

To the Editor-in-Chief  
Transplant Immunology  
Dr. R. Cortesini  
Columbia University  
Dept. of Pathology  
630 West 168 Street  
P&S 14-401  
New York, NY  
USA

Email: rc238@columbia.edu

Dear Dr. Cortesini,

A few days ago I found during a literature search a publication by Hummel et al. entitled "Prevalence of CCR5 $\Delta$ 32 polymorphism in long-term survivors of heart transplantation", which will appear in the April 2007 issue of Transplant Immunology. I would like to bring some very problematic aspects of this study to your attention.

In 2001, our group has published a study in Lancet, which showed an increased renal transplant survival in patients lacking a functional CCR5 receptor (Fischereder and Luckow et al. Lancet 357:1758-1761). In 2002, Dr. Alexander Korn from Novartis asked, whether our laboratory in Munich would be interested to confirm the beneficial effect of CCR5 deficiency on transplant rejection in another study. He proposed to analyze patients with heart transplantation. In January 2003 our laboratory signed a contract with Novartis for this study and Dr. Korn started to recruit suitable transplant centers in Germany. To avoid problems associated with international studies, Novartis Germany was formally responsible for this study. The agreement said, that all blood samples from long-term survivors of heart transplantation collected at the transplant centers in Berlin, Hannover and Kiel should be sent to Munich to my laboratory, where the CCR5 genotype analysis was performed.

On December 1st in 2004 Novartis organized a meeting at the Munich Airport for presentation and discussion of the data obtained so far. The meeting was attended by Dr. Korn (Novartis USA), Dr. Gschaidmeier (Novartis Germany), Dr. Hummel (transplantation center Berlin, Germany), Dr. Bara (transplantation center Hannover, Germany), Frau Weinkauf (Novartis Germany) and myself. I presented the CCR5 genotype data for the 555 study patients and discussed possible explanations for the results observed. Specifically, I presented my hypothesis that the prevalence of the CCR5 $\Delta$ 32 homozygous genotype might be lower in patients waiting for heart transplantation than in the normal population. To support this idea, I presented own published and unpublished data on transplant-associated arteriosclerosis and atherosclerosis in our Ccr5 knockout mice. I tried to convince the participants of that meeting, that the normal population was not a suitable control group for the unequivocal interpretation of our genotyping results and that patients from the waiting list would be

the ideal controls. At the end of the meeting we decided, that we should first obtain additional data for the already genotyped patients (e.g. primary disease, age, age at transplantation, vasculopathy) before we start with the collection of blood samples from patients from the waiting list.

I finished this additional evaluation of the patient data by the end of May 2005 and sent the results to Dr. Gscheidmaier. In the following months, we tried without success to find a date for an additional meeting to discuss the available data. At the end of 2005, Dr. Gscheidmeier informed me, that he had no longer a budget for the CCR5 study and that he wanted to finish it as soon as possible and publish the available data. He also asked me, whether I would be willing to write the paper. I told him, that I find it scientifically unacceptable trying to publish a study with 555 long-term survivors without a single control patient. I tried to convince him again that it would be worthwhile to go on with the study, but I failed. Since I refused to write the manuscript, Dr. Gscheidmeier gave all available data to a professional Medical Writer to write the manuscript. In the following weeks Dr. Gscheidmeier repeated his offer, to put me as the first author or co-author on the planned publication, and I always said no. I informed him, that I would go on alone with the study to bring it to a point where one could draw firm conclusions. On February 15, 2006, I obtained by email the permission of Dr. Gscheidmeier to go on with the study and use the available data generated so far.

To make that point very clear: For scientific reasons I refused to publish data from a study without suitable controls. The lack of controls makes an unequivocal interpretation of the data impossible. This did not mean, however, that I had lost interest in this topic. I informed Novartis, that if the transplant centers were no longer interested, I would go on alone with the study to finally prove or disprove my hypothesis. It is understood, that I never gave the permission to Hummel et al. to use my ideas and hypotheses in their publication, because I am still working on that topic. It is also clear, that they were never allowed to give the impression that they had the idea for the study and that the data in the publication were generated by themselves. As already mentioned, a few days ago I found during a Pubmed search the paper by Hummel et al. and I could not believe what I read after the download of the pdf file.

In addition to the problems described above, the publication contains several errors:

1. The authors suggest that there exist conflicting data concerning our CCR5 renal transplant study published in Lancet. As examples the authors cite reference No. 18 (Yigit et al. 2006, Cell Biochem Funct) and reference 19 (Abdi et al. 2002, JASN). The study by Yigit et al. included 85 patients, which all (?) showed a wildtype CCR5 genotype. The study by Abdi et al. included 163 renal transplant patients. 147 of them had a wildtype genotype and the remaining 16 patients were heterozygous for CCR5 $\Delta$ 32. Therefore, both studies cannot make any conclusions about the role of CCR5 deficiency on renal transplant rejection, because they did not have a single patient with the required homozygous CCR5 $\Delta$ 32 genotype. Furthermore, we genotyped a total of 1227 renal transplant recipients (not only 576) and found 21 homozygous patients (=1.7%). Complete follow-up data were available for 576 patients. The renal transplant recipients were followed up to 23 years post-transplant and not 10 years, as stated in the manuscript.

2. Reference 7 is not about a mouse model of cardiac transplantation, but a porcine pancreatic xenograft model in wildtype mice.
3. From the 10 persons listed in the Acknowledgements, 7 have absolutely nothing to do with the published data. The persons affected are Michael Fischereeder, Klaus Pfeffer, Ulrike Huffstadt, Rudi Balling, Wolfgang Wurst, Hermann-Josef Gröne and Eva Kiss. I had them in the Acknowledgement section of my talk at the Munich Airport where I presented not only the results of the human heart transplantation study but also some heart and carotid transplantation data from Ccr5 knockout mice and the data from our human renal transplant study.

In summary, my major points of criticism are:

1. Hummel et al. did not contribute to the idea of the study.
2. Hummel et al. did not perform any of the genotype analyses presented or any of the statistical analyses. They provided the blood samples and patient data from long-term survivors of heart transplantation.
3. Hummel et al. did not mention that all experimental data presented in the manuscript were generated by other people and not by them.
4. Hummel et al. did not write the manuscript. It was written by a medical writer on behalf of Novartis Germany.
5. Hummel et al. discuss in the manuscript my hypothesis about a potential underrepresentation of the CCR5 $\Delta$ 32 homozygous genotype in patients waiting for heart transplantation without mentioning the source.
6. Hummel et al. did not disclose that the study was initiated and sponsored by Novartis.
7. Hummel et al. did not send me a copy of the manuscript before submission, although it contained exclusively data generated by myself.

Since the study by Hummel et al. violates several important rules of good scientific practice, I expect from "Transplant Immunology" that the publication will be retracted.

Yours sincerely

Bruno Luckow

PS: I will be on vacation from March 17 to March 31, 2007 and I don't know whether I will be able to access my e-mail account during that period.