## Epstein–Barr virus

# Dream or reality of a vaccine?

*from A.J. Beale*

EPSTEIN–BARR virus (EBV) was first recognized in cultures of Burkitt's lymphoma cells and is a member of the herpes virus family. It was soon established as a cause of infective mononucleosis. There has also been a strong association between the virus, Burkitt's lymphoma and nasopharyngeal carcinoma. Since 1976, Epstein and his colleagues have mounted a systematic search for a vaccine against the virus in the hope that the viral aetiology of the two malignancies could be proved, with much benefit to high-risk populations in Africa, China and South-East Asia. Their studies have reached another landmark, as described on page 287 of this issue of *Nature*.

Epstein *et al.* have previously identified as a candidate immunogen an EBV glycoprotein termed gp340, and have devised means for its extraction, techniques for measurement of both gp340 and antibodies to it, and have developed an animal model of EBV-induced lymphomas in cottontop tamarins (*Saguinus oedipus oedipus*). The stage was set for the critical experiment in which vaccinated and unvaccinated tamarins were challenged with EBV. This experiment and the success of the immunization is now reported.

As the test vaccine, gp340 preparations, containing a minimal amount of residual living virus, were given to two tamarins in eight intraperitoneal doses at fortnightly intervals. Both animals developed antibodies that could be detected by an enzyme-linked immunosorbant assay, by immunofluorescence and by neutralization of EBV transformation of cord blood cells. They were both protected against a massive challenge dose of virus which caused disease and multiple tumours in control animals. Isolated gp340 in liposomes was less immunogenic than the membrane preparation: in a group of four animals given this vaccine, only one produced high concentrations of antibodies and was protected against viral challenge. Thereafter, two animals were given 17 intraperitoneal doses of the liposome preparation at fortnightly intervals and were subsequently challenged. Both animals developed transient inguinal lymph node enlargement after challenge; in one case this was accompanied by transient mesenteric node enlargement.

From the successful development of a vaccine against Marek's disease, to which fowl are particularly prone, it is already clear that a vaccine against tumours caused by herpes viruses is feasible, and the work now being reported on EBV shows that the development of a similar vaccine for a human herpes virus is theoretically possible. Is it likely to be a practical proposition to make and test such a vaccine? The candidate vaccines of Epstein *et al.* are not practical: clearly, the membrane preparation of gp340 would need rigorous testing to show it was free of infectious virus before its use in man could be contemplated, and either vaccine would need to be presented in such a way that a protective immune response is achieved with fewer doses of vaccine. Doubtless the schedule could be improved to ensure priming and the elicitation of a secondary response.

The most important advance referred to by Epstein and his colleagues is the cloning and sequencing of EBV and identification of the sequences encoding gp340. It should therefore be possible to produce the protein in large quantities. Since it is glycosylated — more than 50 per cent of the mass is carbohydrate — it may prove best to prepare it in mammalian cells, as is done for many other viral immunogens, rather than in bacteria or yeast. Alternatively it could be expressed in vaccinia virus or some other carrier. The groundwork for developing a vaccine against EBV seems to have been soundly laid and the technology to produce sufficient immunogen is at hand.

The major problems of organizing and financing the procurement and testing of such a vaccine remain to be solved. The problems of organizing trials against diseases caused by EBV are formidable, even when compared with other herpes virus infections. Whereas infectious mononucleosis is an early manifestation of primary infection, Burkitt's lymphoma and nasopharyngeal carcinoma are late manifestations that often take many decades to emerge. No one knows at present whether the late manifestations can be prevented after infection, but current opinion is sceptical. The aim, therefore, must be to prevent infection.

Trials of a vaccine against infectious mononucleosis are a practical and worthwhile proposition, given the will, in Western countries. Proof that EBV infection and this disease can be prevented by a vaccine would warrant the use of a vaccine to prevent Burkitt's lymphoma and nasopharyngeal carcinoma. It is doubtful whether it is practical to carry out a placebo-controlled trial lasting decades, but observation of the effect of vaccine on disease together with more limited trials of the vaccine on viral infections may suffice to demonstrate that EBV is indeed the cause of Burkitt's lymphoma and nasopharyngeal carcinoma.

For a number of diseases, ranging from malaria and pertussis to those caused by hepatitis B and EB viruses, there are now prospects for control by immunization, based on a molecular understanding of the immunogen required to produce protection. To harness this promise, a more determined and imaginative approach to preventive medicine and public health is required. Provided government agencies can see the economic as well as the health benefits of developing such approaches, the benefits to mankind and human health could be immense. □

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## γ-ray sources

# Does Geminga exist yet?

*from Roger W. Romani and Virginia Trimble*

THE peculiar γ-ray source in the constellation Gemini, termed Geminga, is once again puzzling astronomers. Originally found by the SAS-2 satellite[1] and later studied by γ-ray detectors both in space[2] and on Earth, this object presents strange features in every wavelength band. One of the strangest — that it cannot be detected at visible and radio wavelengths — is reflected in its name, which also means "does not exist" or "is not there" in Milanese dialect. New optical observations (refs 4–6 and G.F. Bignami *et al.*, in preparation) have provided a tentative identification but these make Geminga seem even more inexplicable: as G.F. Bignami (Milan) reported at a recent meeting*, the object is exceedingly faint and may have a very large proper motion.

As the brightest of the 20 unidentified γ-ray sources in the COS-B catalogue[2], Geminga is a natural subject of searches for corresponding sources in other energy ranges. The high count rate and large distance from the confusion at the galactic centre allowed the COS-B collaboration to obtain a position that is excellent by γ-ray standards. Images taken with the Einstein X-ray satellite's high resolution imager (HRI) and imaging proportional counter (IPC) led to the identification of Geminga with the bright source 1E0630+178 (ref.7), supported, it then seemed, by the same 59–60-second, gradually lengthening pulse period in both X- and γ-ray data[8]. Buccheri *et al.*[9] and others have doubted the periodicity, without necessarily disbelieving the identification, because there is unlikely to be an unusual

*NATO Advanced Study Institute on "High Energy Phenomena around Compact Stars" held at Cargese, Corsica, 2–13 September, 1985.