]pproximately 62% of all compounds that enter Phase II trials undergo attrition, and again the highest rate of attrition at this phase is in the oncology field: more than 70% of oncology compounds fail in this phase," *Nature Reviews Drug Discovery*, 2004, Vol 3., pp. 711-715 at 712, cited in attached IDS). Accordingly, given the extremely limited nature of the patients described in Mita and the unpredictability and complexity of treatment of cancer, one skilled in the art would not have the requisite reasonable expectation that patients with hormone refractory metastatic prostate cancer, who were previously treated with a docetaxel-containing regimen, could be successfully treated by the claimed method.

Nevertheless, the Examiner asserts that "[g]iven the documented evidence of anti-cancer activity in the Phase I trial taught by Mita against hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes, the skilled artisan would have been imbued with at least a reasonable expectation of success in treating such prostate cancer." (Office Action, page 11). Applicants respectfully disagree.

As noted by the Examiner at page 12 of the Office Action, the abstract of Mita states that "the general tolerability and encouraging antitumor activity in taxane-refractory patients warrant further evaluations of XRP6258 [cabiztaxel]." Even assuming, *arguendo*, that this statement gives a general *incentive* to evaluate cabazitaxel in these taxane-refractory patients, none of the cited references provide the requisite evidence of *predictability* in the treatment of such cancer patients. Absent evidence of predictability, Mita cannot provide a reasonable expectation of success in the treatment of prostate cancer in taxane-refractory patients.

Therefore, Applicant respectfully submits that, based on Mita's preliminary and limited nature of description of effectiveness with respect to cabazitaxel in patients and the lack of evidence of a reasonable correlation between docetaxel-

and cabazitaxel- based prednisone combinations, the present claims would be non-obvious to one skilled in art over the combination of Mita and Tannock. Accordingly, reconsideration and withdrawal of this obviousness-based rejection are respectfully requested.

The rejection of claims 6 and 7 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Mita, in view of Tannock as applied to claims 1 to 5, 8 to 19 and 24 and further in view of Didier et al. (US2005/0065138) has been maintained.

Didier et al. which is cited for allegedly teaching "acetone solvates of cabazitaxel" and "acetone solvates containing between 5% and 8% of acetone" (Office Action, page 9), dose not remedy the deficiencies of Mita and Tannock, as described above. Accordingly, Didier et al., in combination with Mita and Tannock, does not render claims 6 and 7 obvious. Reconsideration and withdrawal of this rejection of claims 6 and 7 are therefore respectfully requested.

Conclusion

There being no remaining issues, this application is believed in condition for favorable reconsideration and early allowance, and such actions are earnestly solicited.

In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

The Director is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. **18-1982**.

Respectfully submitted,

/Kelly L. Bender/
Kelly Bender, Reg. No. 52,610
Attorney for Applicant

Sanofi US
U.S. Patent Operations
55 Corporate Drive
Mail Code: 55A-505A
Bridgewater, New Jersey 08807
email: **uspatent.e-filing@sanofi.com**
Telephone: (908) 981-**6782**
Telefax: (908) 981-7832
Sanofi US Ref. FR2009/121 US CNT

Date: March 17, 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **GUPTA, et al.**		Examiner:	**James D. Anderson**
		Art Unit:	**1629**
Application No.:	**13/456,720**		
Filed:	**April 26, 2012**	Conf. No.	**1083**
Title:	**NOVEL ANTITUMORAL USE OF CABAZITAXEL**		

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §1.56

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicant in order to comply with Applicant's duty of disclosure pursuant to 37 C.F.R. §1.56.

The submission of the document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 C.F.R. §1.56(b). Applicant does not waive any right to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 C.F.R. §1.97(b), as the submission is before the mailing of a first Office Action after the filing of request for continued examination under §1.114.

A concise explanation of the relevance of some or all of the items listed on the attached Form PTO/SB/08 is as follows:

Listed references FR2732340 and WO96/30356 are in the French language. U.S. Patent No. 5,889,043 (also listed) is an English language family member of FR2732340 and WO96/30356, and is believed to have similar content as FR2732340 and WO96/30356.

Shabafrouz et al. is in a non-English language. An English language abstract of Shabafrouz et al. is as follows: "Despite major progress in the understanding of biological mechanisms underlying metastatic prostate cancer, the treatment of men with advanced prostate cancer remains challenging. Several randomized controlled trials with promising or positive results are underway or just released. Here we discuss new treatments which might be used in clinic in the near future: hormonal treatments (Abiraterone and MDV3100), a new chemotherapy (Cabazitaxel), a cellular vaccine (Sipuleucel-T), anti-angiogenic drugs (Bevacizumab, Aflibercept), a new radioactive treatment (Alpharadin) and a new bone-protective agent (Deno-sumab)."

Pouessel et al. is in a non-English language. An English language abstract of Pouessel et al. is as follows: "In urologic oncology, prostate cancer represented, even this year, a wide part during the ASCO 2010 meeting. In the non metastatic diseases, two phase III trials confirmed the benefit of radiotherapy combined with hormonotherapy in locally advanced stage. For patients with metastatic hormonoresistan cancer, two randomized trials will probably change the daily practice in the next months. On the one hand, denosumab versus zoledronate decreased significantly the risk of skeletal-related events in bone metastases. On the other hand, compared with mitoxantrone, cabazitaxel in docetaxel pretreated patients improved overall survival. On the contrary, docetaxel in monotherapy remains the standard of care in first line chemotherapy in castration refractory metastatic prostate cancer. Indeed, in two trials, combination of bevacizumab or calcitriol with docetaxel showed no benefit for patients with more toxicities. Finally, docetaxel-based chemotherapy was again evaluated in two other situations: biological recurrence, and hormono-sensitive metastatic stage. Preliminary results of tolerance were presented this year. No doubt that communications during future ASCO meetings would reporte In urologic oncology, prostate cancer represented, even this year, a wide part during the ASCO 2010 meeting. In the non metastatic diseases, two phase III trials confirmed the benefit of radiotherapy combined with hormonotherapy in locally advanced stage. For patients with metastatic hormonoresistant cancer, two randomized trials will probably change the daily practice in the next months. On the one hand, denosumab versus zoledronate decreased significantly the risk of skeletal-related events in bone metastases. On the other hand, compared with mitoxantrone, cabazitaxel in docetaxel pretreated patients improved overall survival. On the contrary, docetaxel in monotherapy remains the standard of care in first line chemotherapy in castration refractory metastatic prostate cancer. Indeed, in two trials, combination of bevacizumab or calcitriol with docetaxel showed no benefit for patients with more toxicities. Finally, docetaxel-based

chemotherapy was again evaluated in two other situations: biological recurrence, and hormono-sensitive metastatic stage. Preliminary results of tolerance were presented this year. No doubt that communications during future ASCO meetings would reported definitive results of efficiency of these phase III studies."

Miura et al. is in a non-English language. An English language title and abstract of Miura et al. are as follows: "A case of Hormone-Refractory Prostate Cancer (HRPC) with Tumor Fever Responding to Docetaxel Plus Prednisolone Therapy," and "We have experienced a patient with tumor fever from hormone-refractory prostate cancer (HRPC) who was treated successfully using docetaxel plus prednisolone therapy. A 65-year-old male was diagnosed with prostate cancer (T4 N1 M1b). He received androgen-ablation therapy. But six months later he was confirmed to show failure of the previous hormone therapy and disease progression even after anti-androgen withdrawal. Then docetaxel plus prednisolone therapy was started. After two courses of this therapy, the PSA level decreased by 50% or more, and after ten courses an improvement was seen on the bone scan. The patient has survived for twelve months after starting docetaxel plus prednisolone therapy, without serious adverse effects."

The Director is authorized to charge any fees required by this paper or credit any overpayment to Account No. **18-1982**.

Respectfully submitted,

/Kelly L. Bender/
Kelly Bender, Reg. No. 52,610
Attorney for Applicant

Sanofi US
U.S. Patent Operations
55 Corporate Drive
Mail Code: 55A-505A
Bridgewater, New Jersey 08807
email: **uspatent.e-filing@Sanofi.com**
Telephone: (908) 981-**6782**
Telefax: (908) 981-7832
Sanofi US Ref. FR2009/121 US CNT

Date: March 17, 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
GUPTA, et al.

Examiner:
James D. Anderson

Application No.:
13/456,720

Art Unit:
1629

Filed:
April 26, 2012

Title: **NOVEL ANTITUMORAL USE OF CABAZITAXEL**

CERTIFICATE OF EFS-WEB TRANSMISSION
I hereby certify that the correspondence below is being transmitted via the USPTO's electronic filing system in accordance with 1.6(a)(4), on

March 17, 2014
Date of Deposit

/Brian Pritchett/
Signature

TO: Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Attached are the following documents:

			Number of Pages
☐	Application Data Sheet		
☐	Declaration		
☐	Drawings		
☒	Extension of Time		2
☒	Supplemental Information Disclosure Statement and Form 1449		9
☒	Response to Final Office Action		9
☐	Specification, Claims and Abstract	Specification	
		Claims	
		Abstract	
☐	Transmittal Letter:		
☒	Other *(specify):* **REQUEST FOR CONTINUED EXAMINATION (RCE)**		3
☒	Other *(specify):* **REFERENCES**		50
☒	Other *(specify):* **REQUEST FOR PRIORITIZED EXAMINATION**		2

PTO/AIA/22 (10-12)
Approved for use through 1/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): FR2009/121 US CNT

Application Number	Filed
13/456,720	2012-04-26

For: NOVEL ANTITUMORAL USE OF CABAZITAXEL

Art Unit	Examiner
1629	James D. Anderson

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$150	$75	$
☐ Two months (37 CFR 1.17(a)(2))	$570	$285	$
☒ Three months (37 CFR 1.17(a)(3))	$1,290	$645	$ 1,290.00
☐ Four months (37 CFR 1.17(a)(4))	$2,010	$1,005	$
☐ Five months (37 CFR 1.17(a)(5))	$2,730	$1,365	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 18-1982.

☐ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 52,610.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Kelly L. Bender/ — Signature

03-17-2014 — Date

Kelly L. Bender — Typed or printed name

908-981-6782 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	GUPTA, et al.	Nonprovisional Application Number (if known):	13/456,720
Title of Invention:	NOVEL ANTITUMORAL USE OF CABAZITAXEL		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	/Kelly L. Bender/	Date	March 17, 2014
Name (Print/Typed)	Kelly L. Bender	Practitioner Registration Number	52,610

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☐ *Total of _____ forms are submitted.

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(71) Applicant *(for all designated States except US)*: **BELLICUM PHARMACEUTICALS, INC.** [US/US]; 6400 Fannin Street, Suite 2300, Houston, TX 77030 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SLAWIN, Kevin** [US/US]; 2336 Underwood Boulevard, Houston, TX 77030 (US). **SPENCER, David** [US/US]; 2811 Prescott Street, Houston, TX 77025 (US). **LAPTEVA, Natalia** [RU/US]; 6119 Shadow Crest, Houston, TX 77074 (US).

(74) Agents: **SILVERSTEIN, Sheryl, R.** et al.; Grant Anderson LLP, c/o PortfolioIP, P.O.Box 52050, Minneapolis, MN 55402 (US).

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(54) **Title**: METHOD FOR TREATING SOLID TUMORS

(57) **Abstract**: Provided herein are methods for treating a solid tumor in a subject in need thereof by activating an immune response against a tumor antigen. Also provided are methods for treating a solid tumor in a subject in need thereof by activating antigen-presenting cells and eliciting an immune response against a tumor antigen. Also provided herein are optimized therapeutic treatments of solid tumors, which comprise determining the presence, absence or amount of a biomarker after the therapy has been administered, and determining whether a subsequent dose of the therapy should be maintained, increased, or decreased based on the biomarker assessment.

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METHOD FOR TREATING SOLID TUMORS

Related Patent Applications

Priority is claimed to U.S. Provisional Patent Application serial number 61/442,582, filed February 14, 2011, and entitled "Method for Treating Solid Tumors;" to U.S. Provisional Patent Application serial number 61/351,760, filed June 4, 2010, and entitled "Method for Treating Solid Tumors;" and to U.S. Provisional Patent Application serial number 61/325,127, filed April 16, 2010, and entitled "Method for Treating Solid Tumors;" which are all referred to and all incorporated by reference herein in their entirety.

Field

The technology relates generally to the field of immunology and relates in part to methods for treating a solid tumor in a subject in need thereof by inducing an immune response. The technology further relates in part to optimized therapeutic treatments of solid tumors.

Background

Antigen-presenting cells present foreign antigens to naïve T cells, inducing a cytotoxic T lymphocyte response. Dendritic cells are effective antigen presenting cells, and activation of the cells often results in a high level expression of costimulatory and cytokine molecules. In order to have effective immunotherapy against cancer cells, such as tumor cells, any immune response against the cells needs to have a long enough life span to be able to continually activate T cells. For use as a vaccine against cancer cells, the antigen presenting cells need to be sufficiently activated, have sufficient migration to the lymph node, and have a lifespan that is long enough to activate T cells in the lymph node.

Dendritic cells and other vaccines acting through antigen presenting cells have been tested for use as vaccines against prostate cancer, including, for example, Sipuleucel-T and Prostvac, but no statistically significant benefit in time to disease progression was found in treated subjects in randomized clinical trials evaluating either agent. (Drugs R & D (2006) 7:197-201; Kantoff, P., et al.,(2010) New Eng. J. Med. 363:411-422; Kantoff, P., et al. (2010) J. Clin. Onc. 28:1099-1105).

Summary

An inducible CD40 (iCD40) system has been applied to human dendritic cells, and used to reduce tumor size in cancer patients. These features form the basis of cancer immunotherapies for treating or preventing such cancers as advanced, hormone-refractory prostate cancer, for example. Accordingly, it has been found that inducing CD40 in antigen presenting cells, and activating an antigenic response against a prostate cancer antigen, for example, a prostate specific membrane antigen (PSMA) provides an anti-tumor effect against not only prostate cancer associated tumors, but also other solid tumors by both direct effects and by targeting tumor vasculature. By inducing an immune response against prostate specific protein antigen, for example, a PSMA polypeptide, the size or growth of solid tumors may be reduced. The therapeutic course of treatment may be monitored by determining the size and vascularity of tumors by various imaging modalities (e.g. CT, bonescan, MRI, PET scans, Trofex scans), by various standard blood biomarkers (e.g. PSA, Circulating Tumor Cells), or by serum levels of various inflammatory, hypoxic cytokines, or other factors in the treated patient.

Thus featured in some embodiments are methods of treating or preventing prostate cancer in a subject, comprising administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with a prostate cancer antigen, such as, for example, a prostate specific protein antigen, for example, a prostate specific membrane antigen; and administering a multimeric ligand that binds to the multimeric ligand binding region, whereby the antigen presenting cell and ligand are administered in an amount effective to treat or prevent the prostate cancer in the subject.

Thus also featured in some embodiments are methods of inducing an immune response against a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen, in a subject, comprising administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric

ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen or a prostate specific membrane antigen; and administering an FK506 dimer or a dimeric FK506 analog ligand. whereby the antigen presenting cell and ligand are administered in an amount effective to induce an immune response in the subject. In some embodiments, the immune response is a cytotoxic T-lymphocyte immune response.

Also featured in some embodiments are methods of reducing tumor size or inhibiting tumor growth in a subject, comprising inducing an immune response against a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen in the subject. In some embodiments, the immune response is a cytotoxic T-lymphocyte immune response. In some embodiments, the method comprises administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with an antigen, for example, a prostate specific membrane antigen; and administering a multimeric ligand that binds to the multimeric ligand binding region, whereby the antigen presenting cell and ligand are administered in an amount effective to treat reduce tumor size or inhibit tumor growth in the subject. In some embodiments, the subject has prostate cancer. In some embodiments, the tumor is in the prostate. In some embodiments, the tumor is in a lung, bone, liver, prostate, brain, breast, ovary, bowel, testes, colon, pancreas, kidney, bladder, neuroendocrine system, lymphatic system, or is a soft tissue sarcoma, glioblastoma, or malignant myeloma. In some embodiments, the transduced or transfected antigen presenting cell is loaded with an antigen, for example, a prostate specific membrane antigen by contacting the cell with a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen. In some embodiments, the transduced or transfected antigen presenting cell is loaded with an antigen, for example, a prostate specific membrane antigen by transducing or transfecting the antigen presenting cell with a nucleic acid coding for a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen. In some embodiments, the tumor is in the prostate, in some embodiments the subject has prostate cancer. In some embodiments, wherein the tumor is in the lung; in some embodiments,

the subject has lung cancer. In some embodiments, the tumor is in the lung, lymph node, bone, or liver.

Also featured in some embodiments are methods of reducing tumor vascularization or inhibiting tumor vascularization in a subject, comprising inducing an immune response against a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen in the subject. In some embodiments, the immune response is a cytotoxic T-lymphocyte immune response. In some embodiments, the method comprises administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with an antigen, for example, a prostate specific membrane antigen; and administering a multimeric ligand that binds to the multimeric ligand binding region, whereby the antigen presenting cell and ligand are administered in an amount effective to treat reduce tumor vascularization or inhibit tumor vascularization in the subject. In some embodiments, the subject has prostate cancer. In some embodiments, the tumor is in the prostate. In some embodiments, the tumor is in a lung, bone, liver, prostate, brain, breast, ovary, bowel, testes, colon, pancreas, kidney, bladder, neuroendocrine system, lymphatic system, or is a soft tissue sarcoma, glioblastoma, or malignant myeloma. In some embodiments, the transduced or transfected antigen presenting cell is loaded with an antigen, for example, a prostate specific membrane antigen by contacting the cell with an antigen, for example, a prostate specific membrane antigen. In some embodiments, the transduced or transfected antigen presenting cell is loaded with an antigen, for example, a prostate specific membrane antigen by transducing or transfecting the antigen presenting cell with a nucleic acid coding for the antigen, for example, a prostate specific membrane antigen. In some embodiments, the level of vascularization is determined by molecular imaging. In some embodiments, wherein the molecular imaging comprises administration of an iodine 123-labelled PSA, for example, PSMA inhibitor. In some embodiments, the inhibitor is TROFEX™/MIP-1072/1095.

Also featured in some embodiments are methods of reducing or slowing tumor vascularization in a subject, comprising administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic

acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen; and administering a multimeric ligand that binds to the multimeric ligand binding region, whereby the antigen presenting cell and ligand are administered in an amount effective to reduce or slow tumor vascularization in the subject.

In some embodiments, the tumor vascularization is reduced in the prostate. In some embodiments, the subject has prostate cancer. In some embodiments, the tumor is in the lung, liver, lymph node, or bone.

In some embodiments, the membrane targeting region is selected from the group consisting of a myristoylation region, palmitoylation region, prenylation region, and transmembrane sequences of receptors. In some embodiments, the membrane targeting region is a myristoylation region. In some embodiments, the multimeric ligand binding region is selected from the group consisting of FKBP, cyclophilin receptor, steroid receptor, tetracycline receptor, heavy chain antibody subunit, light chain antibody subunit, single chain antibodies comprised of heavy and light chain variable regions in tandem separated by a flexible linker domain, and mutated sequences thereof. In some embodiments, the multimeric ligand binding region is an FKBP12 region. In some embodiments, the multimeric ligand is an FK506 dimer or a dimeric FK506 analog ligand. In some embodiments, the ligand is AP1903. In some embodiments, the antigen presenting cell is administered to the subject by intravenous, intradermal, subcutaneous, intratumor, intraprotatic, or intraperitoneal administration. In some embodiments, the prostate cancer is selected from the group consisting of metastatic, metastatic castration resistant, metastatic castration sensitive, regionally advanced, and localized prostate cancer. In some embodiments, at least two doses of the antigen presenting cell and the ligand are administered to the subject. In some embodiments, the antigen presenting cell is a dendritic cell. In some embodiments, the CD40 cytoplasmic polypeptide region is encoded by a polynucleotide sequence in SEQ ID NO: 1. In some embodiments, the prostate specific membrane antigen comprises the amino acid sequence of SEQ ID NO: 4, or a fragment thereof, or is encoded by the nucleotide sequence of SEQ ID NO: 3, or a fragment thereof. In some embodiments, the antigen presenting cell is transfected with a vector, for example, a virus vector, for example, an adenovirus vector. In some embodiments, the antigen presenting cell is

transfected with an Ad5f35 vector. In some embodiments, the FKB12 region is an FKB12v36 region.

In some embodiments, the method further comprises determining the level of IL-6 in the subject after the administration of the antigen presenting cell and the ligand. In some embodiments, the method further comprises determining whether to administer an additional dose or additional doses of the antigen presenting cell and the ligand to the subject, wherein the determination is based upon the level of IL-6 in the subject after administration of at least one dose. In some embodiments, an additional dose is administered where the IL-6 level is above normal. In some embodiments, the IL-6 is from serum.

In some embodiments, the methods further comprise determining the level of VCAM-1 in the subject after the administration of the antigen presenting cell and the ligand. In some embodiments, the method further comprises determining whether to administer an additional dose or additional doses of the antigen presenting cell and the ligand to the subject, wherein the determination is based upon the level of VCAM-1 in the subject after administration of at least one dose. In some embodiments, an additional dose is administered where the VCAM-1 level is above normal. In some embodiments, the VCAM-1 is from serum.

In some embodiments, the progression of prostate cancer is prevented or progression of prostate cancer is delayed in the subject. In some embodiments, the transduced or transfected antigen presenting cell is loaded with a prostate cancer antigen, for example, a prostate specific protein antigen or a prostate specific membrane antigen by contacting the cell with a prostate cancer antigen, for example, a prostate specific membrane antigen. In some embodiments, the transduced or transfected antigen presenting cell is loaded with a prostate cancer antigen, for example, a prostate specific membrane antigen by transducing or transfecting the antigen presenting cell with a nucleic acid coding for a prostate cancer antigen, for example, a prostate specific membrane antigen. In some embodiments, the nucleic acid coding for the prostate cancer antigen, for example, a prostate specific membrane antigen is DNA. In some embodiments, the nucleic acid coding for the prostate cancer antigen, for example, a prostate specific membrane antigen is RNA. In some embodiments, the antigen presenting cell is a B cell. In some embodiments, the chimeric protein further comprises a MyD88 polypeptide or a truncated MyD88 polypeptide lacking the TIR domain. In some embodiments, the truncated MyD88 polypeptide has the peptide sequence of SEQ ID NO: 6, or a fragment thereof, or is encoded by the nucleotide

sequence of SEQ ID NO: 5, or a fragment thereof. In some embodiments, the prostate cancer antigen, for example, a prostate specific membrane antigen is a prostate specific membrane antigen polypeptide.

Also featured in some embodiments are methods of treating or preventing prostate cancer in a subject, comprising administering a composition comprising a nucleotide sequence that encodes a chimeric protein and a nucleotide sequence encoding a prostate cancer antigen, for example, a prostate specific protein antigen or a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain; and administering a multimeric ligand that binds to the multimeric ligand binding region; whereby the composition and ligand are administered in an amount effective to treat or prevent the prostate cancer in the subject. Also featured in some embodiments are methods of treating or preventing prostate cancer in a subject, comprising administering a nucleotide sequence that encodes a chimeric protein, and a nucleotide sequence encoding a prostate cancer antigen, for example, a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, wherein the nucleotide sequence encoding the chimeric protein and the nucleotide sequence encoding a prostate cancer antigen, for example, a prostate specific membrane antigen are delivered using a vector, for example, a virus vector, for example, an adenovirus vector; and administering a multimeric ligand that binds to the multimeric ligand binding region; whereby the composition and ligand are administered in an amount effective to treat or prevent the prostate cancer in the subject.

In some embodiments, progression of prostate cancer is prevented or delayed at least 6 months. In some embodiments, progression of prostate cancer is prevented or delayed at least 12 months. In some embodiments, the prostate cancer has a Gleason score of 7, 8, 9, 10, or greater. In some embodiments, the subject has a partial or complete response by 3 months after administration of the multimeric ligand. In some embodiments, the subject has a partial or complete response by 6 months after administration of the multimeric ligand. In some embodiments, the subject has a partial or complete response by 9 months after administration of the multimeric ligand. In some embodiments, the level of serum PSA in the subject is reduced 20%, 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 6 weeks after administration of the multimeric ligand. In some embodiments, the level of serum PSA in the subject is reduced by 3 months 20%, 30%, 40%. 50%, 60%, 70%,

80% 90% or 95% after administration of the multimeric ligand. In some embodiments, the level of serum PSA in the subject is reduced 20%, 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 6 months after administration of the multimeric ligand. In some embodiments, the level of serum PSA in the subject is reduced 20%, 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 9 months after administration of the multimeric ligand. In some embodiments, the size of the prostate cancer tumor is reduced 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 3 months after administration of the multimeric ligand. In some embodiments, the size of the prostate cancer tumor is reduced 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 6 months after administration of the multimeric ligand. In some embodiments, the size of the prostate cancer tumor is reduced 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 9 months after administration of the multimeric ligand. In some embodiments, the vascularization of the prostate cancer tumor is reduced 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 3 months after administration of the multimeric ligand. In some embodiments, the vascularization of the prostate cancer tumor is reduced 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 6 months after administration of the multimeric ligand. In some embodiments, the vascularization of the prostate cancer tumor is reduced 30%, 40%. 50%, 60%, 70%, 80% 90% or 95% by 9 months after administration of the multimeric ligand. In some embodiments, a T_H1 or T_H2 antigen-specific immune response is detected in the subject after administration of the multimeric ligand.

Also featured in some embodiments are methods of inducing an immune response against a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen in a subject, comprising administering a composition comprising a nucleotide sequence that encodes a chimeric protein and a nucleotide sequence encoding an antigen, for example, a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain; and administering a multimeric ligand that binds to the multimeric ligand binding region. In some embodiments, the composition and the ligand are administered in an amount effective to induce an immune response in the subject. Also featured in some embodiments are methods of inducing an immune response against a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen, in a subject, comprising administering a nucleotide sequence that encodes a chimeric protein, and a nucleotide sequence encoding an antigen, for example, a prostate specific membrane antigen to a subject in need

thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, wherein the nucleotide sequence encoding the chimeric protein and the nucleotide sequence encoding the antigen, for example, a prostate specific membrane antigen are delivered using a vector, for example, a virus vector, for example, an adenovirus vector; and administering a multimeric ligand that binds to the multimeric ligand binding region. In some embodiments, the nucleotide sequences and the ligand are administered in an amount effective to induce an immune response in the subject. In some embodiments, the immune response is a cytotoxic T-lymphocyte immune response.

Also featured in some embodiments are methods of reducing tumor size or inhibiting tumor growth in a subject, comprising inducing an immune response against a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen, in the subject. In some embodiments, the method comprises administering a composition comprising a nucleotide sequence that encodes a chimeric protein and a nucleotide sequence encoding an antigen, for example, a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain; and administering a multimeric ligand that binds to the multimeric ligand binding region. In some embodiments, the method comprises administering a nucleotide sequence that encodes a chimeric protein, and a nucleotide sequence encoding an antigen, for example, a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, wherein the nucleotide sequence encoding the chimeric protein and the nucleotide sequence encoding the antigen, for example, a prostate specific membrane antigen are delivered using a vector, for example, a virus vector, for example, an adenovirus vector; and administering a multimeric ligand that binds to the multimeric ligand binding region. In some embodiments, the composition or nucleotide sequences and the ligand are administered in an amount effective to reduce tumor size or inhibit tumor growth in the subject. In some embodiments, the subject has prostate cancer. In some embodiments, the tumor is in the prostate. In some embodiments, the tumor is in a lung, bone, liver, prostate, brain, breast, ovary, bowel, testes, colon, pancreas, kidney, bladder, neuroendocrine system, lymphatic system, or is a soft tissue sarcoma, glioblastoma, or malignant myeloma. In some embodiments, the tumor is in the lung, liver, lymph node, or bone.

Also featured in some embodiments are methods of reducing tumor vascularization or inhibiting tumor vascularization in a subject, comprising inducing an immune response against a tumor antigen, for example a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen in the subject. In some embodiments, the method comprises administering a composition comprising a nucleotide sequence that encodes a chimeric protein and a nucleotide sequence encoding an antigen, for example, a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain; and administering a multimeric ligand that binds to the multimeric ligand binding region. In some embodiments, the method comprises administering a nucleotide sequence that encodes a chimeric protein, and a nucleotide sequence encoding an antigen, for example, a prostate specific membrane antigen to a subject in need thereof, wherein the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, wherein the nucleotide sequence encoding the chimeric protein and the nucleotide sequence encoding the antigen, for example, a prostate specific membrane antigen are delivered using a vector, for example, a virus vector, for example, an adenovirus vector; and administering a multimeric ligand that binds to the multimeric ligand binding region. In some embodiments, the composition or nucleotide sequences and the ligand are administered in an amount effective to reduce tumor vascularization or inhibit tumor vascularization in the subject. In some embodiments, the subject has prostate cancer. In some embodiments, the tumor is in the prostate. In some embodiments, the tumor is in a lung, bone, liver, prostate, brain, breast, ovary, bowel, testes, colon, pancreas, kidney, bladder, neuroendocrine system, lymphatic system, or is a soft tissue sarcoma, glioblastoma, or malignant myeloma. In some embodiments, the tumor is in a bone, lung, liver, or lymph node. In some embodiments, the level of vascularization is determined by molecular imaging. In some embodiments, the molecular imaging comprises administration of an iodine 123-labelled PSA, for example, PSMA inhibitor. In some embodiments, the inhibitor is TROFEX™/MIP-1072/1095.

Thus featured in some embodiments are methods comprising: administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular

domain, the transduced or transfected antigen presenting cell is loaded with a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen,, administering a multimeric ligand that binds to the multimeric ligand binding region; identifying the presence, absence or amount of a biomarker in the subject, wherein the biomarker is IL-6 or VCAM-1, or a portion of the foregoing; and maintaining a subsequent dosage of the cells or ligand or adjusting a subsequent dosage of the cells or ligand to the subject based on the presence, absence or amount of the biomarker identified in the subject.

Also featured in some embodiments are methods comprising: administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with a tumor antigen, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen; administering a multimeric ligand that binds to the multimeric ligand binding region; identifying the presence, absence or amount of a biomarker in the subject, wherein the biomarker is IL-6 or VCAM-1, or a portion of the foregoing; and determining whether the dosage of the cells or ligand subsequently administered to the subject is adjusted based on the presence, absence or amount of the biomarker identified in the subject.

Thus featured in some embodiments are methods comprising: administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen, or a prostate specific membrane antigen; administering a multimeric ligand that binds to the multimeric ligand binding region; identifying the presence, absence or amount of a biomarker in the subject, wherein the biomarker is uPAR, HGF, EGF, or VEGF, or a portion of the foregoing; and maintaining a subsequent dosage of the cells or ligand or adjusting a subsequent dosage of the cells or ligand to the subject based on the presence, absence or amount of the biomarker identified in the subject.

Also featured in some embodiments are methods comprising: administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a membrane targeting region, a multimeric ligand binding region and a CD40 cytoplasmic polypeptide region lacking the CD40 extracellular domain, the transduced or transfected antigen presenting cell is loaded with a tumor antigen, such as, for example, a prostate cancer antigen, a prostate specific protein antigen, or a, prostate specific membrane antigen; administering a multimeric ligand that binds to the multimeric ligand binding region; identifying the presence, absence or amount of a biomarker in the subject, wherein the biomarker is uPAR, HGF, EGF, or VEGF, or a portion of the foregoing; and determining whether the dosage of the cells or ligand subsequently administered to the subject is adjusted based on the presence, absence or amount of the biomarker identified in the subject.

In some embodiments, at least two doses of the antigen presenting cells and the ligand are administered to the subject with 10 to 18 days between each dose. In some embodiments, six doses of the antigen presenting cell and the ligand are administered to the subject with 10 to 18 days between each dose. In some embodiments, three doses of the antigen presenting cell and the ligand are administered to the subject, with 24-32 days between each dose. In some embodiments, six doses of the antigen presenting cell and the ligand are administered to the subject, with two weeks between each dose. In some embodiments, three doses of the antigen presenting cell and the ligand are administered to the subject, with four weeks between each dose. In some embodiments, each dose of antigen presenting cells comprises about 4×10^6 cells. In some embodiments, each dose of antigen presenting cells comprises about 12.5×10^6 cells. In some embodiments, each dose of antigen presenting cells comprises about 25×10^6 cells.

In some embodiments, the methods further comprise administering a chemotherapeutic agent. In some embodiments, whereby the composition, ligand, and the chemotherapeutic agent are administered in an amount effective to treat the prostate cancer in the subject. In some embodiments, the composition or the nucleotide sequences, the ligand, and the chemotherapeutic agent are administered in an amount effective to treat the prostate cancer in the subject. In some embodiments, the chemotherapeutic agent is selected from the group consisting of carboplatin, estramustine phosphate (Emcyt), and thalidomide. In some embodiments, the chemotherapeutic agent is a taxane. The taxane may be, for example, selected from the group consisting of docetaxel (Taxotere), paclitaxel, and cabazitaxel. In some embodiments, the taxane is docetaxel.

In some embodiments, the chemotherapeutic agent is administered at the same time or within one week after the administration of the antigen presenting cell or the ligand. In other embodiments, the chemotherapeutic agent is administered after the administration of the ligand. In other embodiments, the chemotherapeutic agent is administered from 1 to 4 weeks or from 1 week to 1 month, 1 week to 2 months, or 1 week to 3 months after the administration of the ligand. In other embodiments, the methods further comprise administering the chemotherapeutic agent from 1 to 4 weeks, or from 1 week to 1 month, 1 week to 2 months, or 1 week to 3 months before the administration of the antigen presenting cell. In some embodiments, the chemotherapeutic agent is administered at least 2 weeks before administering the antigen presenting cell. In some embodiments, the chemotherapeutic agent is administered at least 1 month before administering the antigen presenting cell. In some embodiments, the chemotherapeutic agent is administered after administering the multimeric ligand. In some embodiments, the chemotherapeutic agent is administered at least 2 weeks after administering the multimeric ligand. In some embodiments, wherein the chemotherapeutic agent is administered at least 1 month after administering the multimeric ligand.

In some embodiments, the methods further comprise administering two or more chemotherapeutic agents. In some embodiments, the chemotherapeutic agents are selected from the group consisting of carboplatin, Estramustine phosphate, and thalidomide. In some embodiments, at least one chemotherapeutic agent is a taxane. The taxane may be, for example, selected from the group consisting of docetaxel, paclitaxel, and cabazitaxel. In some embodiments, the taxane is docetaxel. In some embodiments, the chemotherapeutic agents are administered at the same time or within one week after the administration of the antigen presenting cell or the ligand. In other embodiments, the chemotherapeutic agents are administered after the administration of the ligand. In other embodiments, the chemotherapeutic agents are administered from 1 to 4 weeks or from 1 week to 1 month, 1 week to 2 months, or 1 week to 3 months after the administration of the ligand. In other embodiments, the methods further comprise administering the chemotherapeutic agents from 1 to 4 weeks or from 1 week to 1 month, 1 week to 2 months, or 1 week to 3 months before the administration of the antigen presenting cell.

Also featured in some embodiments are methods of increasing the chemosensitivity of a tumor, comprising administering a transduced or transfected antigen presenting cell to a subject in need thereof, wherein: the antigen presenting cell is transduced or transfected with a nucleic acid including a nucleotide sequence that encodes a chimeric protein, the chimeric protein comprises a