CC/NUMBER 45
NOVEMBER 9, 1981

This Week's Citation Classic

Klein E & Klein G. Antigenic properties of lymphomas induced by the Moloney agent. J. *Nat. Cancer Inst.* 32:547-68, 1964.
[Institute for Tumor Biology, Karolinska Institutet Medical School, Stockholm, Sweden]

Mouse lymphomas induced by the Moloney agent were strongly antigenic in isologous hosts, as indicated by transplantation and serologic tests. Specific transplantation resistance was established by pretreattnent of the recipients with homografts of other Moloney lymphomas, small isografts of the same lymphoma, or virus-containing lymphoma homogenates. Extensive cross-resistance was demonstrated between different Moloney lymphomas, while there were no certain cross-reactions between Moloney lymphomas and lymphomas induced by the Gross virus, or between Moloney lymphomas and a number of long-transplanted lymphomas. [The *SCI*® indicates that this paper has been cited over 310 times since 1964.]

Eva Klein
Department of Tumor Biology
Karolinska Institutet
Box 60400
S-104 01 Stockholm
Sweden

September 18, 1981

"The important step that led to the work presented in this paper was the discovery of the tumor specific transplantation antigen (later called TSTA) of polyoma virus induced mouse tumors.[1] The discovery of the polyoma virus in the 1950s was unexpected and very surprising. In the beginning, it was difficult to accept that a single virus could induce so many different types of tumors. Since polyoma virus was cytopathic for mouse cells, we speculated that it may induce tumors *not* by direct transformation but by damaging cells that participate in central growth controlling mechanisms. The possibility that polyoma tumors were not autonomous was also suggested by some of the original papers, claiming that they were not transplantable. We know now that this was an artifact, due to the use of genetically heterogeneous mice.

"On the basis of the hypothesis, two young medical students at the time (Sjögren and Hellström) and one of us (GK) set up what we thought was a critical experiment. Since polyoma was known to spread quickly by horizontal infection in mouse colonies, we set up a provisional isolated quarantine facility, free of polyoma virus. They all belonged to highly inbred, homozygous strains. In another laboratory, polyoma tumors were induced by the inoculation of newborn mice of the same inbred strains. When tumors appeared, they were grafted to two groups of mice: artificially polyoma-infected recipients and critically polyoma-free controls, kept at the isolated facility. The results were the opposite of what we expected. According to our hypothesis, the virus treated mice should have supported the growth of the transplanted cells, in contrast to the untreated mice. The opposite was found: all tumors grew in untreated syngeneic hosts, but were rejected by the polyoma-infected mice. Subsequent analysis of the rejection mechanism by Sjögren[2] and independently by Habel[3] showed that the virus infected mice responded immunologically to a target antigen, present on the surface of the polyoma transformed cells, later designated as TSTA.

"We then asked the question whether similar antigens also appeared on tumor cells transformed by oncogenic RNA viruses. Our first choice was the Gross virus system where we did find a similar transplantation resistance in virus immunized mice, but a very weak one.[4] Around the same time, Old, Boyse, and co-workers[5] demonstrated a similar phenomenon with the Friend and the Rauscher virus induced leukemias. We then went on to the Moloney system which led to the work that has become the *Citation Classic.* The reason why this, rather than the polyoma or the Cross papers, has become a *Citation Classic* is due to the fact, we tend to believe, that more workers use the Moloney system (or related systems) for their work. Also, Moloney virus induced tumors are relatively strongly antigenic and have therefore become more widely used.

"In summary, we believe that this history illustrates how a paper that does not represent the first introduction of a new concept but rather a follow-up on a related but different system can become a *Citation Classic* because the system described is more frequently used, for reasons of convenience, than the actual experiment system that served as the basis for the original discovery. For a recent bibliography, consult the reviews in *Viral.* Onco/ogy."[6]

1. **Sjögren H O, Hellström I & Klein** G. Resistance of polyoma virus immunized mice against transplantation of established polyoma tumors. *Exp. Cell Res.* 23:204-8. 1961.
2. **Sjögren H** O. Studies on specific transplantation resistance induced by polyoma virus infection. *J. Nat. Cancer Inst.* 32:361-74, 1964.
3. **Habel K.** Immunological determinants of polyoma virus oncogenesis. J. *Exp.Med.* 115:181-93, 1962. [The *SCI* indicates that this paper has been cited over 180 times since 1962.]
4. **Klein G, Sjögrea H O & Klein** E. Demonstration of host resistance against isotransplantation of lymphomas induced by the Gross agent. *Cancer Res.* 22:955-61, 1962. [The *SCI* indicates that this paper has been cited over 165 times since 1962.]
5. **Old L J & Boyse** E **A.** Immunology of experimental tumors. *Annu. Rev. Med.* 15:167-86. 1964.
6. **Klein** G, ed. *Viral oncology.* New York: Raven Press, 1980. 842 p.