Excerpt from Letter of Recommendation:

After a successful early career in the study of endothelial cell biology and adhesion receptors, Dr. Albelda began his major effort to establish a bench-to-bedside research career, concentrating on mesothelioma as well as lung cancer. He developed a multidisciplinary group, the Thoracic Oncology Research Laboratory, which has been extremely productive over almost 2 decades. Via this group, he has recruited, supervised, mentored and collaborated with multiple investigators in an effort to advance the care of patients with mesothelioma.

Under Dr. Albelda's leadership, the TORL pioneered the use of gene therapy in mesothelioma and other cancers. Dr. Albelda and colleagues first conducted preclinical studies demonstrating efficacy of an adenovirus expressing the herpes simplex thymidine kinase suicide gene for the localized tumor, malignant mesothelioma. They then performed preclinical toxicology studies, obtained regulatory approvals, and successfully wrote and obtained an IND from the FDA- the first trial allowed to use gene therapy as the primary treatment for a cancer. Importantly, Dr. Albelda successfully obtained a Program Project Grant from the National Cancer Institute that provided the funding and infrastructure for his group to conduct three gene therapy clinical trials. This PO1 has been active for 11 years and a renewal is being sought. Between 1994 and 1999 (when the trials were shut down at Penn due to the Jesse Gelsinger incident), Dr. Albelda's group (now including Dr. Daniel Sterman as the primary clinical investigator) treated 32 mesothelioma patients in a series of three trials. In addition to safety and efficacy, the trials were also designed to measure gene transfer and detect anti-adenoviral immune responses. Remarkably, I understand that two mesothelioma patients are alive and well more than six and one half years after therapy!

Based on data suggesting that these clinical effects were due to immunological responses, Dr. Albelda changed the direction of his preclinical lab studies to focus on immunogene therapy and showed that an adenovirus encoding the cytokine, interferon-beta, was even more effective than the previous suicide gene approach. Despite an extremely "challenging regulatory climate", both here at Penn and nationally, Dr. Albelda (assisted by Kaiser and Sterman) was able to redirect his Program Project away from suicide gene therapy and toward immunogene therapy, enlist new collaborators, convince a biotech company (Biogen) to provide him with clinical grade adenoviral vector at no charge, conduct GLP level toxicology studies, and successfully obtain permission to conduct a clinical trial from the Penn regulatory agencies, the DNA Recombinant Advisory Committee, and the FDA (requiring a new IND)! A Phase 1 clinical trial using Ad.IFNbeta for patients with mesothelioma and with metastatic pleural disease has been completed (10 patients). A number of exciting clinical and immunologic responses were noted. A second Phase 1 trial using a repeat dosing schedule is being submitted to the IRB and FDA next month and will be supported by BiogenIdec. Based on strong preclinical studies, two larger Phase 2 trials combining immunogene therapy with surgery and chemotherapy are planned. The Program Project renewal application received excellent preliminary scores and is awaiting review by the Parent Committee.

Overall, Dr. Albelda and his group have conducted the first trials of gene therapy in patients with mesothelioma. Over the last 15 years, he has continued to pursue this direction, with increasing excitement about the efficacy of this approach. Although it is difficult to select among Dr.

Albelda's outstanding publications, his major contributions can be outlined in the following 4 papers:

1) Smythe, W.R., Hwang, H.C, Elshami, A.A., Amin, K.M., Eck, S.L., Davidson, B.L., Wilson, J.M., Kaiser, L.R., Albelda, S.M. Successful treatment of experimental human mesothelioma using adenovirus transfer of the herpes simplex-thymidine kinase gene. Annals of Surgery, 222:78-86, 1995.

In this study, Dr. Albelda and his colleagues showed that a peritoneal model of mesothelioma could be treated by the instillation of suicide adenovirus gene, Ad HSVtk. This positive result allowed approval for a clinical trial.

2) Sterman, D.H., Treat, J., Litzky, L.A., Amin, K.M., Molnar-Kimber, K.L., Wilson, J.M., Albelda, S.M., Kaiser, L.R. Adenovirus-mediated herpes simplex virus thymidine kinase gene delivery in patients with localized malignancy: Results of a phase 1 clinical trial in malignant mesothelioma, Human Gene Therapy, 9:1083-1092, 1998

This was the first report of the clinical use of gene therapy in patients with mesothelioma. As such, it was a landmark in the field. Follow-up of treated patients continues, with one patient still alive today.

3) Sterman D.H., Recio A., Haas A.R., Vachani A., Katz S.I., Gillespie C.T., Cheng G., Sun J., Moon E., Pereira L., Wang, X., Heitjan D.F., Litzky, L., June, C.H., Vonderheide R.H., Carroll R.G., Albelda, S.M. A Phase I Trial of Repeated Intrapleural Adenoviral-Mediated Interferon Beta Gene Transfer for Mesothelioma and Metastatic Pleural Effusion. Molecular Therapy, 18:852-860, 2010.

This is the most recent paper describing a newer strategy, that of using gene therapy to augment immune responses to mesothelioma (and metastatic pleural effusion). The adenovirus is still being used as the vector, but now an interferon beta gene is being transferred to augment the immune responses against the tumor. Encouraging results have led to a trial in which the AdINF will be used in combination with front line or second line chemotherapy.

4) Kim, S, Buchlis, G., Fridlender, Z.G., Sun, J., Kapoor, V., Cheng, G, Haas, A., Cheung, H.K., Zhang, X., Corbley, M, Kaiser, LR, Ling, LE., Albelda, SM. Systemic Blockade of Transforming Growth Factor-Beta Signaling Augments the Efficacy of Immunogene Therapy. Cancer Research, 68:10247-10256, 2008.

This report is a recent one of a series of papers showing a benefit in blocking TGF beta, an immunosuppressive mediator of mesothelioma. This preclinical data suggests that blocking this immunosuppressive cytokine may be effective. In this paper, it is shown to augment the efficacy of immunogenetic therapy. This approach is now heading to a clinical trial in which an anti-TGF beta antibody will be used in patients with relapsed mesothelioma.

His curriculum vitae is replete with significant contributions to the field of mesothelioma, from writing of multiple influential review articles, to serving on the IMIG Executive Board and the

MARF Scientific Advisory Board, to writing the Up-To-Date sections on mesothelioma, to hosting the IMIG Meeting in Philadelphia in 1997. In addition, he has trained those that have also had a significant contribution to the field, from Dr. Dan Sterman to Dr. Roy Smythe.

Last, but not least, Dr. Albelda has advanced the entire field, not just his own corner of it. He is a generous collaborator and happy to share his reagents and his ideas with colleagues. This has served to amplify his positive impact in the international work in mesothelioma. Indeed, collaboration and collegiality is of critical importance in this farflung community, in which investigators work apart and in distant countries. Dr. Albelda has helped make the international group of mesothelioma researchers into a productive and interactive community.

In summary, Dr. Steve Albelda is one of the rare individuals that have made outstanding contributions in both the basic biology of mesothelioma and in clinical application of this knowledge to patients. His work has made significant inroads in understanding the best approach in treatment of mesothelioma and is poised to make significant therapeutic advances for this intractable malignancy. His creativity and persistence in pursuit of this aim has been remarkable. I cannot think of another candidate more worthy for the IMIG Wagner Medal.