The Royal Free Hospital
HAEMOPHILIA CENTRE & HAEMOSTASIS UNIT

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Ref: PBAK/cb

15th March 1983

Mr C R Bishop
Manager, Plasma Division
Armour Pharmaceutical Company
St. Leonards House
St. Leonards Road
Eastbourne
Sussex

Dear Mr Bishop

Re: Proposal for research support into AIDS at the Royal Free Hospital

Further to our previous discussions, I now enclose a brief formal proposal requesting support for our AIDS-related project in haemophiliacs.

As you will see, the request is mainly for a 1 year period of salary support for a Senior technician (MLSO) in Professor Janossy's department here, starting 1st April 1983. The gross sum needed, which would be of course be spread over the year, is a little over £12,000.

I should of course be very pleased to supply you with any further information you may need. Any help Armour is able to give us would be greatly appreciated.

Yours sincerely

GRO-C

P B A Kernoff
Consultant Haematologist
Director of Haemophilia Reference Centre

BRIEF RESEARCH PROPOSAL

A0000113/ 2

1. TITLE OF PROJECT

EFFECTS OF BLOOD PRODUCTS ON THE IMMUNE SYSTEM OF PATIENTS WITH HAEMOPHILIA.

2. PRINCIPLE INVESTIGATORS

Dr. P.B.A.Kernoff, Director, Haemophilia Reference Centre, Royal Free Hospital, London, UK

Professor G. Janossy, Head of the Department of Immunology, Royal Free Hospital, London, UK.

3. BACKGROUND

Several recent reports in leading medical journals 1-6 have indicated that many haemophiliacs treated with coagulation factor concentrates develop abnormalities in their blood suggestive of impaired immunological function. A minority of patients have clinical evidence of altered immunity, and a small number in the USA have developed the very serious 'acquired immune deficiency syndrome' (AIDS), characterised by opportunistic infections and a high mortality rate.

The causes of these abnormalities are unknown, but may include transmission of a previously unrecognised virus or other agent. The predictive value of simple tests of immunological function is also unknown. However, the possibility that infusion of essential therapeutic products may be complicated by very serious hazards is causing extreme concern amongst patients and those responsible for their care. It has been suggested that profound changes may have to be made in management practices, particularly as regards the use of imported commercial concentrates.

We regard the acquisition of further information about the immunological defects in haemophiliacs, and their relationships with clinical disease and blood product exposure, to be a matter of the highest priority.

4. FACILITIES AND EXPERTISE AVAILABLE AT THE ROYAL FREE HOSPITAL

The problems outlined above are being studied by several groups, particularly in the USA. However, we believe we are particularly well placed at the Royal Free Hospital to make a unique contribution because:

(a) The Haemophilia Centre at the RFH is one of the largest in the UK, has an intensively-followed group of patients who have been exposed to a variety of different types of commercial and non-commercial blood products, and has comprehensive records of treatment extending back for many years. Many of these records are computerized, and the related problem of hepatitis is a major departmental research interest. Full clinical backup is available for this project, using NHS and research-funded staff and facilities.

(b) The Department of Immunology at the RFH is in the forefront of the development of the new immunological methods which are necessary for

in-depth investigation of this problem (7,8). Special techniques for histological examination have been standardised, the most modern equipment (EPICS V) has recently been provided by the Medical Research Council, and tissue biopsy samples from other groups of patients at risk of and with AIDS are readily available for comparative purposes.

5. WORK PROPOSED

Preliminary studies using the limited laboratory manpower available have shown that immunological abnormalities in haemophiliacs are not confined to those patients who have received commercial concentrates, and have a close association with chronic liver disease. The objective of the proposed work, which will extend over a one year period, is to reach more definitive conclusions about the relative morbidity associated with exposure to different blood products, and the relationships between immunological abnormalities in the blood and those in tissue biopsy samples. Comparisons will be made with other groups of patients at increased risk of AIDS. The work will include:

- analysis of blood lymphoid populations (T cell subsets: T4 and T8 positive cells: B cells) and macrophages with monoclonal antibodies using the EPICS V flowcytometer.
- analysis of activated lymphocytes by double marker methods using the fluorescence microscope.
- lymphocyte functional assays : PHA tests and cytotoxicity against virus-infected target cells.
- analysis of the immunohistological changes in lymph nodes of haemophiliacs with lymphadenopathy : study of T lymphoid, B lymphoid and macrophage subsets, and viral antigens. This is a novel study of great scientific and possibly diagnostic interest.

6. REASONS FOR REQUESTING SUPPORT

Because we regard the questions raised by the recognition of immune abnormalities in haemophiliacs to be of profound scientific and clinical importance, we are preparing a grant application for longer term support from a major grant-giving organisation. The decision about the allocation of this grant will necessarily take at least 8 months, and we are seeking 1 year 'bridging' support to allow us to start organised detailed analysis at once.

Our immediate problem is lack of skilled technical manpower in the Department of Immunology. A trained technician, whose funding on a related study will end of 1st April 1983, is available to start on this project. The funds we are seeking are mainly for a one year period of salary support, plus a small amount for laboratory consumables.

7. COMPUTATION OF FUNDS REQUIRED - see over

Computation of Funds

Senior MLSO Basic Salary (mid point of scale)	8,500
London Weighting	997
	9,497
20% Superanuation/NI	1,899
Total	11,396
Estimate of consumable expenditure (mainly reagents used in the Department of Immunology)	1,000
Total sum requested	£12,396

8. REFERENCES

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2. Menitove, J.E., Aster, R.H., Casper, J.T., Lauer, S.J., Gottschall, J.L., Williams, J.E., Gill, J.C. Wheeler, D.V., Piaskowski, V., Kirchner, P. & Montgomery, R.R. 1983. T-Lymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. New Engl.J.Med., 308:83-86.

3. Ragni,M., Lewis, J., Spero, J.A. & Bontempo, F.A. 1983. Acquired-immunodeficiency-like syndrome in two haemophiliacs. Lancet, i:213-214.

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5. Pneumocystis carinii pneumonia among persons with hemophilia A. Morbidity and Mortality Weekly Report, 1982, 31.365

6. Precautions against acquired immunodeficiency syndrome. Lancet, i. (Editorial, Jan.22nd)

7. Janossy, G., Tidman, N., Papageorgiou, E.S., Kung, P.C. & Goldstein, G. 1981. Distribution of T lymphocyte subsets in the human bone marrow and thymus: an analysis with monoclonal antibodies. J.Immunol., 126:1608-1613.

8. Janossy, G., Thomas, J.A., Pizzolo, G., Granger, S., McLaughlin, J., Habeshaw, J., Stansfield, A.G., & Sloane, J. 1980. Immunohistological diagnosis of lymphoproliferative diseases by selected combinations of anti-sera and monoclonal antibodies. Br.J.Cancer, 42:224-242.