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Borel J F, Feurer C, Gubler H U & Stähelin H. Biological effects of cyclosporin A: a new antilymphocytic agent. *Agents and Actions* **6**:468-75, 1976.
[Biological and Medical Res. Div., Sandoz Ltd., Basel, Switzerland]

The fungus metabolite cyclosporin A is a small peptide which acts as a novel antilymphocytic agent. It strongly depressed antibody formation in mice. Skin graft rejection and graft-versus-host reaction in rodents were much delayed. It also prevented the development of experimental allergic encephalomyelitis and Freund's adjuvant arthritis. Cyclosporin A is not myelotoxic, and affects an early stage of mitogenic triggering of the immunocompetent lymphocytes. [The *SCI*® indicates that this paper has been cited in over 235 publications since 1976, making it the 3rd most-cited paper published in this journal.]

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"I had joined the Cellular Biology Division of Sandoz Ltd. in 1970 and was working mainly on immunosuppression and inflammation. Hartmann Stähelin, my then chief, and I used a complex mouse model for screening both cytostatic and immunosuppressive compounds. In collaboration with Zoltan L. Kis and his colleagues from the microbiology department, we had learned from experience that compounds of microbial origin often showed cytostatic or other pharmacological activities greater than the antimicrobial activity for which they had been selected. Of special interest for our pharmacological screen were purified or semipurified extracts with little antibiotic activity and low toxicity.

"It happened to be me who discovered, in January 1972, the marked immunosuppressive effect of the partially purified two-component mixture which contained cyclosporin A as an active principle. To our surprise, however, the compound had no effect on the survival time of leukaemic mice, indicating that immunosuppression was not linked to general cytostatic activity!

"In the following years, the compound was investigated in a battery of additional *in vitro* and *in vivo* experimental models. Meanwhile, my colleagues in microbiology were concentrating on purification and characterisation of the molecule, and on substantial improvement of the yield, an exceedingly difficult task. On the pharmacological side, Hans Ulrich Gubler was showing that cyclosporin A could both prevent and cure the chronic inflammatory process of Freund's adjuvant arthritis, but was ineffective in the models of acute inflammation. Camille Feurer was performing a number of crucial experiments demonstrating the almost complete lack of effect on haemopoiesis. Together with her and Dorothee Wiesinger, we were already starting to investigate the mechanism of action. All this work was published around the same time.[1-3]

"The reproducible immunosuppressive effects, and the remarkable lack of side effects as compared with reference drugs in clinical use, clearly supported the concept of a selective action on lymphoid cells and, together with the novel chemical structure, induced us to consider cyclosporin A as the prototype of a new generation of immunosuppressants.

"Because the paper was the first to report several of these results, it is not surprising that it is often cited, especially in view of the great impact that cyclosporin A is having today as a drug in the field of organ transplantation and as a probe in basic immunology. More extensive reviews have been published in references 4 and 5."

1. **Borel J F.** Comparative study of in vitro and in vivo drug effects on cell-mediated cytotoxicity. *Immunology* **31**:631-41, 1976.
2. **Borel J F, Fearer C, Magnée C & Stähelia H.** Effects of the new antilymphocytic peptide cyclosporin A in animals. *Immunology* **32**:1017-25, 1977.
3. **Borel J F & Wiesinger D.** Effect of cyclosporin A on murine lymphoid cells. (Lucas D O, ed.) *Regulatory mechanisms in lymphocyte activation.* New York: Academic Press, 1977. p. 716-18.
4. **Borel J F.** The history of cyclosporin A and its significance. (White D J G, ed.) *Cyclosporin A.* Amsterdam: Elsevier Biomedical Press, 1982. p. 5-17.
5. **Morris P J.** Cyclosporin A. (Overview.) *Transplantation* **32**:349-54, 1981.