

# Dr. Howard I. Scher: Series of UNDISCLOSED Conflicts of Interest

Note: The information presented within is believed accurate, however, no representation or guarantee of accuracy is being made because the author does not control or have the ability to verify such 3<sup>rd</sup> party public postings. The reader shall draw their own conclusions; the only intent to present verifiable publicly obtained information about Scher, his written and verbal claims of Conflict of Interest and how they differ.

## Dr. Howard Isidor Scher has Ten Reasons to Worry about Provenge<sup>®</sup>'s Approval

Dr. Scher, according to information obtained from public sources, is closely associated with the following companies – all of which deal prostate cancer (PCa) therapies.

1. Novacea: grants and research support; study chair of DN-101
2. GPB Biotech: financial conflict of interest
3. Pharmion: financial conflict of interest
4. Sanofi Aventis: grants and research support
5. Bristol Myers Squibb: consultant, grants and research support
6. Millennium Pharmaceuticals: grant of research support
7. Cougar Biotechnology: advisory board
8. Innovive Pharmaceuticals: advisory board
9. Infinity Pharmaceuticals: principal investigator
10. ProQuest Investments: consultant, scientific advisory board, limited partner

The purpose of this report is to explain Dr. Howard I. Scher's motivation not to approve Provenge, and to shed more light on the FDA decision to allow Dr. Scher's participation in the Advisory Committee that discussed Provenge's approval despite Scher's COIs which he did NOT disclose to the FDA in his waiver application.

By misleading the FDA, Dr. Scher was granted the FDA Waiver and subsequently leveraged his participation in the Advisory Committee to send an unprecedented letter to the FDA, which was then leaked to a tabloid, that created huge pressure on the FDA that led to the FDA's wrong decision not to approve Provenge despite the favorable recommendation of the vast majority of its own Advisory Committee.

Section I of this report will briefly explain the legal requirements for full disclosure of COI and will discuss how Scher represented his COI to the FDA with regards to Provenge (as well as to a Wall Street Journal reporter). Section II will further discuss Scher's interests in not having Provenge available to prostate cancer patients. Section III of this report will dig into the details of various cases in which Scher is associated with competing companies – most of which he did NOT disclose to the FDA. Section IV will move another step forward and describe how Scher's actions bode well with the financial and professional interests of the leading prostate cancer oncologists.

Appendix A is a copy of Dr. Scher's "Letter to the FDA" and Appendix B is a copy of a letter co-written to the FDA by 5 MDs and 2 PhD's that points to MANY misrepresentations and basic errors in Scher's email – so of which can only be explained by Scher's COIs. These letters are a MUST read in order to get the full picture.

## I. Scher's Publicly Represented COI

- A. The Law
- B. Scher's COI Waiver (to the FDA)
- C. Interview with WSJ's Marilyn Chase

### A. The Law Requires FULL Disclosure

As per Sec. 208 "Acts affecting a personal financial interest":

[http://www.law.cornell.edu/uscode/html/uscode18/usc\\_sec\\_18\\_00000208----000-.html](http://www.law.cornell.edu/uscode/html/uscode18/usc_sec_18_00000208----000-.html)

" ... if the officer or employee first advises the Government official responsible for appointment to his or her position of the nature and circumstances of the judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, charge, accusation, arrest, or other particular matter and makes full disclosure of the financial interest and receives in advance a written determination made by such official that the interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such officer or employee; "

### B. What did Scher report to the FDA?

Dr. Scher's DISCLOSURE to FDA as filed on February 26, 2007:

I acknowledge that contingent upon public disclosure of the following financial interest listed below related to the review of Sipuleucel-T, Dendreon Corp., for the treatment of men with asymptomatic metastatic hormone refractory prostate [sic] cancer. I am eligible to receive waivers under 18 U.S.C. §208(b)(3) and 21 U.S.C. §355(n)(4)

<u>Type of Interest</u>	<u>Nature</u>	<u>Magnitude</u>
Grant (related)	Competing Firm	\$100,000-\$300,000
Grant (related)	Competing Firm	\$100,000-\$300,000
Stock	Competing Firm	\$5,000-\$100,000

I hereby request that FDA make this information publicly available on my behalf. I understand that without public disclosure of the interests the waiver is not valid.

\_\_\_\_\_/ s /\_\_\_\_\_  
Howard I. Scher, M.D.

\_\_\_\_\_  
2/26/07

Relevant FDA Waiver COI information:

" ... Dr. Scher advised the FDA that he has a financial interest related to the above topic that could potentially be affected by his participation in the matter at issue.

Dr. Scher reported that he has joint stock in \_\_\_\_\_ at a current value of \$5,000 - \$100,000

Additionally he reported that his institution has a grant from a \_\_\_\_\_( competing firm) . The grant is current and his institution receives \$100,000 - \$300,00 per year from 2006-2007. Dr. Scher receives no salary from the grant. The grant is to study a licensed, approved drug (\_\_\_\_\_) in prostate cancer trials. \_\_\_\_\_ is a licensed drug currently used in other cancer therapies.

Dr. Scher also reported that his institution has a grant from \_\_\_\_\_(competing firm). The grant is current and his institution receives \$100,000 - \$300,00 per year from 2006-2008. Dr. Scher receives no salary from the grant. The grant is to study an investigational drug (\_\_\_\_\_) that is also being studied in several types of cancer. "

Link to original document:

<http://www.fda.gov/ohrms/dockets/ac/07/waivers/2007-4291-w-07-Sche-208r.pdf>

See Appendix A for Scher's filing to the FDA and Appendix B for the complete COI Waiver by the FDA

**Did Dr. Howard I sidor Scher make a FULL DISCLOSURE to the FDA?**

C. Scher's WSJ Online interview with Marilyn Chase, May 11, 2007

" ... I try to keep to the **high ground**," Scher said, adding that he doesn't work with any companies in direct competition with Dendreon... He serves as advisor to Innovive, a small biotech not involved in prostate cancer, and works with Bristol-Myers Squibb in an unpaid capacity on early stage drugs that may hold promise in prostate cancer. He and his wife hold small amounts of stock in Biogen Idec and Pfizer, he said."

Link to original document:

<http://blogs.wsj.com/health/2007/05/11/dendreons-ups-and-downs-at-fda-and-on-nasdaq/>

**One's "HIGHER GROUND" might be someone else's sub-standards...**

## II. Scher's REAL concerns regarding Provenge

- ❖ Provenge becoming the new standard of care for cancer patients, hence, ELEVATING the bar for alternative therapeutics seeking approval (especially the ones that Scher is the Lead Investigator)
  - ❖ Financial merits ("investors") are more important than patients
- A. Scher's concerns - per his "letter to the FDA"
  - B. What did Scher have in mind while voting at the Advisory Committee?

### A. Scher's concerns - per his "Letter to the FDA"

Scher cited "interesting" reasons to oppose the approval of Provenge, as he wrote in the Letter, supposedly sent to the FDA and then leaked to the "Cancer Letter" tabloid (see Appendix C for the full version of the Letter):

"... An approval recommendation has far reaching implications beyond making the product available that the data simply do not support or justify. For one, it provides the Agency's endorsement of Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S.

The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future randomized phase 3 trials that are being designed for the regulatory approval of any new experimental agent or approach. It also opens the door to the premature approval of drugs based on inconclusive data..."

As per Scher, once approved, Provenge will quickly become the Standard of Care (SoC) for late stage prostate cancer. The drug candidates that Scher will be investigating in the future will have to demonstrate statistical significant superiority over the SoC. Today's SoC is Taxotere, a toxic chemotherapy agent that showed 2.5 months survival benefit over placebo (no-treatment) with terrible side effects (see section III for more info about Taxotere's side effects), so a modest survival benefit and a not-so-horrible side effect profile is all that is required for a new drug to get an approval. However, having Provenge as a potential SoC, new drug candidates for HRPC will be approved only after statistically "beating" a MUCH higher bar – 4.5 months survival benefit and merely no side effects; whereas recruiting patients for chemo trials in slightly different stages of prostate cancer could be problematic due to the reluctance of many men to accept chemotherapy treatment.

Dr. Howard Isidor Scher is a lead investigator in many prostate cancer clinical trials. Having a high quality "placebo" (standard of care drug) is a REAL CONCERN for his future research success.

## B. What was Scher thinking about during the VOTING at the Advisory Committee?

"DR. SCHER: I think we are really poised at the beginning of what will be hopefully an outstanding era of immunotherapy. I think there is sufficient evidence demonstrated which justifies the definitive study, and obviously there are investors in that who concurred, but I think it does not meet the -- as the question was phrased, to establish the efficacy. I think this is still an open question..."

Source: page 386 of the transcript of the Advisory Committee (AdCom):  
<http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4291T1.pdf>

What did the good doctor think about during the voting ... INVESTORS????!?!?!?!

Would an Advisory Committee member, without financial COIs, think about investors while casting his vote, or should he think about the patients? Note that Provenge offers late-stage prostate cancer patients a choice to receive non-toxic treatment that would prolong their lives with minimal side effects.

## III. Scher's Documented Conflict Of Interest

Dr. Howard Isidor Scher is closely associated with at least 10 companies – all of which develop prostate cancer drugs. These findings are a sharp contrast to Scher's PARTIAL disclosure to the FDA regarding his COIs.

### Conflict of Interest: Novacea

" ... Dr. Scher reported that he receives grants and research support from Novartis, Novacea, Bristol-Myers Squibb and Sanofi-Aventis. "

Source: <http://www.medpagetoday.com/HematologyOncology/ASCOProstate/tb/5142>

"In the first quarter of 2006, Novacea began enrolling patients in its Phase 3 ASCENT-2 trial. ASCENT-2 is scheduled to enroll 900 patients at over 200 clinical sites in the United States, Canada and Europe. Dr. Howard Scher, Chief, Genitourinary Oncology Service, and the D. Wayne Calloway Chair in Urologic Oncology of Memorial Sloan-Kettering Cancer Center, New York, USA, is serving as Study Chair. "

"... Phase 3 trial for Asentar in androgen-independent prostate cancer (AIPC)..."

"...ASCENT-2 Phase 3 clinical trial of Asentar..."

Source: <http://phx.corporate-ir.net/phoenix.zhtml?c=175681&p=irol-newsArticle&ID=978064&highlight=>

## NOTES

- Dr. Scher is the chief researcher of ASCENT-2, a 900 patient phase III trial for Novacea's Asentar which is used in conjunction with Taxotere in prostate cancer
- On May 30 (three weeks after the FDA issued the "Complete Response" to Dendreon – denying an immediate approval of Provenge), Schering-Plough agreed to form a partnership with Novacea. Schering-Plough made immediate cash payment of \$60 million to Novacea and will pay an additional \$380 million upon reaching certain milestones with respect to Asentar.
- What would one think about the impact of Schering-Plough decision to partner with Novacea had the FDA approved Provenge instead of delaying the approval by a few years?
- What would have then happen to the enrollment of this 900-patients trial headed by Dr. Scher? Could he might have had trouble getting patients to enroll in his trial – where all the participants receive chemotherapy – having Provenge on the market with its superior survival benefit coupled with minor side effects of flu-like symptoms for 1 or 2 days and a superior Quality of Life (QoL)? It is important to note that around 50% of today's PCa patients refuse to take Taxotere because of its horrible side effects.

## Conflict of Interest: GPC Biotech

" ... Dr. Scher reported **financial conflicts of interest** for **GPC Biotech** and Pharmion ..."

Source: bottom of <http://www.medpagetoday.com/MeetingCoverage/ASCOProstate/tb/5822>

About Pharmion and GPC Biotech:

CHICAGO, June 4 /PRNewswire-FirstCall/ --Pharmion Corporation (Nasdaq: PHRM) and GPC Biotech AG (Frankfurt Stock Exchange: GPC; TecDAX index; Nasdaq: GPCB) today announced the presentation of additional data from the double-blind, randomized satraplatin Phase 3 registrational trial, the SPARC trial (Satraplatin and Prednisone Against Refractory Cancer). The data are being presented today at the Annual Meeting of the American Society for Clinical Oncology (ASCO) in Chicago. The SPARC trial is evaluating satraplatin plus prednisone versus placebo plus prednisone in 950 patients with hormone-refractory prostate cancer (HRPC) whose prior chemotherapy has failed. A New Drug Application (NDA) for satraplatin is currently under priority review by the U.S. Food and Drug Administration (FDA).

Source:

<http://investor.pharmion.com/phoenix.zhtml?c=142045&p=irol-newsArticle&ID=1010774&highlight=>

## Conflict of Interest: Pharmion

" ... Dr. Scher reported **financial conflicts of interest** for GPC Biotech and **Pharmion** ..."

Source: bottom of <http://www.medpagetoday.com/MeetingCoverage/ASCOProstate/tb/5822>

About Pharmion and GPC Biotech:

CHICAGO, June 4 /PRNewswire-FirstCall/ --Pharmion Corporation (Nasdaq: PHRM) and GPC Biotech AG (Frankfurt Stock Exchange: GPC; TecDAX index; Nasdaq: GPCB) today announced the presentation of additional data from the double-blind, randomized satraplatin Phase 3 registrational trial, the SPARC trial (Satraplatin and Prednisone Against Refractory Cancer). The data are being presented today at the Annual Meeting of the American Society for Clinical Oncology (ASCO) in Chicago. The SPARC trial is evaluating satraplatin plus prednisone versus placebo plus prednisone in 950 patients with hormone-refractory prostate cancer (HRPC) whose prior chemotherapy has failed. A New Drug Application (NDA) for satraplatin is currently under priority review by the U.S. Food and Drug Administration (FDA).

Source:

<http://investor.pharmion.com/phoenix.zhtml?c=142045&p=irol-newsArticle&ID=1010774&highlight=>

## Conflict of Interest: Sanofi Aventis

" ... Dr. Scher reported that he receives grants and research support from Novartis, Novacea, Bristol-Myers Squibb and Sanofi-Aventis. "

Source: <http://www.medpagetoday.com/HematologyOncology/ASCOProstate/tb/5142>

Sanofi Aventis is the maker of Taxotere (docetaxel), today's only approved drug for late stage prostate cancer. To better understand the concerns of Sanofi-Aventis from Provenge, especially in light of Provenge's mild side effects profile, it is worthwhile to check Taxotere's side effects:

In the two studies that led to Taxotere's approval, 1-2% of the patients died from side effect directly attributed to the drug.

In addition to these deaths, " ... Many people have one or more of the following side effects

- Fatigue - patients say this is the most disruptive side effect of all. Tiredness often carries on after treatment has ended. Most people find their energy levels are back to normal from 6 months to a year after their treatment finishes.
- Temporary effect on the bone marrow. The bone marrow makes blood cells and a drop in its function can cause
  - An increased risk of getting infections. This is due to a temporary drop in the number of white blood cells produced by the bone marrow. Having a low white blood count means that you are less able to fight infections and can become very unwell. You may have headaches, aching muscles, cough, sore throat, pain passing urine or feel cold and shivery. Infections can sometimes be life threatening. You should contact your doctor urgently if you think you have an infection.
  - Tiredness and shortness of breath. This is due to a drop in the number of red blood cells

made by your bone marrow which is called anaemia. You may need a blood transfusion to treat anaemia.

- Bruising or bleeding more easily. This is due to a drop in the number of platelets produced by your bone marrow. You may have lots of tiny red spots or bruises on your arms or legs. You may have nosebleeds or notice your gums bleed when you brush your teeth.

- Fluid retention. This occurs in about half the patients treated with docetaxel. You may have swelling of the hands and feet, shortness of breath and weight gain. The steroids you will be given with the drug can help to prevent this side effect.
- Rash which may be itchy. This happens in half the patients treated. You may also notice that your fingernails become discoloured. Some people also develop soreness, redness and peeling on hands and feet (palmar – plantar syndrome).
- Hair loss is usually complete and affects 8 out of 10 people (80%) treated. A cold cap may help to stop you losing your hair, but you need to talk to your doctor about how advisable this is with your type of cancer.
- Sore mouth affects about 4 out of every 10 (40%) patients treated
- Diarrhea affects about 4 out of every 10 (40%) patients treated
- Tiredness affects up to 8 out of 10 (80%) people treated

#### Occasional side effects

Some people have the following side effects

- Feeling or being sick this is usually mild and lasts for only a short time after having each treatment
- Numbness and tingling in hands and feet
- Loss of fertility - it is not known exactly what effect this drug may have on your fertility. It is important to talk to your doctor before starting treatment. Women may stop having periods (amenorrhoea). This may only be temporary.
- Aching muscles and joints
- Raised temperature (fever)
- While you are having your treatment, docetaxel can leak into the tissues around the needle (cannula) and cause damage. It is important to tell your doctor or nurse straight away if you have any
  - Stinging or burning around the needle
  - Leakage of fluid
  - Redness or swelling around the cannula site after the infusion has finished... "

Source: <http://www.cancerhelp.org.uk/help/default.asp?page=4004>

It is understandable why 50% of today's eligible prostate cancer patients refuse to take Taxotere. One can only speculate what might happen to Sanofi's revenues (from Taxotere)

once Provenge is approved.

## Conflict of Interest: ProQuest Investments

Scher serves on the Scientific Advisory Board of this \$900 million venture capital fund

(<http://www.proquestvc.com/scienceadvisory.asp> )

that was founded in 1998 focusing initially on Prostate Cancer

([http://sis.windhover.com/buy/abstract.php?id=1998900165&utm\\_source=company](http://sis.windhover.com/buy/abstract.php?id=1998900165&utm_source=company))

A "companion fund" is a typical investment vehicle within the settings of a Venture Capital Fund offering the "friends and family" of the Fund to co-invest with the fund (it has the same portfolio as the Main Fund). So Scher is not just on the Fund's "Advisory Board" - he directly benefits from the Fund's success (and one can recall that ProQuest has a couple of prostate-cancer related companies AND that Milliken is among its large investors).

"Such Selling Shareholder is a **Limited Partner in ProQuest Companion Fund**, L.P. "

Source: <http://www.secinfo.com/dsBqn.51Cy.htm> - note that Howard Scher is associated with footnote #3 (bottom of document)

## Conflict of Interest: Bristol-Myers Squibb

" ... Dr. Scher reported that he **receives grants and research support** from Novartis, Novacea, **Bristol-Myers Squibb** and Sanofi-Aventis. "

Source: <http://www.medpagetoday.com/HematologyOncology/ASCOProstate/tb/5142>

" ... He has acted as a **consultant for Bristol-Myers Squibb**, Conforma Therapeutics, ProQuest Investments, and Wyeth-Ayerst Pharmaceuticals..".

Source: <http://www.mskcc.org/mskcc/html/2270.cfm?IRBNO=06-030>

Info about Bristol-Myers Squibb's prostate cancer clinical trial:

"A PHASE I DOSE-ESCALATION STUDY OF BMS-641988 IN PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER

Patients must have a confirmed diagnosis of prostate cancer that has progressed despite hormonal therapy.

...

For more information and to see if you are eligible for this study, please contact Dr. Howard I. Scher at 646-422-4330."

Note that Dr. Scher is one of the 3 leading researchers of this study (managing site #001):

Source: <http://clinicaltrials.gov/ct/show/NCT00326586>

## Conflict of Interest: Millennium Pharmaceuticals

Link to original document:

<http://www.millennium.com/rd/oncology/candidates/velcade.asp>

A number of Phase I and Phase II clinical trials in which bortezomib (Velcade) is being studied as a single agent or in combination with other chemotherapeutic agents as a potential treatment for hematologic malignancies including non-Hodgkin's lymphoma and Waldenstrom's macroglobulinemia, and various solid tumors including lung, breast, prostate and ovarian cancers are ongoing.

"MLN2704 is a conjugated monoclonal antibody that shows activity in prostate cancer tumors in a novel way," said Howard Scher, M.D., Chief of Genitourinary Oncology at Memorial Sloan-Kettering Cancer Center in New York, and the study's lead investigator. "We are continuing with early phase I/II trials to assess the optimal dose and schedule of MLN2704."

Source: [http://investor.millennium.com/phoenix.zhtml?c=80159&p=irol-newsArticle\\_Print&ID=709948&highlight=](http://investor.millennium.com/phoenix.zhtml?c=80159&p=irol-newsArticle_Print&ID=709948&highlight=)

Howard I Scher, MD: D Wayne Calloway Chair in Urologic Oncology; Chief, Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York. Grants/Research Support: Millennium Pharmaceuticals Inc, Sanofi-Aventis; Consulting Fees: Abbott Laboratories.

Source: <http://www.patternsofcare.com/2005/4/cme.htm>

## Conflict of Interest: Cougar Biotechnology

Link to original document:

<http://www.cougarbiotechnology.com/docs/CougarBiotechnology2006AnnualReport.pdf>

(See page 6 - Scher serves on its Advisory Board)

Page 12 of this document lists the following:

" ... We currently have rights to three clinical stage drug candidates:

- CB-7630 (Abiraterone Acetate), which we are developing for the treatment of advanced prostate cancer patients;
- CB-3304 (Noscapine and related analogs), which we are developing for the treatment of hematological malignancies (non-Hodgkin's lymphoma and multiple myeloma);
- CB-1089 (Seocalcitol), an analog of Vitamin D that we are developing to be used in the treatment of prostate cancer ..."

## Conflict of Interest: Innovive Pharmaceuticals

Link to original document:

[http://www.innovivepharma.com/content/scientific\\_advisory\\_board.html](http://www.innovivepharma.com/content/scientific_advisory_board.html)

As of now, Innovive is NOT active in PCa, but it is worth noting the following

([http://www.advfn.com/news\\_INNOVIVE-Pharmaceuticals-Presents-Additional-Phase-I-Data-on-INNO-406-for-Treatm\\_20882511.html](http://www.advfn.com/news_INNOVIVE-Pharmaceuticals-Presents-Additional-Phase-I-Data-on-INNO-406-for-Treatm_20882511.html)):

About INNO-406 INNO-406 (formerly known as NS-187) is a potent, oral, rationally designed, dual Bcr-Abl and Lyn-kinase inhibitor currently in Phase I clinical studies. According to a study published in the journal Blood (Dec. 1, 2005):

- INNO-406 is 25 to 55 times more potent than imatinib in vitro, and at least 10 times as effective as imatinib mesylate in suppressing the growth of Bcr-Abl bearing tumors.
- INNO-406 has demonstrated activity in 12 of 13 imatinib-resistant cell lines.
- In addition to its Bcr-Abl inhibitory properties, INNO-406 inhibits Lyn-kinase. Upregulation of Lyn-kinase activity is a well-recognized cause of imatinib resistance. Lyn-kinase activation has also been documented in a variety of solid tumors, including prostate cancer.

## Conflict of Interest: Infinity Pharmaceuticals (Discovery Partners International)

Link to original document:

<http://www.secinfo.com/d14D5a.v5AKx.htm#1stPage>

Scher is mentioned among the company's Key Principal Investigators for prostate cancer

(See bottom of the above document)

## IV. Scher Represents the Oncologists COI

Since Dr. Scher is so deeply involved in Taxotere adjuvant clinical trials, and since adjuvant chemotherapy trials in prostate cancer have been dismal failures as nearly all have been cancelled due to lack of enrollment, especially in comparison to breast cancer. For example, over two years ago, nearly 10 planned adjuvant Taxotere trials did not get off the ground. This has concerned prostate cancer research academics to no end since fewer trials mean less chance for academic, financial and professional glory. The solution that Sanofi-Aventis (maker of Taxotere) came up with was to appoint multiple "lead" investigators on most of these trials, including Dr. Scher, among other leading prostate cancer oncologists.

It is hard to overestimate the fear in the prostate oncologist community of seeing this new set of trials fail to enroll. Leading prostate cancer oncologists will do most anything, or rationalize most any behavior, to prevent anything from interfering with the success enrollment of these trials.

As described above, the most telling thing in Dr. Scher's letter to the FDA was his worry that Provenge would become a standard of care. The actual argument is nonsense because the FDA has nothing to do with determining SoC. That's the job of ASCO and other professional organizations. The subtext of the

argument, however, is much more interesting.

While prostate oncologists like to publicly complain the reason for poor enrollment in adjuvant chemotherapy trials is refusal to participate by urologists – they'll actually admit that the REAL reason is that men simply don't want to take chemotherapy. This is important in terms of Provenge because a Provenge approval potentially represents a major complication to successful enrollment to these Taxotere adjuvant trials.

All it would take is one cooperative group to launch a Provenge adjuvant trial and enrollment in the adjuvant Taxotere trials would dry up to nothing. One can further assume that the lead investigators on an adjuvant Provenge trial could actually be urologists.

Hence, another conflict of interest in the prostate oncology community is their desire NOT to change the current climate in order to ensure that these adjuvant trials are enrolled. This filters through to the FDA process as it means that there is no way Provenge gets a fair hearing in front of the dominant oncologists (mainly of ODAC). This also explains why it is so easy for Provenge bears and Pazdur's gang in the FDA to recruit prostate cancer oncologists with very negative views on the drug (Hussain, Fleming, DeVita – just to name a few).

# Appendix A

## Dr. Scher's "Letter to the FDA"

Dr. Scher's Confidential letter to the FDA several weeks after the March 29<sup>th</sup> FDA Advisory Committee meeting. This Confidential letter somehow found it's way to a publication called, The Cancer Letter, and it is reportedly printed in their Vol. 33 No. 14 April 13, 2007 issue.

One has to wonder HOW did The Cancer Letter was able to get a copy of an allegedly Confidential FDA letter?

I am writing to express concerns about the recent review of Sipuleucel-T at the FDA Advisory Meeting on March 29, 2007. These concerns are: a recommendation for approval based on data that fall short of the regulatory requirements; an inadequate statistical construct to determine definitive benefit; incomplete data on product safety; and what appear to be different criteria for approval by two Advisory Committees to the Agency. All but the latter were discussed in the open meeting, but warrant further consideration given the outcome. The concerns are based on my experience as a voting member on several ODACs representing the Agency, and separately, as a Presenter to ODAC for Industry Sponsors. I have been one of the Academic Leaders of the Prostate Cancer Clinical Trial Endpoints initiative begun under the joint Sponsorship of the FDA, AACR, ASCO and PCF in 2004, which were presented at the February 2007, Prostate ASCO Meeting in Orlando. The final manuscript is currently under review at the NCI, FDA and the Group of established Prostate Cancer Clinical Trial experts who together, formulated the recommendations. I am also the Principal Investigator of a Multicenter Prostate Cancer Clinical Trials Consortium funded by the Department of Defense that focuses on phase 1 and 2 trials in this disease.

Let me state at the outset that I was one of the four Committee Members who voted "no" to the question whether the trials presented by the Sponsor established the efficacy or demonstrated substantial evidence of benefit to justify an approval recommendation to the FDA. My vote was based on the fact that neither of the two trials presented met their primary endpoint, which renders the significance of results from any subsequent analyses as "exploratory" and "hypothesis generating." As such, the results do not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit. The trial data were not consistent. Even if one accepts the posthoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a "placebo"), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory. Consequently, the only conclusion that can be reached is that the survival difference observed may have occurred by chance alone, and that the results do not support an approval recommendation. This, and the Sponsor's recognition that an additional prospective study was needed, mandates deferring any decision on whether an approval should be granted until the results of the ongoing 500 patient phase 3 trial that is powered on a primary endpoint of survival, is accrued and analyzed.

Concerns about the validity of the findings were reinforced by the absence of other signals of an antitumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or boney disease radiographically, health related quality of life, or that administration of the product delayed the development of pain. Even the time to the administration of chemotherapy, an indication to the treating Physicians that the clinical course had worsened, was similar between the two groups. Reinforcing the uncertainty was the fact that in response to a direct question at the meeting, none of the Physicians representing the Sponsor could articulate how treatment with the product had "helped" any individual patient.

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for Sipleucel-T treated patients (HR = 1.92, alpha =0.05, two sided, with 80% power). A total of 127 patients were enrolled using a 2:1 randomization in favor of the experimental therapy. The study was double blind and included an independent review of all imaging results. The estimated time to progression on which the trial was

powered proved to an overestimate, as the actual observed median time to progression was 9 to 11 weeks for both arms: a difference that was not statistically significant. A summary of the progression events showed that 90% (97/114) were by imaging, 10 were clinical, and 7 were for the new onset of disease related pain. Unrecognized at the time of the design of the trial, was that the eight week interval between disease assessments was too short to observe clinically significant changes by bone scan, and that in many cases, apparent "progressions" eight weeks after the start of a therapy are more a reflection of disease worsening that led to trial entry, and not a failure of the treatment. (CCR 13:1488, 2007) This is similar to what was observed in the trial with the endothelin antagonist, atrasentan, in which a 12 week disease assessment interval was used and a large proportion of patients were withdrawn at the time of scheduled scans in the absence of clinical worsening of disease (ODAC, September 13, 2005). Recognizing this, the Prostate Cancer Working Group 2 was advised that an apparent progression on bone scan at a three month assessment, be confirmed by documenting further progression on a subsequent scan six or more weeks later before considering a patient to have failed the treatment. (ASCO Multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007). Although the Sponsor suggested that the effect of the product was delayed, this hypothesis could not be explored because serial imaging to assess disease at defined intervals were not performed once a patient was considered to have "progressed" and taken off study. As a result, individual sites of disease were no longer being monitored, so that no statements could be made regarding a possible "delayed effect" of the product on disease status.

At 3-years, a prespecified survival analysis was performed which showed a 4.5 month difference in median survival favoring Sipuleucel-T, and while a significant p-value for the difference was determined, the type 1 error rate is surely inflated by this additional analysis. Imbalances in disease aggressiveness and disease extent were noted between the Sipuleucel-T and "control" groups including a higher proportion with Gleason 6 disease or less at diagnosis (26.8% vs. 15.6%), and a lower proportion with both bone and soft tissue disease (52% vs. 69%) at the time therapy was started. Both factors favored the Sipuleucel-T arm, predicting a longer survival for the "treated" patients independent of therapy. The 2:1 randomization increased the power of the experimental arm, but it may have inadvertently made the small 43 patient control group more heterogeneous and less representative of the global population of men for whom the indication was proposed. The potential impact of heterogeneity in small patient cohorts was shown when a post-study change in the progression times of two patients (a change not accepted by the Agency), resulted in a change in the significance estimates.

The first question the Agency posed to the Committee was whether the product was "reasonably safe" for the intended population. While the vote was yes, the issue of cerebrovascular events as a potential safety signal was raised. This concern was based on the finding that 4.9% (17/345) of the Sipuleucel-T and 1.7% (3/172) of "placebo" treated patients who were enrolled on randomized trials for the indication, experienced a cerebrovascular event ( $p=0.092$ ). The odds ratio for developing a cerebrovascular event was 2.92, with wide confidence intervals (0.82 to as high as 10 fold). Deaths due to CVA's were recorded in 1.5% of Sipuleucel-T patients and 0.9% of those receiving "placebo." Unclear is why there is no mention of CVA's in the published report of the study in the Journal of Clinical Oncology (JCO 24:3089, 2006). Given that the product is released for administration based on the increase in the proportion of CD54+ cells and not the absolute number of any particular cell type and that CD54+ cells actually represent only 20% of the final product, the contribution of the other cell populations and cytokines that may be present in the administered product on the development of a cerebrovascular event is not known. More important, and perhaps underappreciated during the discussion, is the recognition that the "placebo" used in this trial, a portion of the leukopheresis product that is cultured without the immunizing antigen and reinfused, may not be inert and in itself contributed to a relative worsening of survival for the control group in this trial. To place the frequency of the neurologic events in perspective, no cerebrovascular events were observed in TAX-327, a 997 patient three arm randomized trial that evaluated two different dose schedules of docetaxel in comparison to mitoxantrone, (NEJM 351:1052, 2004) or ASCENT1, a 251 patient randomized comparison of docetaxel weekly with or without high dose calcitriol (DN-101)(JCO 25:669, 2007). Neurologic events that were not detailed further were observed in 7% of the 338 patients who received estramustine which is known to be thrombogenic, in combination with docetaxel on the SWOG 99-16 trial (NEJM 351:1513, 2004).

Another concern is that the requirements for regulatory approval appear to differ between the ODAC and CBER Advisory Committee. As an example, ASCENT1 was a prospective randomized phase 2 trial of weekly docetaxel with or without high dose calcitriol (DN-101). The trial was powered to detect a 20% difference in the PSA response rate at six months between the two groups as the primary endpoint, but also included a pre-specified survival analysis, similar to that included in the Sipuleucel-T 9901 trial as one of the secondary endpoints. PSA response was defined as a 50% or greater decline from baseline according to Consensus Criteria (JCO 17:3461, 1999). A total of 250 patients, 125 per arm were enrolled and followed. The 9% difference in the PSA response rate observed at six months was not statistically significant ( $P < .16$ ), yet here too, the pre-specified survival analysis showed a difference for docetaxel plus DN-101 vs. docetaxel plus placebo: median not reached but estimated to be 24.5 months vs. 16.4 months respectively with a hazard ratio for death of 0.67 ( $p=0.04$ ) (JCO 25:669-74, 2007). The safety of the combination was no worse and perhaps better than docetaxel alone. Appropriately in my view, the results were not considered definitive by ODAC, no approval filing was made, and a new 900 patient phase 3 trial powered to test the hypothesis whether the combination of docetaxel in combination with DN-101 conferred a survival advantage relative to docetaxel alone was designed, initiated and continues to accrue. I am the International Principal Investigator on this trial. Contrast this with the regulatory filing history of Sipuleucel-T where the primary endpoint of the registration trial was also not met, yet, it is being considered for approval based on a similar post-hoc analysis with roughly half the total number of patients, and a control arm that is roughly one third the size. Why do the Sipuleucel-T results establish efficacy, while the DN-101 results do not?

An approval recommendation has far reaching implications beyond making the product available that the data simply do not support or justify. For one, it provides the Agency's endorsement of Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future randomized phase 3 trials that are being designed for the regulatory approval of any new experimental agent or approach. It also opens the door to the premature approval of drugs based on inconclusive data. Finally, the original question posed by the Agency to the Advisory Committee at the meeting was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no." The question was then changed to: Do the data show "substantial evidence." A series of "yes" votes followed.

Consider the conclusion in the manuscript describing the results of trial 9901, published in the Journal of Clinical Oncology in Volume 24, page 3093, in 2006. (JCO 24:3089, 2006) In it, the Investigators state "that while sipuleucel-T fell short of demonstrating a statistically significant difference in TTP, it MAY provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway to confirm this effect." All of the difficulties cited, and the Investigator's own conclusions, show how there are simply too many alternative explanations for the observed survival difference beyond treatment with Sipuleucel-T. Couple this with that fact that were no secondary signals of an antitumor effect and no confirmatory trial however flawed, mandates that any decision for approval be deferred until the phase 3 study, currently underway, has been completed and analyzed.

# Appendix B

## A Response to Dr. Scher's "Letter to the FDA"

This letter was co-written by 5 MD's, 2 Phd's and a research advisor

**TO: U.S. Food and Drug Administration (FDA)**

**SUBJECT: Response to Dr. Howard Scher's Opposition to Provenge (Sipuleucel-T).**

Dear FDA:

As a group of medical doctors and scientists we are writing to express our concern with the contents of a letter reportedly sent by Howard Scher, M.D. of the Memorial Sloan-Kettering Cancer Center, to the FDA, and published in Volume 33, No. 14 of The Cancer Letter, on April 13, 2007. Dr. Scher reportedly warned the FDA about flaws in the Provenge (Sipuleucel-T) trial data (Sponsor, Dendreon Corporation). The FDA decision about Provenge approval is presently pending. As Dr. Scher acknowledged, he served as a member of the Cellular, Tissue and Gene Therapy Advisory Committee on March 29, 2007, which voted positively on the FDA questions placed before it. The Advisory Committee efficacy vote was 13-4 in favor of Sipuleucel-T; Dr. Scher was among the four Committee members who voted in disapproval on that point though the transcript reveals that he voted Yes to the question of "substantial evidence" and No to "established efficacy" but changed his vote in an unclear manner (EXHIBIT-1).

The Advisory Committee safety vote was a unanimous 17-0. In Dr. Scher's letter, there were a number of questionable, or debatable, assertions, and a number of seeming logical flaws. This response to his letter is an attempt to address some of those items.

Dr. Scher opens by stating his concerns on a Committee recommendation for approval based on: (a) data that fall far short of regulatory requirements; (b) "an inadequate statistical construct to determine definitive benefit"; (c) incomplete data on product safety; and, (d) "what appears to be different criteria for approval by two Advisory Committees to the Agency" Dr. Scher acknowledges that all but the latter were discussed at the open meeting, but warrant further consideration given the outcome".

To begin with, one must ask why an expert invited by the FDA as a "special Federal employee" with expert knowledge in the given field, given a waiver of Conflict of Interest requirements (we are delighted that the outdated conflict of interest waiver guidelines under which Dr. Scher's waiver was issued are currently being revised by the FDA) to participate in an Advisory Committee (EXHIBIT-2) with respect to "a particular matter", and given access to Briefing Materials, the opportunity to comment, question and vote, chooses to question the outcome of the Committee's recommendation, including his own vote on Safety, after the fact. Absent new material information, Committee members, if no one else, should respect the fairness of the process and the final vote of the Committee.

In addressing his efficacy concerns, Dr. Scher stated: "My vote was based on the fact that neither of the two trials presented met their primary endpoint, which renders the significance of results from any subsequent analyses as "exploratory" and "hypothesis generating. "As such, the results do not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit."

The FDA has allowed increases in overall survival to be statistically tested for significance where it was not a primary endpoint and has approved a supplementary NDA, where the primary endpoint of survival was not statistically significant. The pre-specified primary endpoints in both the 9901 and the supporting 9902a trial were the time to disease progression (TTP). While not reaching statistical significance, a probability of 0.052 was undeniably close. It is understood that the positive Advisory Committee (AC) vote was primarily on the basis of the survival benefit subsequently discovered (and agreed by the FDA for the proper endpoint for filing of the Provenge BLA). The FDA has, in the past, considered an increase in overall survival in a life threatening disease, as a "gold standard"

worthy of its own "alpha" of 0.05. See:

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=10027498&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10027498&dopt=Abstract) In addition, the FDA has given Accelerated Approval to a supplementary NDA in NSCLC to Alimta, which failed to reach its primary endpoint of survival with a p value=0.93.: The Oncologist, Vol. 10, No. 6, 363-368, June 2005: FDA Drug Approval Summary: Pemetrexed for Injection (Alimta®) for the Treatment of Non-Small Cell Lung Cancer. <http://theoncologist.alphamedpress.org/cgi/content/full/10/6/363>

The FDA, NCI and academic experts from around the world have agreed on a new Clinical Trial Paradigm for cancer vaccines which, if applied to the Provenge 9901 clinical trial would have made the increase in Time to Progression (TTP) statistically significant. See: "A Clinical Development Paradigm for Cancer Vaccines and Related Biologics"

<http://www.sabin.org/files/PDF/CVCTWe.clinical.development.paradigm,JiT.2007.pdf>.

Specifically, "Other Time-to-event End Points" on page 6 of the Clinical Development Paradigm stated: "Therapeutic cancer vaccines pose the possibility of a delayed onset of activity based on the time required to mount an effective immune response and the time for that response to be translated into an observable clinical effect, Drs. Paul B. Chapman, M.D. and James Allison, M.D. Memorial Sloan- Kettering, where Dr. Scher also practices medicine, participated in this development effort. There was further discussion of this Paradigm during the second day of the FDA / NCI Workshop on "Bringing Therapeutic Cancer Vaccines and Immunotherapies through Development to Licensure"

The agenda for the Workshop is accessible at:

[https://cms.palladianpartners.com/cms/1156354418/materials/final\\_agenda.pdf](https://cms.palladianpartners.com/cms/1156354418/materials/final_agenda.pdf) and a video webcast of the Conference is accessible at:

<http://videocast.nih.gov/PastEvents.asp?c=1>

Dr. Scher debates whether there was a "Delayed Effect" observed in the Provenge 9901 trial, but strangely goes on to implicitly suggest that more modern methods of measuring progression could have made Provenge's TTP statistically significant without the need for a "Delayed Effect" adjustment. Dr. Scher disputes the existence of a Delayed Effect in the 9901 trial since: "serial imaging to assess disease were not performed once a patient was considered to have "progressed" and taken off study. As a result, individual sites were no longer being monitored so that no statements could be made regarding a possible "delayed effect" of the product on disease status". Please refer to the Provenge 9901 plot (Slide 7) and the ITT and control group separation of curves at approximately 12 weeks accessible at: <http://investor.dendreon.com/downloads/22568dndn.pdf> Dr. Scher comments that: "the Prostate Cancer Working Group 2 has advised that an apparent progression on bone scan at a three month assessment, be confirmed by documenting further progression on a subsequent scan six or more weeks later before considering a patient to have failed the treatment." (ASCO Multidisciplinary Prostate Cancer Symposium, (ASCO Abstract #221) February 22-24, 2007, Orlando FL, 2007). With respect to the Provenge trial : "the eight week interval between disease assessments was too short to observe clinically significant changes by bone scan, and that in many cases apparent progressions eight weeks after the start of a therapy are more a reflection of disease worsening that lead to trial entry, and not a failure of the treatment (CCR1 3: 1488, 2007)". Thus, the Provenge Phase 3 protocol adopted in 2001 used a method of measuring progression that needlessly penalized treatment effects during the early months by actually documenting as progression, metastases that existed at randomization. So long as the measurement protocol was consistent between ITT and control groups during the entire time that Time to Progression was assessed, this logic suggests that eventual separation of curves could be expected and the actual Provenge TTP p value was much better than the p value of 0.052 reported. Thus, consideration of the recommended Delayed Effect for immunotherapies would have been unnecessary.

If Provenge's 9901 trial's TTP, its pre-specified primary end point, was statistically significant due either to a "Delayed Effect" or a methodology that, in effect censured early progression events due to metastases present at the time of randomization, then statistical analysis of overall survival to confirm that TTP is a surrogate for a meaningful clinical benefit is required. The Kaplan-Meier log rank p value for increased overall survival was 0.01 for the 127 patient 9901 trial and 0.011 for the integrated 225 patient database of the 9901/9902a trials. Dr. Scher should be particularly sensitive to the desired use of overall survival in AIPC/ HRPC since he participated in the Oncology Drugs Advisory Committee (ODAC) meeting on March 3, 2004 when ODAC unanimously recommended that overall survival should be the primary endpoint in all AIPC / HRPC clinical trials. The 3/3/05 ODAC

afternoon transcript discussing endpoints in ADPC and AIPC, and mentioning the importance of control crossover in the FDA approval of Mitoxantrone is accessible (starting at page 204)  
<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4095T1.pdf> The Power Point Slides prepared for the meeting are available at: [http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4095s1\\_index.htm](http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4095s1_index.htm)

The transcript and slides of the March 3, 2005 ODAC meeting further reveal conflicting inconsistencies with Dr. Scher's letter. Dr. Scher writes; "Concerns about the validity of the findings were reinforced by the absence of other signals of an antitumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or boney disease radiographically, health related quality of life, or that administration of the product delayed the development of pain. Even the time to the administration of chemotherapy, an indication to the treating Physicians that the clinical course had worsened, was similar between the two groups. Reinforcing the uncertainty was the fact that in response to a direct question at the meeting, none of the Physicians representing the Sponsor could articulate how treatment with the product had "helped" any individual patient." Is it really necessary for one physician to tell another physician that increased survival "helps" a patient? Slide 15 of Dr. Small's presentation at 2005 ASCO shows that, although not statistically significant, there was a positive trend in the delay of onset of Time To Disease Related Pain (TTDP) in the Provenge 9901 Phase 3 trial:

[http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst\\_detail\\_view&confID=34&abstractID=31910](http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=34&abstractID=31910)

Consider Dr. Scher's issue of " a favorable effect on PSA". Dr. Scher's Slide Presentation at the same 3/3/05 ODAC meeting included a slide titled: "Post Therapy Based Outcomes and Survival", which states at item " 3. May not apply to non-cytotoxic agents or drugs directed at different aspects of the metastatic process". Later under "The Association Between Time Dependent PSA Levels and Relative Risk of Death is Modest" Dr. Scher shows that "A large part of the treatment effect is not explained by PSA" At page 285 of the Transcript: "So, where does this leave us in terms of PSA change and survival? Trial 9916 showed that there was an association of PSA decline and the treatment effect was eliminated when adjusting for the intermediate, did not see the same effect in both arms of the TAX-327 study. The Q3 week arm was the only arm to show a survival difference."

Dr. Scher's letter states: "Finally, the original question posed by the Agency to the Advisory Committee at the meeting was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no." The question was then changed to: Do the data show "substantial evidence." A series of "yes" votes followed." Dr. Scher fails to point out that the question was changed by the FDA to conform with Federal law and FDA published guidelines. The FDA Guidance points out that: " Congress adopted the 1962 Drug Amendments, which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." Substantial evidence was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." See:

<http://www.fda.gov/cber/gdlns/clineff.pdf>

More surprising is the fact that Dr. Scher clearly knew what the proper standard was and not only failed to suggest clarification at the meeting but now objects to its use. Dr. Scher noted at page 289 of the Transcript of the 3/3/05 ODAC meeting: "The regulations for accelerated approval are very clear. They require substantial evidence from well-controlled trials regarding a surrogate endpoint." Thus, "Substantial evidence", not "establish" were the correct operative words. Dr. Scher went on the say at that same ODAC meeting at page 294: " One could certainly consider an accelerated approval based on an interim evaluation assuming the trial endpoint was met, with the proviso that the trial accrual and monitoring continue until accrual was complete, the analysis complete, to assess the primary endpoint, which in this case would be survival." Thus, if the 9901 Provenge trial TTP was corrected for a Delayed Effect or realizing that early progression is often misleading and followed by a delayed increase in time to progression, the 9901 TTP would have been significant, and FDA approval could have been granted in 2002, with trial accrual, monitoring, and analysis for survival to follow in a confirmatory trial. This is

exactly what the Committee recommended on March 29, that the accrual, monitoring and analysis of the 500-patient Provenge 9902b trial be continued, but that FDA Approval be given now. It is also in accord with the FDA's comments of November 11, 2005 that the FDA has the authority to require that Sponsor conduct a Phase 4, post Regular Marketing Approval Phase 4 confirmatory trial, and to withdraw or modify its Regular Approval should such trial fail to confirm the efficacy or safety of the therapy. See: (pages 59 to 65) at [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4191B1\\_01\\_02-21CFR-314-601.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4191B1_01_02-21CFR-314-601.pdf)

To our knowledge the FDA has never approved the use of a nomogram in place of a control group, however, there is no question that such nomograms become valuable reference checks.

Dr. Scher raises questions about trial size, but a prior FDA approval of Mitoxantrone in AIPC /HRPC and the use of the "Halabi nomogram" as a check on the heterogeneity of the control group suggests that this concern is not justified. : Dr. Scher states: "The 2: 1 randomization increased the power of the experimental arm, but it may have inadvertently made the small 43 patient control group more heterogenous and less representative of the global population for whom the indication was proposed". At that same March 3, 2005 ODAC meeting, much was made of the few – four – number of FDA approvals in AIPC /HRPC. One of these was a 1996 FDA approval of Mitoxantrone for quality of life (QOL) / palliation of pain; The Mitoxantrone pivotal Phase 3 trial enrolled 160 patients. That trial had a high crossover rate (approximately 62%) which negatively impacted a potentially more significant p value by effectively making the treatment given to the Intent to Treat (ITT) group ultimately be measured against itself when the control group receives the treatment upon crossover. Mitoxantrone's p value for palliation of pain was 0.01. The crossover rate in the Provenge trials was higher ( over 70%) than the crossover rate in the Mitoxantrone trial, the number of enrollees in the integrated 9901/9902a trials (225) higher in the Provenge trial, and the Provenge p value for overall survival of 0.011 remarkably similar to the Mitoxantrone's p value for palliation of pain of 0.01. See: <http://www.jco.org/cgi/reprint/14/6/1756?ijkey=096710dbfe48978dddc72695d6a12e46ea5cd8c0>

Dr. Scher coauthored and published in 2002 a study based on a 409 patient reference group of AIPC / HRPC patients detailing a nomogram which predicted survival based on certain diagnostic and functional patient characteristics. See: <http://jco.ascopubs.org/cgi/content/full/20/19/3972> A year later, Dr. Susan Halabi and several distinguished coauthors, including Dr. Eric Small, the lead investigator of the Provenge 9901 clinical trial, published a similar study and nomogram. See: <http://jco.ascopubs.org/cgi/content/full/21/7/1232?ck=nck> The "Halabi nomogram" has since become a standard reference tool in comparing the survival it predicts for any group of AIPC / HRPC patients with the actual survival of the same group of patients treated with a new therapy. Since none of the Halabi reference group of 1100 patients benefited from any therapy extending survival in the period from 1991 to 2001, when no such therapies were available, the nomogram is based on a truly untreated group of patients where the confounding effects of a crossover trial protocol would not be a factor and the large number would assure heterogeneity. Dr. Small tested the Provenge 9901 ITT group against the Halabi nomogram and reported that median survival increased from 4.5 months to 5.8 months. See Slide 14 accessible at: <http://investor.dendreon.com/downloads/22568dndn.pdf>

While the FDA does not accept a nomogram in place of a control group in a randomized clinical trial there is no question that an appropriate nomogram serves as an invaluable check on the heterogeneity of both the intent to treat and control groups in a clinical trial.

Dr. Scher makes no reference to, or indication that he is aware of, a November 2006 presentation by Dr. Daniel Petrylak, a lead investigator of the Taxotere SWOG 9916 Phase 3 trial, at the Chemotherapy Foundation in New York that reported a remarkable increase in survival of AIPC /HRPC patients who received Taxotere after Provenge when compared to their survival predicted by the Halabi nomogram. See: (a) Dendreon's November Press Release at <http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=218144&Header=News> and (b) Dr. Petrylak's presentation at: [http://chemotherapyfoundation.org/professional\\_education/meetingarchives\\_tcf2006\\_main.html](http://chemotherapyfoundation.org/professional_education/meetingarchives_tcf2006_main.html)

Although this presentation was indeed a retrospective analysis of 9901/ 9902a Provenge data, it was also supported by some very strong immunology data reported by Dendreon in November, 2006 regarding the potential efficacy of a Provenge booster infusion with a follow-up presentation at the annual AACR meeting on March 16, 2007, See:

<http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=217760&Header=News> and <http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={34D88016-D025-4791-BC3D-376B1A56F452}&MKey={E3F4019C-0A43-4514-8F66-B86DC90CD935}&AKey={728BCE9C-121B-46B9-A8EE-DC51FDFC6C15}&SKey={3C35BA5D-859E-460D-9E6F-F2F95D90CD9D}>

Dr. Petrylak reported that 81 AIPC /HRPC patients in the 9901 and 9902a Provenge trials who received Taxotere 4 to 6 months after Provenge, showed an astonishing increase in median survival of some 14 months as compared to the 2.4 month increase in median survival reported in the Taxotere TAX327 pivotal trial, and the 4.5 month increase in median survival reported in the Provenge 9901 trial when compared to that predicted by the Halabi nomogram. This analysis was per the 9901 and 9902a trial protocols, which did not allow any booster dose of Provenge after the initial three dose therapy. The Dendreon P11 immunology trial data, where a single booster is given per its protocol in Androgen Dependent Prostate Cancer (ADPC), reported that Provenge primed long lasting, highly avid T cells against the PAP antigen (strongly supporting the conclusion that these are "memory" T cells), but also that the avidity of these T cells could be substantially increased with a single booster. Dr. Petrylak's presentation anticipated follow-up clinical trials in which the sequencing of Provenge, followed by some Taxotere, followed by a Provenge booster may be explored to further increase patient survival, perhaps in the absence of any prolonged chemotherapy. These findings further supports the NCI's Dr. Niederhuber's comments at the outset of the second day of the February FDA / NCI Workshop that chemotherapies may be the first combinations used and approved to further improve cancer vaccines.

Provenge is an active immunotherapy, not a cytotoxic drug. Dr. Scher should look to reported successes in immunotherapy to inform the proper analysis of its likely method of action. Dr. Steven Rosenberg and his NCI colleagues are making startling advances with immunotherapy in end stage melanoma. See his presentation during the first day of the FDA.NCI Workshop at :

<http://videocast.nih.gov/PastEvents.asp?c=1> To briefly summarize the method that Dr. Rosenberg uses in his adoptive immunotherapy, it is the infusion of (a) large numbers of (b) long lasting T cells, (c) primed against a single melanoma antigen, into (d) patients who have been preconditioned with chemotherapies to deplete regulatory T cells. Provenge can be described as an active immunotherapy, which infuses (a) large numbers of dendritic antigen presenting cells, which in vivo prime even larger numbers of (b) long lived memory T cells against (c) an AIPC/HRPC antigen, Prostatic Acid Phosphatase (PAP). Instead of preconditioning patients to deplete regulatory T cells, which could also deplete the available pool of naïve T cells for Provenge's dendritic antigen presenting cells to prime, the Taxotere (docetaxel) post Provenge analysis suggests that docetaxel, which preferentially targets rapidly proliferating regulatory T cells and cancer cells expressing bcl-2, (d) "post-conditions" and depletes the regulatory T cells in an established tumor and its microenvironment, potentiating a patient's powerful immune response against cancer. See, for example, the fundamental research coming out of the laboratories of Professor Hans Schreiber at the University of Chicago at: <http://www.jem.org/cgi/content/full/201/5/779> and the presentation at the NIH of Professor Ulrich von Andrian of Harvard explaining how the ex vivo maturation of dendritic antigen presenting cells leads to the priming of long lived memory T cells upon their infusion. See: Migratory Properties and Immunological Consequences of Dendritic Cell Migration Wednesday, October 25, 2006 Uli Von Andrian Total Running Time: 01:03:39 <http://videocast.nih.gov/PastEvents.asp?c=28&s=11>

The Provenge trials excluded men who had known metastases to visceral organs. It is just such metastases, frequently undetected, that ultimately cause death in AIPC/HRPC. Androgen-Independent Prostate Cancer Is a Heterogeneous Group of Diseases Lessons from a Rapid Autopsy Program Cancer Research 64, 9209-9216, December 15, 2004

<http://cancerres.aacrjournals.org/cgi/content/full/64/24/9209> A logical hypothesis to explain how an immunotherapy such as Provenge, can fail to cause the regression of an established tumor, and yet increase overall survival is that it may slow or stop cancer metastases by destroying targeted cancer cells in the bloodstream that are shed by an established tumor and are relatively unprotected by regulatory T cells. When Taxotere or some other post-conditioning agent depletes regulatory T cells, some tumor regression should result until and unless too much or too long administration of Taxotere also depletes attacking CD8 effectors T cells. At that point a Provenge booster may be given to initiate a further sequence of tumor destruction. While only a logical hypothesis, this would explain Provenge's method of action far more plausibly than proposed methods of action, or absence thereof, for many drugs on the market today.

Dr. Scher raises question concerning the safety of Provenge and of his own Committee meeting vote on safety by making irrelevant and somewhat absurd comparisons to the cardiovascular side effects of chemotherapies while not addressing Dendreon's direct statements regarding

Provenge safety. The safety issue is not the cardiovascular side effects of Taxotere or of DN-101, which Dr. Scher discusses, but the safety of Provenge. At the Committee meeting, Dendreon's Dr. Frohlich responded to the safety question by pointing out that there were no CVA's in the ADPC Provenge treated patients (P16, 9906 and P11), there were no CVA's in the 3 months following Provenge dosing for men who experienced CVA's, and that reference to a large database of men with similar advanced cancer indicated that there was nothing extraordinary about the Provenge CVA rate. Dr. Frohlich then described the proposed FDA / DNDN 3,000 patient monitoring plan for CVA's in men treated with Provenge. That obviously satisfied the Committee on the safety issue leading to a 17 to 0 vote. If Dr. Scher has problems with any of the Sponsor's comments, he should discuss those comments as they deal with Provenge safety and not digress to safety issues in two unrelated chemotherapy trials.

Scher's letter concludes with a warning regarding the far reaching implications of any FDA approval of Provenge: "For one, it provides the Agency's endorsement of Sipuleucel-T as a "standard of care" treatment for asymptomatic androgen independent (castration resistant) disease that represents upwards of 45,000 men in the US. The second is that by extension it elevates Sipuleucel-T to a position of being the new "control" arm for future randomized Phase 3 trials that are being designed for the regulatory approval of any new experimental agent or approach. It also opens the door to the premature approval of drugs based on inconclusive data".

"The "standard of care" designation comes with ethical and possible legal implications for doctors. Marketing data makes it clear that far fewer AIPC / HRPC patients choose to take the only standard of care presently FDA approved that extends survival, Taxotere, than it is indicated for, reportedly due to the side effects patients experience over its 7 month course of therapy. Taxotere's pivotal Phase 3 TAX327 trial showed only a 2.4-month increase in median survival. If the FDA approves Provenge doctors would be expected to fully discuss treatment options to this dying AIPC/HRPC patient population with explanations of what clinical trials for various FDA approved therapies demonstrated, and did not demonstrate, and even, perhaps, to ask for signed acknowledgments that they were given this information before making a therapy choice. What a revolutionary idea! Doctors would actually give a dying man the best available information about his disease, and allow him to make his own informed decision after consulting, if he chooses, with one or more doctors. How would most asymptomatic AIPC / HRPC patients respond to a question as to whether or not they would consider a three dose course of Provenge, if: (a) the side effects were much like 3 flu shots and were generally resolved within a couple of days; (b) the chances of being alive three years hence would double or triple, (c) there was a possibility, however, that the risk of stroke might increase by about 1% over that period of time, and, (d) if Provenge is chosen, a later choice to take some Taxotere, or other taxane, and a possible Provenge booster might further increase survival substantially?

The FDA can make decisions with sponsors of new trials of experimental drugs or therapies in AIPC / HRPC, as to whether the use of Provenge treated patients in a control arm would be appropriate pending completion and analysis of the 9902b Provenge Phase 3 confirmatory trial. Sponsors of future trials may have reason to be concerned and potentially have a high bar to overcome if, when, and subsequent to, Dr. Petrylak introducing the sequencing of Provenge, then limited Taxotere or other taxane, then a Provenge booster into a FDA Phase 3 pivotal trial. AIPC / HRPC patients and their families may benefit enormously, but competitive therapies may indeed suffer.

The March 3, 2005 ODAC meeting dealt with the issue of clinical trial endpoints in prostate cancer, in part, because there have been so few that have received FDA approval in a cancer where there is a significant unmet need. A slide presentation to ODAC listed four therapies approved by the FDA: (a) Taxotere (docetaxel) approved in 2004 for increased survival; (b) Zoledronic Acid approved in 2003 for QOL; (c) Mitoxantrone approved in 1996 for QOL; and (d) Estramustine approved in 1981 under the "Old Rules". It is disheartening to think that so few therapies have been tested in clinical trials and approved by the FDA for such a large population of critically ill men. ODAC gave a recommendation to the FDA during its March 3, 2005 meeting that survival should be the primary end point in all AIPC /HRPC trials. It is disheartening to see an oncologist, as distinguished as Dr. Scher, use a scientifically outdated analysis of Time to Progression, a proposed surrogate for survival to argue against an intelligent analysis of survival, and then failing that, to criticize the Provenge trials as too small, when comparison of the Provenge trials to the FDA approval of Mitoxantrone in AIPC /and HRPC, and the actual survival of Provenge treated patients compared to that predicted by an 1100 patient reference control group in the Halabi study strongly support the finding of substantial evidence of efficacy.

In retrospect, with what we now know about the measurement and analysis of increased Time to Progression in therapeutic cancer vaccines, Provenge theoretically could have filed its BLA and received FDA Accelerated Approval in 2002, and continued with the data collection and analysis of 36 month survival data to receive Regular Approval. Time has long since passed when this valuable new tool in the treatment of prostate cancer should be made available to all AIPC/ HRPC patients.

For all of the above reasons, but most of all for the benefit of all present and future prostate cancer patients and their families, we urge the FDA to approve the Biologics License Application submitted by Dendreon Corporation for Provenge (Sipuleucel-T).

Very truly yours,

<contact addresses snipped>

## Exhibit 1.—Text of Dr. Scher’s vote on efficacy

The following discussion took place after a round of voting on safety of Provenge (unanimous Yes) took place. The discussion below and reference to two questions are regarding efficacy, the original question was regarding the efficacy was established. The question was revised into a second question of “substantial evidence”. Due to quality of audio transmission the text below is deemed “complete and accurate to better than 95% of the transcript” by the transcriber.

Dr. Mulé - Dr. Scher?

Dr. Scher -

I think is complete and accurate to better than 95% of the transcript of Scher's vote on efficacy.

I think we are really poised at the beginning of what will be hopefully an outstanding era of immunotherapy. I think there is sufficient evidence demonstrated which justifies the definitive study, and I would say there are investors in that who concur. But I think it does not meet the ... umm ... as the question was phrased, to establish the efficacy, I think this is still an open question.

M - So I take I you’re saying “yes” with these provisos?

S. You have two questions, I would say yes to one, no to the second.

Pausing, murmuring laughter and confusion in the room.

S - If the question is posed as “establish”, I say “no”.

M - No, its, uh, “substantial evidence”.

S - No.

M - No.

# Appendix C

## Dr. Scher's FDA COI Waiver Application

### Acknowledgment and Consent for Disclosure of Potential Conflict(s) of Interest and Waivers under 18 U.S.C. §208(b)(3) and 21 U.S.C. §355(n)(4)

Name of Participant: Howard I. Scher, M.D.

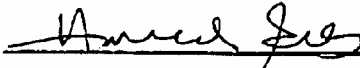
Committee: Cellular, Tissue and Gene Therapies Advisory Committee

Meeting Date: March 29, 2007

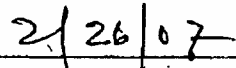
I acknowledge that contingent upon public disclosure of the following financial interest listed below related to the review of Sipuleucel-T, Dendreon Corp., for the treatment of men with asymptomatic metastatic hormone refractory prostate cancer. I am eligible to receive waivers under 18 U.S.C. §208(b)(3) and 21 U.S.C. §355(n)(4).

<u>Type of Interest</u>	<u>Nature</u>	<u>Magnitude</u>
Grant (related)	Competing Firm	\$100,000-\$300,000
Grant (related)	Competing Firm	\$100,000-\$300,000
Stock	Competing Firm	\$5,000-\$100,000

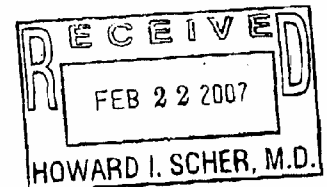
I hereby request that FDA make this information publicly available on my behalf. I understand that without public disclosure of the interests the waiver is not valid.

  
\_\_\_\_\_

Howard I. Scher, M.D.

  
\_\_\_\_\_

Date



# Appendix D

## FDA COI Waiver Letter – Scher - Page 1



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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MEMORANDUM

DATE: February 5, 2007

FROM: William Freas, Ph.D. WJF  
Director, Division of Scientific Advisors and Consultants, CBER

SUBJECT: 208(b)(3) Conflict of Interest Waiver for Howard I. Scher, M.D.

TO: Randall Lutter, Ph.D.  
Associate Commissioner for Policy and Planning

Through: Vince Tolino  
Director, Ethics and Integrity Staff  
Division of Management Programs, OM

I am writing to request a waiver from conflict of interest prohibitions of 18 U.S.C. 208(a) for Howard I. Scher, M.D., a special Government employee for the Center for Drug Evaluation and Research. Dr. Scher was invited to participate as a consultant at the Cellular, Tissue and Gene Therapies Advisory Committee meeting on March 29, 2007. The Committee will discuss and make recommendations on issues related to Sipuleucel-T, Dendreon Corp., indicated for the treatment of men with asymptomatic metastatic hormone refractory prostate cancer. This is a particular matter involving specific parties. Waivers under Section 208(b)(3) may be granted by the appointing official where "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved" and where the individual has made a disclosure of the financial interests at issue. Because you are the appointing official, you have the authority to grant Dr. Scher a waiver under Section 208(b)(3).

Section 208(a) prohibits Federal executive branch employees, including special Government employees, from participating personally and substantially in matters in which, to his knowledge, the employee, his spouse, minor children, or general partner; an organization in which he is serving as officer, director, trustee, general partner, or employee, or a person or organization with which he is negotiating for or has arrangement concerning prospective employment has a financial interest. Dr. Scher is a special Government employee and is under a statutory obligation to refrain from participating in any deliberations that involve a particular matter having a direct and predictable effect on a financial interest attributable to him or to his employer.

# Appendix D

## FDA COI Waiver Letter – Scher - Page 2

Page 2 -- Randall Lutter, Ph.D.

Associate Commissioner for Policy and Planning

The function of the Committee, as stated in its Charter, is to advise the Commissioner of the Food and Drug Administration in discharging responsibilities as they relate to assuring safe and effective biological products for human use and, as required, any other product for which the Food and Drug Administration has regulatory responsibility.

Dr. Scher advised the FDA that he has a financial interest related to the above topic that could potentially be affected by his participation in the matter at issue. Dr. Scher reported that he has joint stock in [REDACTED] at a current value of [REDACTED]. Additionally he reported that his institution has a grant from [REDACTED] (competing firm). The grant is current and his institution receives [REDACTED] per year from 2006-2007. Dr. Scher receives no salary from the grant. The grant is to study a licensed, approved drug ([REDACTED]) in prostate cancer trials. [REDACTED] is a licensed drug currently used in other cancer therapies. Dr. Scher also reported that his institution has a grant from [REDACTED] (competing firm). The grant is current and his institution receives [REDACTED] per year from 2006-2008. Dr. Scher receives no salary from the grant. The grant is to study an investigational drug ([REDACTED]) that is also being studied in several types of cancer. It is unlikely that Dr. Scher's participation in the discussions on March 29 of a cellular therapy for prostate cancer will have a direct and predictable effect on his financial interest.

Under Section 208, Dr. Scher is prohibited from participating in any matter affecting these interests, unless he receives a waiver. However, as noted above, you have the authority under 18 U.S.C. 208(b)(3) to grant a waiver.

For the following reasons, I believe that it would be appropriate for you to grant a waiver to Dr. Scher that would allow him to participate in the discussions before the Committee.

The Committee has a special need for Dr. Scher's services because of his expertise as a practicing clinician with extensive experience in prostate cancer clinical trials. Dr. Scher is the D. Wayne Calloway Chair in Urologic Oncology, Chief, Genitourinary Oncology Services, Department of Medicine, Sidney Kimmel Center for Prostate Cancer Center, Memorial Sloan-Kettering Cancer Center. The committee has a critical need for prostate cancer clinical trial expertise to assist the committee in the evaluation of appropriate clinical trial end points for a novel prostate cancer cellular therapy. Dr. Scher has been involved in a national effort to define guidelines for patient participation in studies for the treatment of prostate cancer patients who have relapsed. His experience in evaluating patient eligibility and outcome criteria are crucial to the committee discussions of product efficacy. Additionally, Dr. Scher has prior FDA advisory committee experience as a consultant of the Oncology Drugs Advisory Committee and understands the FDA mission to move new therapies forward at the same time protecting the welfare of patients. His expertise and perspective are critical. Nine other special Government employees and members of the Oncology Drugs Advisory Committee with related oncology expertise were considered. Five did not have equivalent expertise, two were determined to have equal or greater conflicts of interest and two were unavailable.

