

Response to the Comment by D. Bresson and M. von Herrath

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First of all we would like to thank Dr. von Herrath, who has long-standing experience in transgenic models in which autoimmunity is triggered by viral agents, and who has also been a close collaborator, for the very stimulating comments on our editorial article. It was indeed the aim of our opinion paper to generate debate. We are pleased that the editor has given us the opportunity to express our views in this reply.

Concerning the mouse models, our purpose was to highlight the preclinical importance of the spontaneous overtly diabetic, but not prediabetic, NOD female model. We agree that this is not, for obvious reasons, an easy model to handle and that some time is needed to get the best results from it. This does not mean at all, however, that CD3 antibodies did not show a high efficacy in other experimental models. We fully acknowledge K. Herold's work in the streptozotocin-induced diabetes model in normal mice [1]. We ourselves provided evidence in support of the efficacy of CD3 antibody treatment in the cyclophosphamide-induced diabetes model in NOD mice [2, 3] and, in collaboration with Dr. von Herrath, the LCMV-induced diabetes model in LCMV GP-RIP transgenic mice [4]. The problem is, however, that in addition to CD3 antibodies, an exceedingly high number of other strategies were effective in disease prevention and/or treatment in these other models that were not active at

all in overtly diabetic NOD mice, and which, interestingly enough, have not made it to the clinic so far.

Concerning the clinical data, the points raised by Drs. Bresson and von Herrath are well taken. We would nevertheless like to express some words of caution about drawing conclusions too fast from the combination of data from trials which were conducted in different ways. In our view, it is neither surprising nor contradictory that the results in the trial conducted by K. Herold did not show a long-term effect in CD3 antibody-treated responder patients, as we observed in our trial. We believe that differences in the design of the study (the European trial was a placebo-controlled phase II study), the patient populations (children and adult patients were enrolled in the American trial, while young children were not included in the European study) and the method used to evaluate β -cell function (the mixed meal test in the American trial versus the clamp test in the European trial) greatly affected the results obtained, generating the apparent discrepancies. We still believe that the significant effect on insulin doses we observed 18 months after just a 6-day treatment in the absence of generalized immunosuppression is in strong support of operational tolerance induction in these patients, whatever the future outcome may be. Of course, we agree with Drs. Bresson and von Herrath that unfortunately at present

there are no reliable antigen-specific T cell assays that can directly prove the presence of active tolerance in CD3 antibody-treated responder patients.

Because of our long-standing interest in CD3 antibodies not only in autoimmunity, but also in transplantation, we are very pleased that several groups are now interested in applying and refining the strategies for their use. The larger the critical mass around their

clinical development, the better the chances that CD3 antibodies may reach the approval stage by regulatory authorities. This is the real struggle we are facing today before we can proceed to a large-scale use of these antibodies that, at least in our view, are endowed with unique tolerogenic properties that no other biological agents have shown so far. Are we wrong? Are we right? Only time will show.

■ References

1. **Herold KC, Bluestone JA, Montag AG, Parihar A, Wiegner A, Gress RE, Hirsch R.** Prevention of autoimmune diabetes with nonactivating anti-CD3 monoclonal antibody. *Diabetes* 1992. 41:385-391.
2. **Chatenoud L, Thervet E, Primo J, Bach JF.** Remission de la maladie établie chez la souris NOD diabétique par l'anticorps monoclonal anti-CD3. *C R Acad Sci III* 1992. 315:225-228.
3. **Chatenoud L, Thervet E, Primo J, Bach JF.** Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice. *Proc Natl Acad Sci USA* 1994. 91:123-127.
4. **Von Herrath MG, Coon B, Wolfe T, Chatenoud L.** Nonmitogenic CD3 antibody reverses virally induced (rat insulin promoter-lymphocytic choriomeningitis virus) autoimmune diabetes without impeding viral clearance. *J Immunol* 2002. 168:933-941.