

# The Physics of Viral Immunology, to Medicines.

Patrick Kearns (Gilbert Lab, IGC)

## MEDICAL INTELLIGENCE



### DISSEMINATED VACCINIA IN A MILITARY RECRUIT WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE

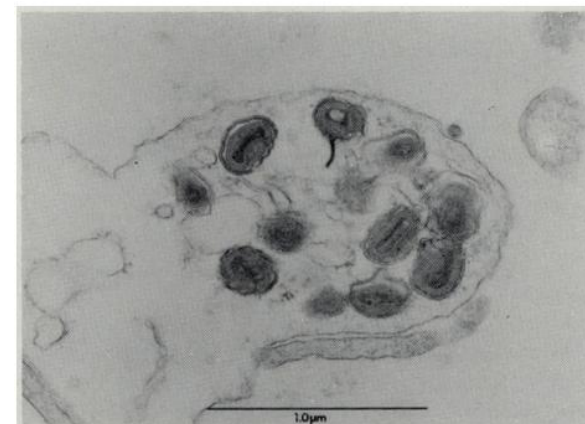
ROBERT R. REDFIELD, M.D.,  
D. CRAIG WRIGHT, M.D., WILLIAM D. JAMES, M.D.,  
T. STEPHEN JONES, M.D., CHARLES BROWN, M.S.,  
AND DONALD S. BURKE, M.D.

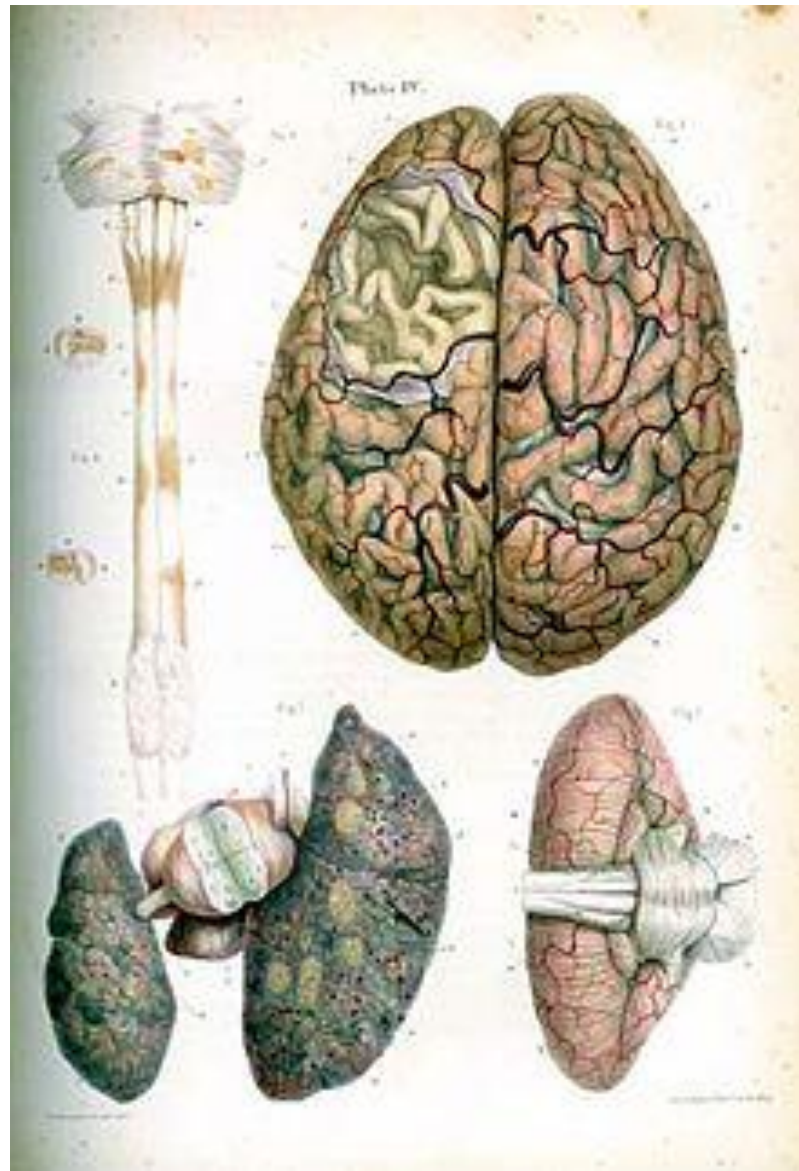
**L**IVE-VIRUS vaccines have been well recognized as a cause of severe complications when inadvertently administered to recipients with impaired immunologic function.<sup>1</sup> The acquired immunodeficiency syndrome (AIDS) has been recognized as a severe immunodeficiency state caused by infection with a retrovirus, human immunodeficiency virus (HIV).<sup>2</sup> HIV infection and disease include a wide spectrum of clinical presentations, such as asymptomatic infections, chronic generalized lymphadenopathy, and frank T-cell deficiency (AIDS-related complex and AIDS).<sup>3</sup> Although the natural history of HIV infection has only been partly defined, it is clear that patients with AIDS represent only a minority of the total number of T-cell-deficient patients with HIV disease.

## CASE REPORT

A 19-year-old black man from the mid-southwestern United States began basic training at a military base in April 1984. He had been healthy throughout high school, taking part in competitive athletics without difficulty. In February 1984 the results of a complete physical examination including a complete blood count (6200 white cells with 24 percent lymphocytes) were reported to be within normal limits. The patient received multiple immunizations (including the following vaccines — adenoviruses 4 and 7, measles, rubella, bivalent influenza, trivalent poliomyelitis, tetravalent meningococcus, tetanus, and diphtheria) within the first three days of basic training, followed by a primary smallpox vaccination at the end of the first week (May 8). He participated fully in basic training until 2½ weeks after the smallpox vaccination, when fever, headache, neck stiffness, and night sweats developed. Cerebral spinal fluid analysis showed 12 white cells per milliliter (100 percent mononuclear cells), a glucose concentration of 26 mg per deciliter (1.4 mmol per liter), a protein level of 37 mg per deciliter, and a cryptococcal antigen titer of 1:128; a culture was positive for *Cryptococcus neoformans*. On May 30 the patient was transferred to Walter Reed Army Medical Center for treatment of cryptococcal meningitis and further evaluation.

Interviews with the patient and family members, conducted by trained investigators, failed to reveal evidence of homosexual activity or intravenous drug use. The patient did admit to multiple heterosexual contacts, including some with prostitutes over the previous five years. He had no history of prior smallpox vaccination or any clinical evidence of a scar consistent with such vaccination. Four weeks after vaccination, while the patient was hospitalized for treatment of meningitis, an ulcer 3 by 4 cm developed at the vaccination site and a satellite ulcerated lesion 0.25 by 0.50 cm developed nearby. Over 48 to 72 hours (June 7 through 9), 80 to 100 pustular lesions appeared on the buttocks and the posterior aspects of the legs, rapidly progressing to ulceration (Fig. 1A). A skin biopsy revealed acanthosis with ballooning degeneration of the keratinocytes of the lower half of the epidermis. Paranuclear oval hyalinized intracytoplasmic inclusion bodies (Guarnieri's bodies) of vaccinia were clearly demonstrated in cells in various stages of ballooning degeneration (Fig. 2). Vaccinia was cultured in chorioallantoic membrane inoculated with material obtained during skin biopsy of the disseminated lesion and from scrapings of both the vaccination site and the disseminated lesions (Fig. 3). The patient was treated with vaccinia immune globulin, 50 ml given intramuscularly weekly for 12 weeks. The ulcers gradually epithelialized and were completely healed by mid-August (Fig. 1B).

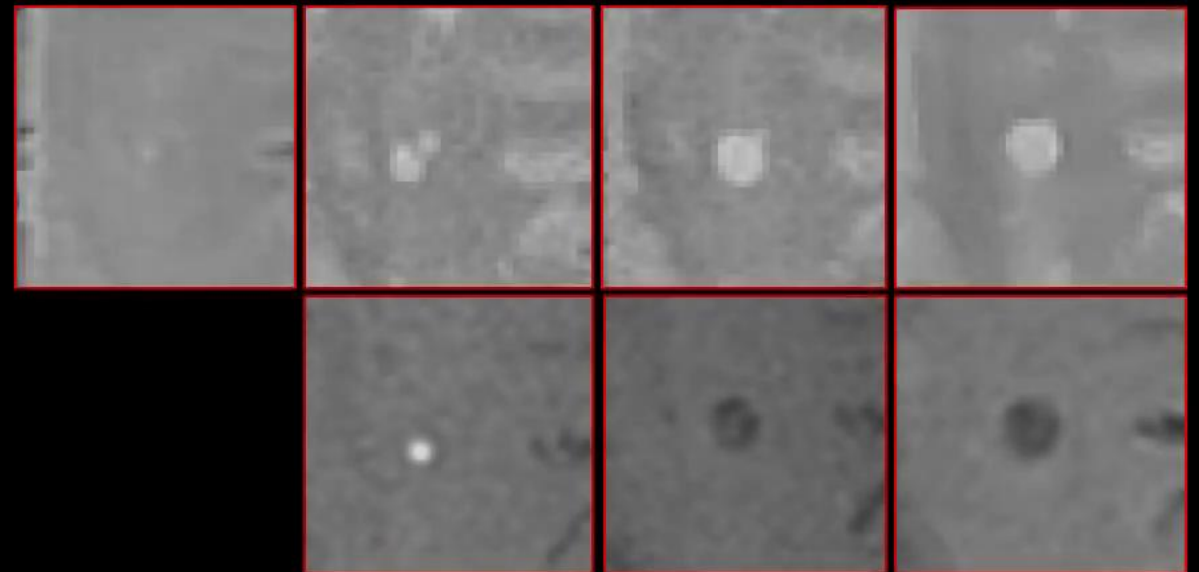




Sclerose en Plaques, Carswell, 1838

# Time-lapse Magnetic Resonance Imaging (MRI) From a Patient With Multiple Sclerosis (MS) Showing an Expanding Rim+ and a Shrinking Rim- Lesion

JAMA Neurology



## Primary Infection with the Epstein-Barr Virus and Risk of Multiple Sclerosis

Lynn I. Levin, PhD, MPH,<sup>1</sup>

Kassandra L. Munger, ScD,<sup>2</sup>

Eilis J. O'Reilly, ScD,<sup>2,3</sup> Kerstin I. Falk, PhD,<sup>4,5</sup>

and Alberto Ascherio, MD, DrPH<sup>2,3,6</sup>

To determine whether multiple sclerosis (MS) risk increases following primary infection with the Epstein-Barr virus (EBV), we conducted a nested case-control study including 305 individuals who developed MS and 610 matched controls selected among the >8 million active-duty military personnel whose serum has been stored in the Department of Defense Serum Repository. Time of EBV infection was determined by measuring antibody titers in serial serum samples collected before MS onset among cases, and on matched dates among controls. Ten (3.3%) cases and 32 (5.2%) controls were initially EBV negative. All of the 10 EBV-negative cases became EBV positive before MS onset; in contrast, only 35.7% ( $n = 10$ ) of the 28 controls with follow-up samples seroconverted (exact  $p$  value = 0.0008). We conclude that MS risk is extremely low among individuals not infected with EBV, but it increases sharply in the same individuals following EBV infection.

ANN NEUROL 2010;67:824–830

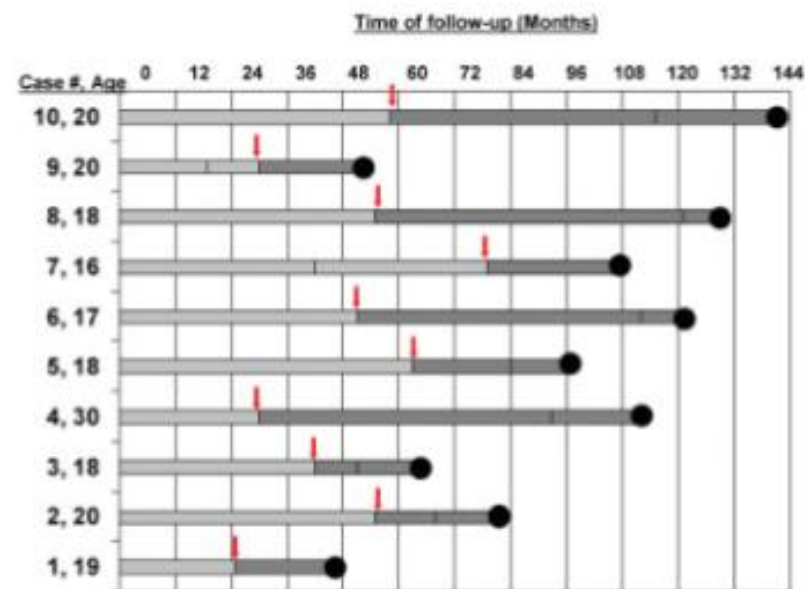
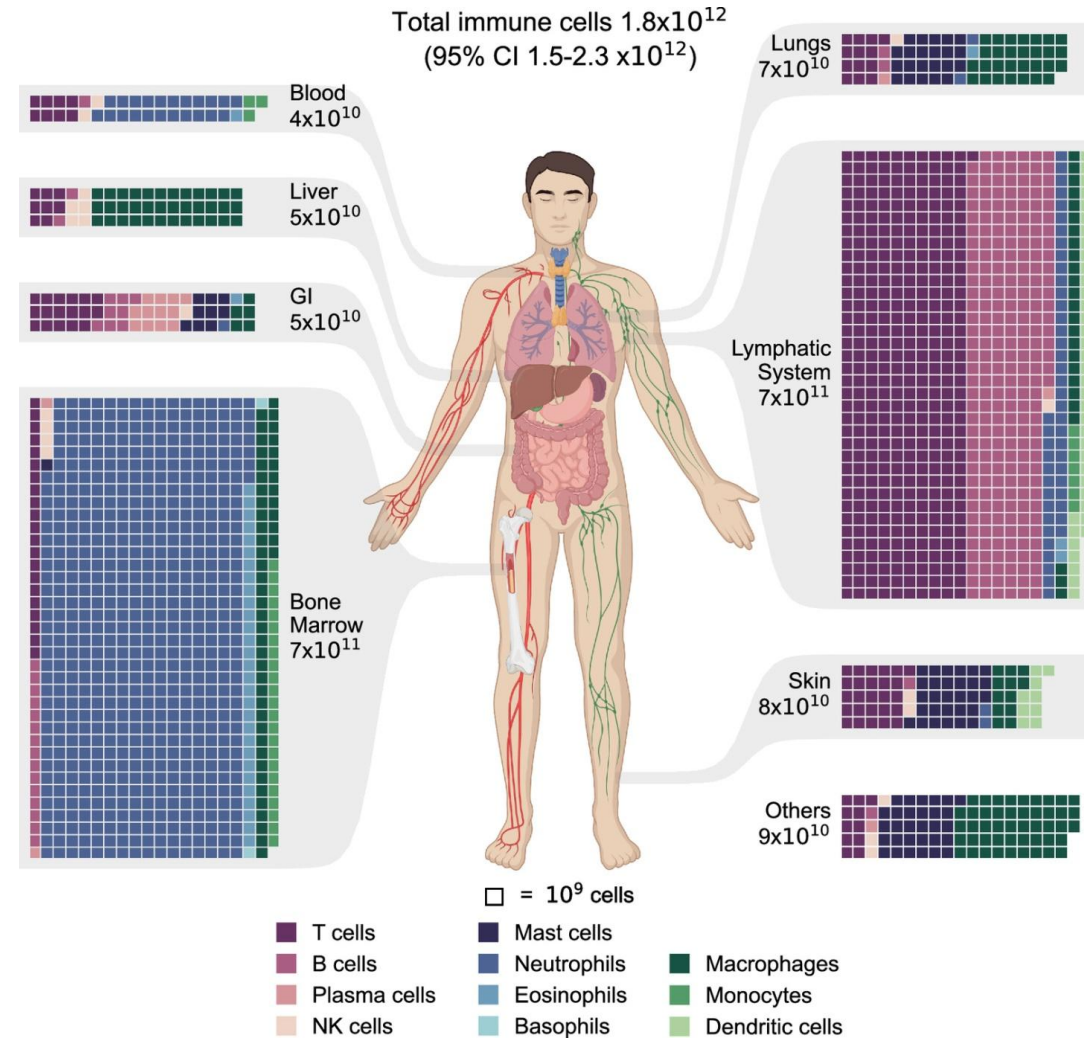
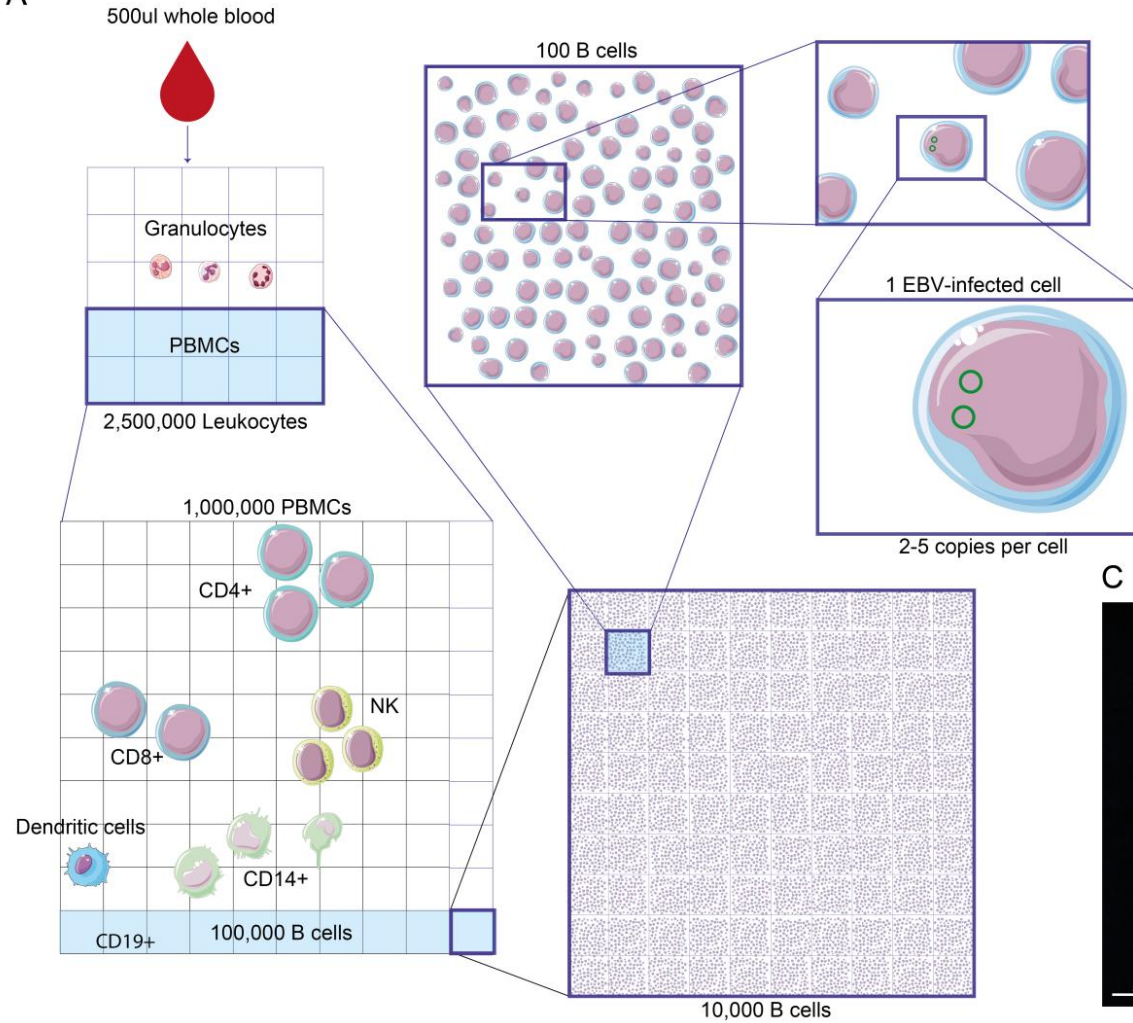


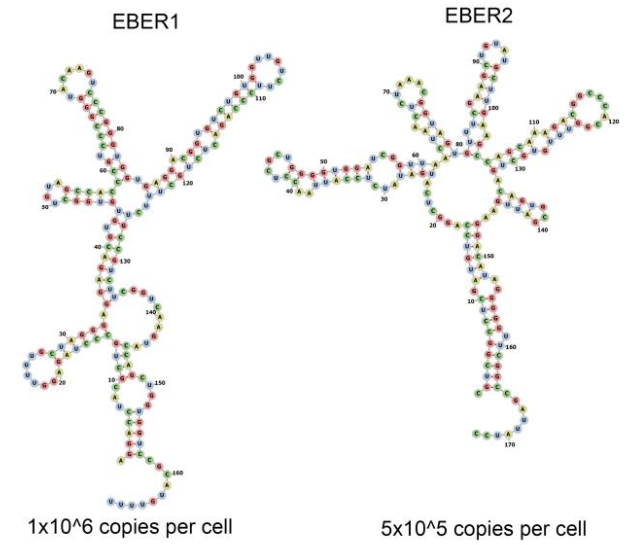
FIGURE: Time of Epstein-Barr virus (EBV) seroconversion and multiple sclerosis (MS) onset in the 10 cases who were seronegative at baseline. The vertical lines within each bar represent the time of blood collections after the initial sample, which was taken at time zero for each individual. The arrows and bar darkening mark the time of the first EBV-positive serum. The black circles are drawn at the time of MS onset. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]



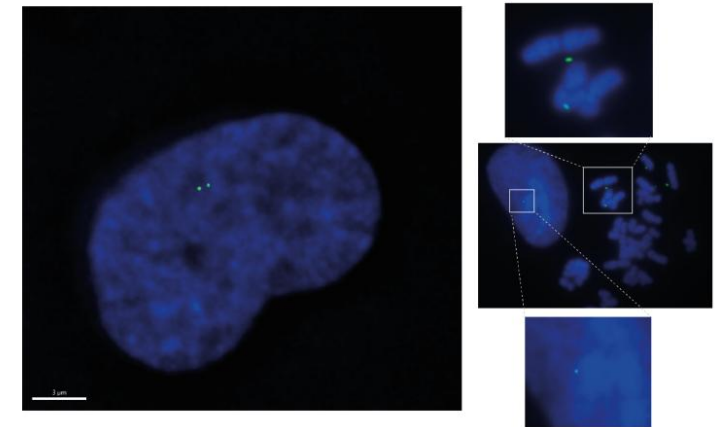
**A**



**B**



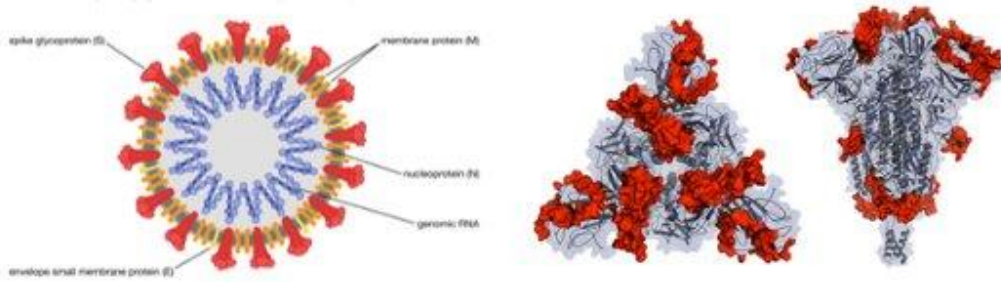
**C**



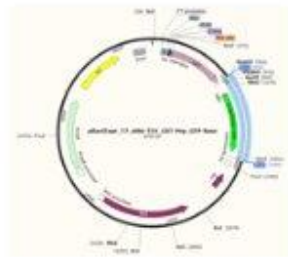
Purification: Ni-NTA magnetic beads on Kingfisher Flex Robot

Expression: Expi293 cells

## Marsh lab – structure based epitope prediction



## Design and optimising plasmid vectors for expression



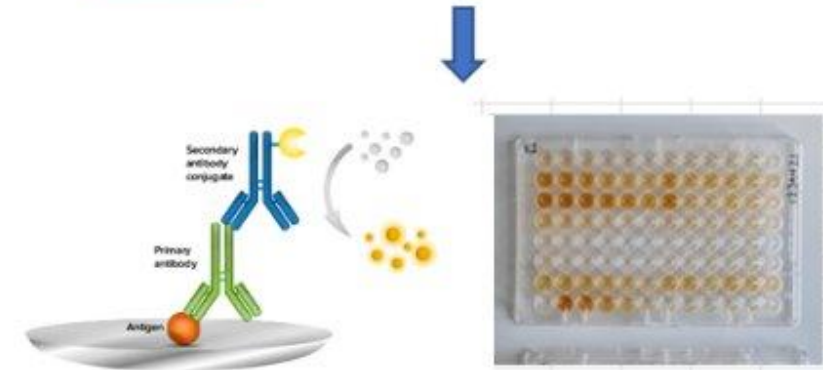
DNA synthesis: G-blocks from IDT



Expression: T7 Express



### Cleanup: Sephadex G-25 spin columns

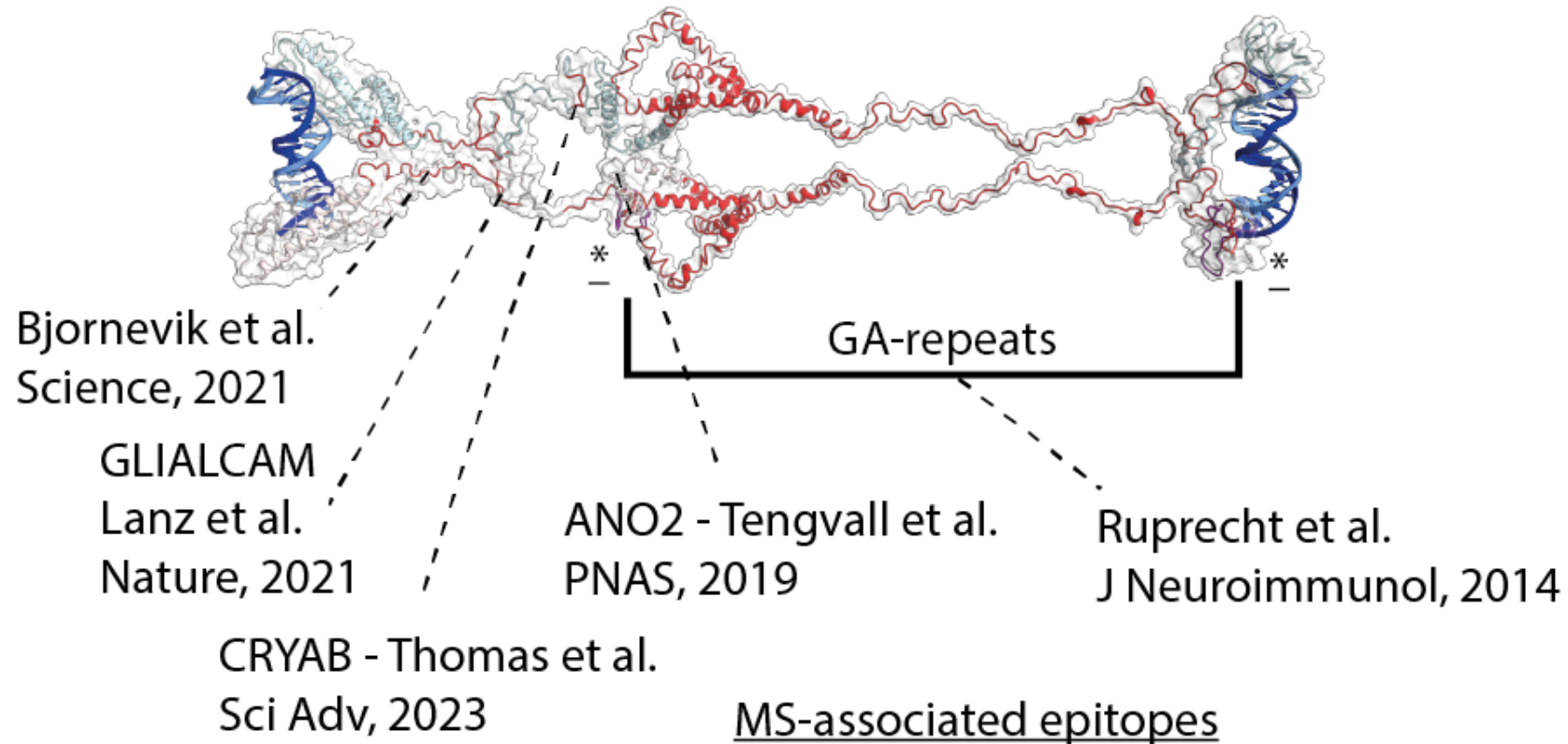


## Cloning: Edinburgh Genome Foundry

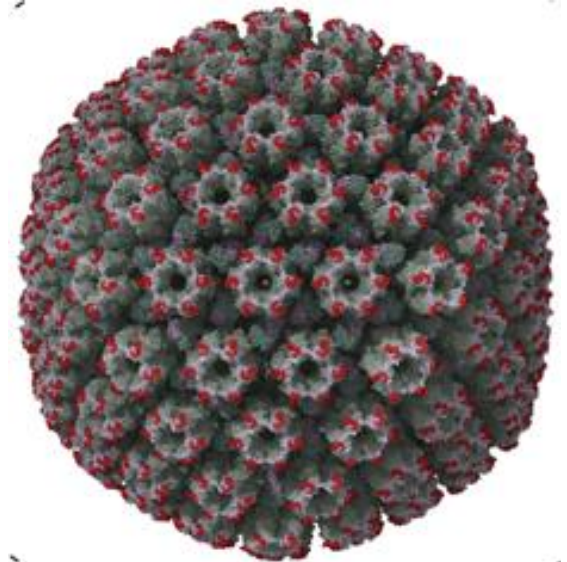
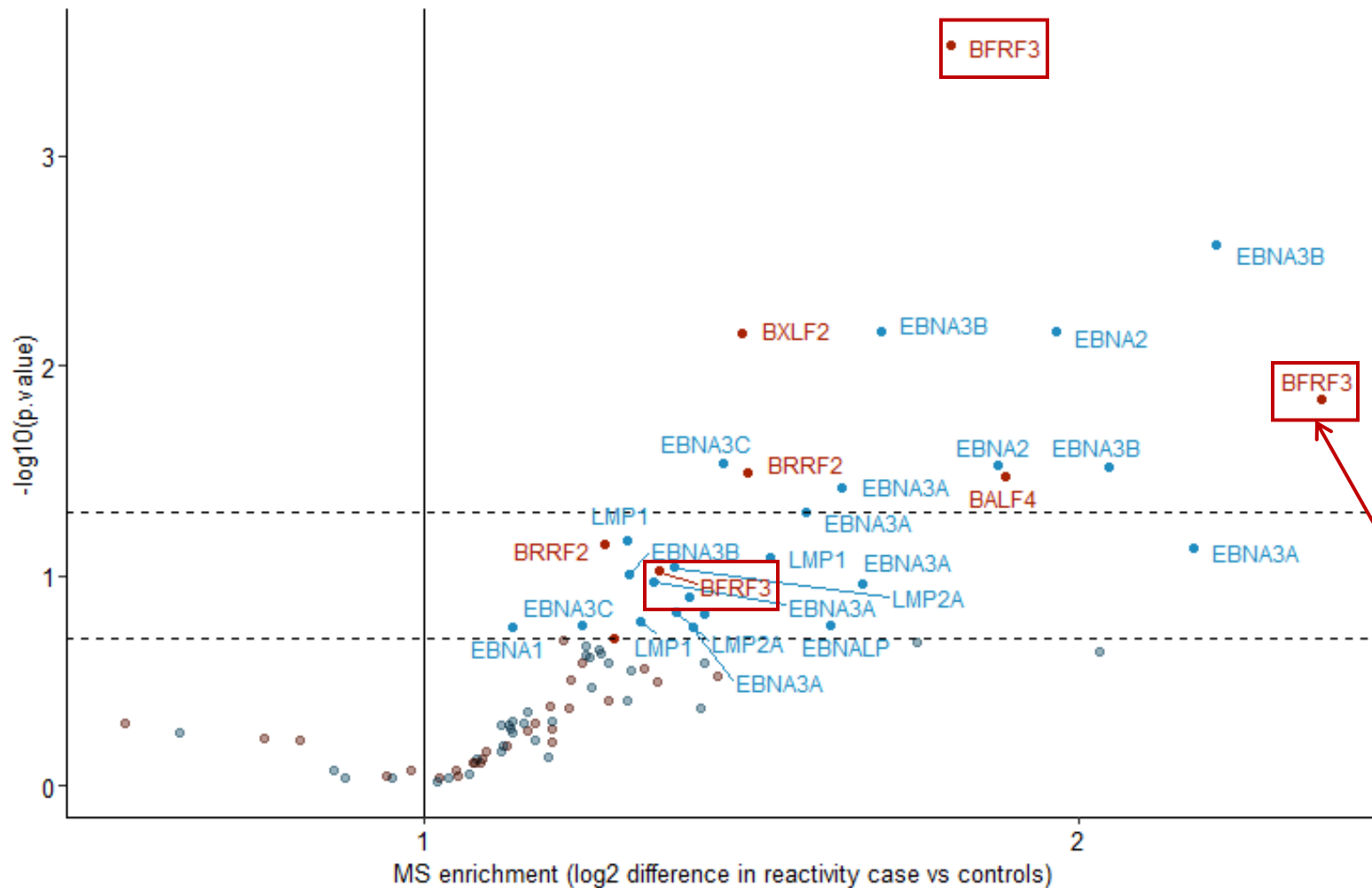
## EBNA-1 dimer

EBV DNA

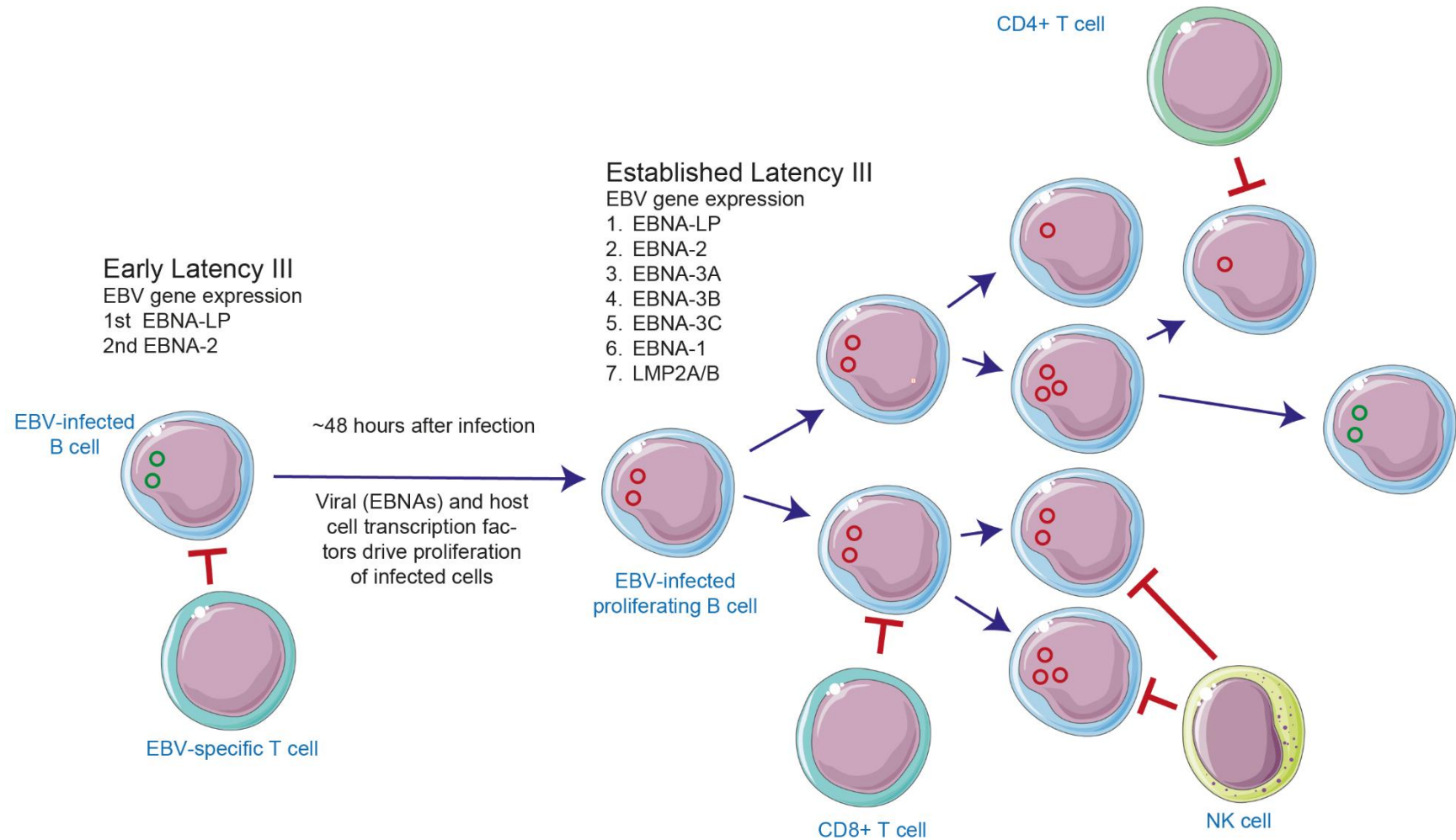
Chromosomal DNA



# EBV antibodies to viral proteins



BFRF3 - Repetitive quaternary structure (VCA-p18)





Dr Patrick Kearns



Prof Nick Gilbert



Prof Joe Marsh

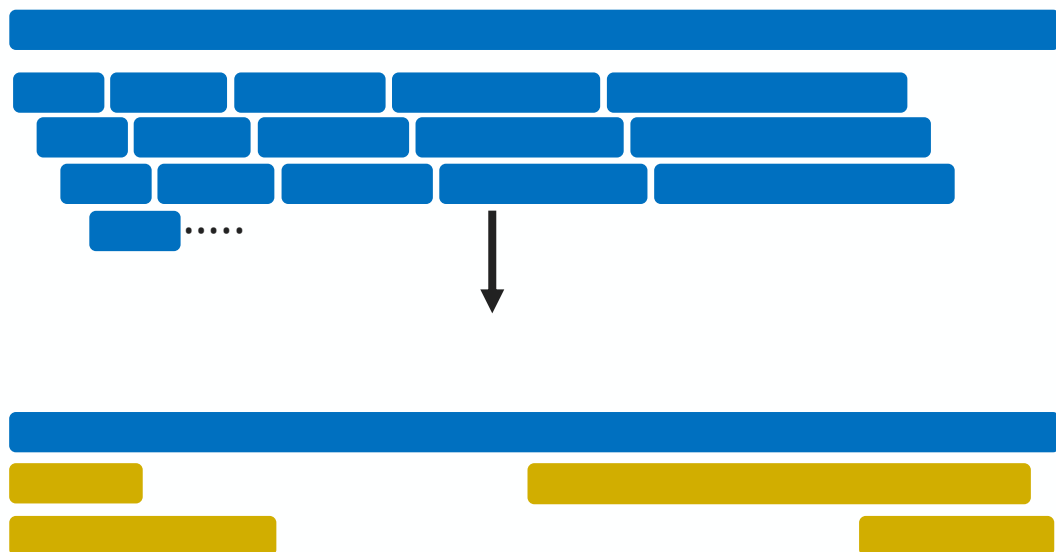


Dr Charles Dixon

# Maxitope: a journey from B cell epitope prediction to developing immune therapies

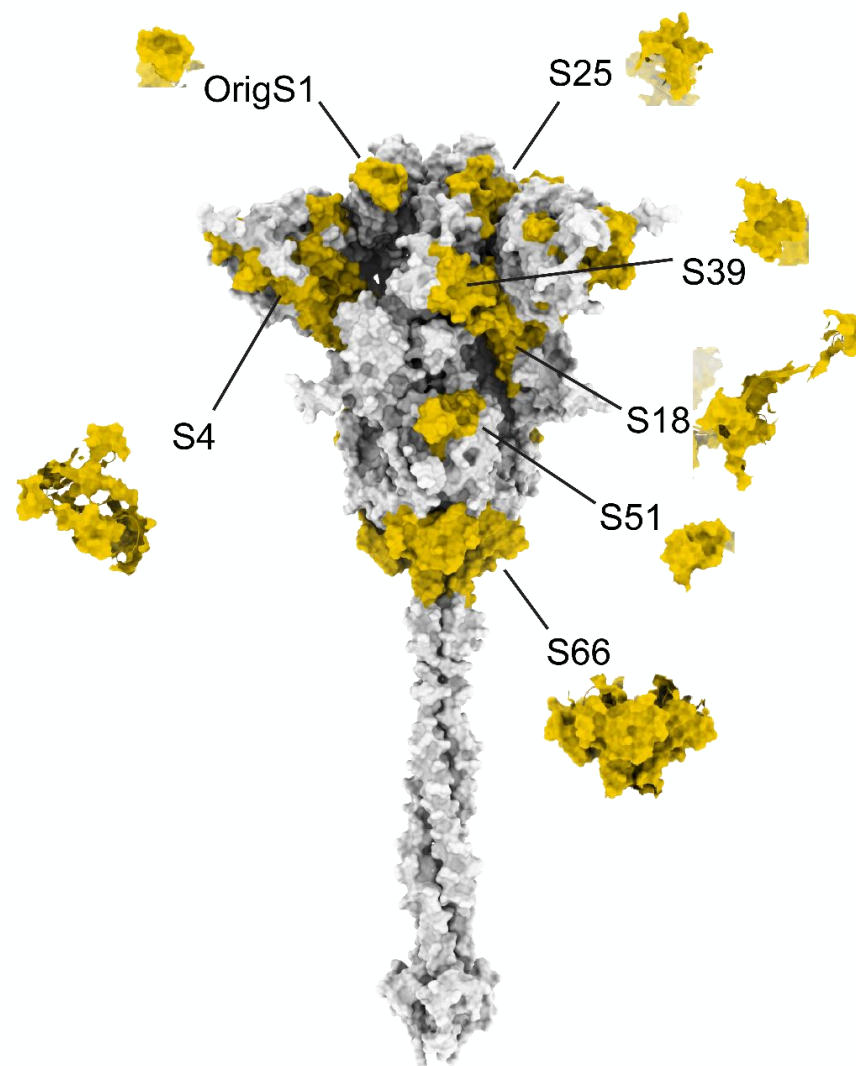
# High performance target discovery

Using thermodynamic modelling we focus on the best targets

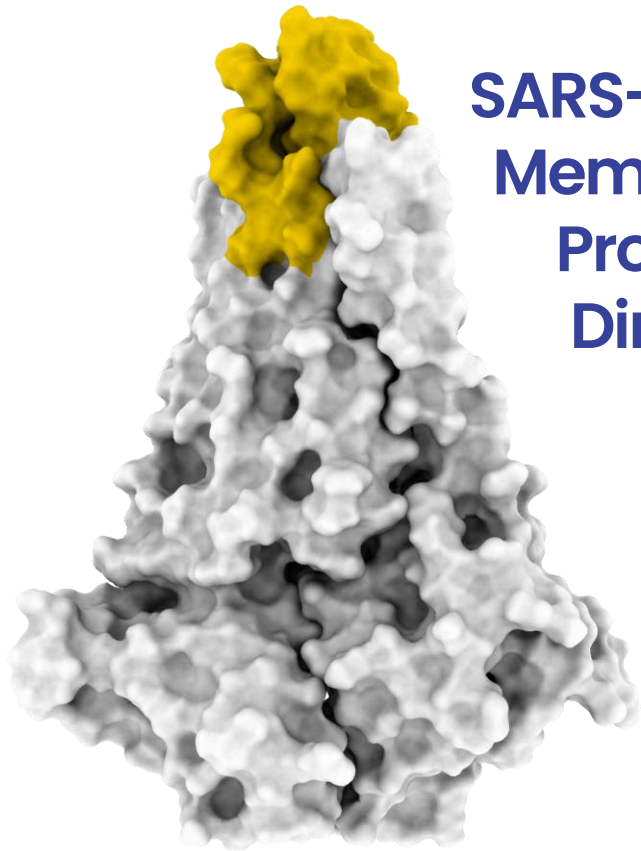


Possible  
Targets:  
100,000s

Lead  
Candidates:  
10s

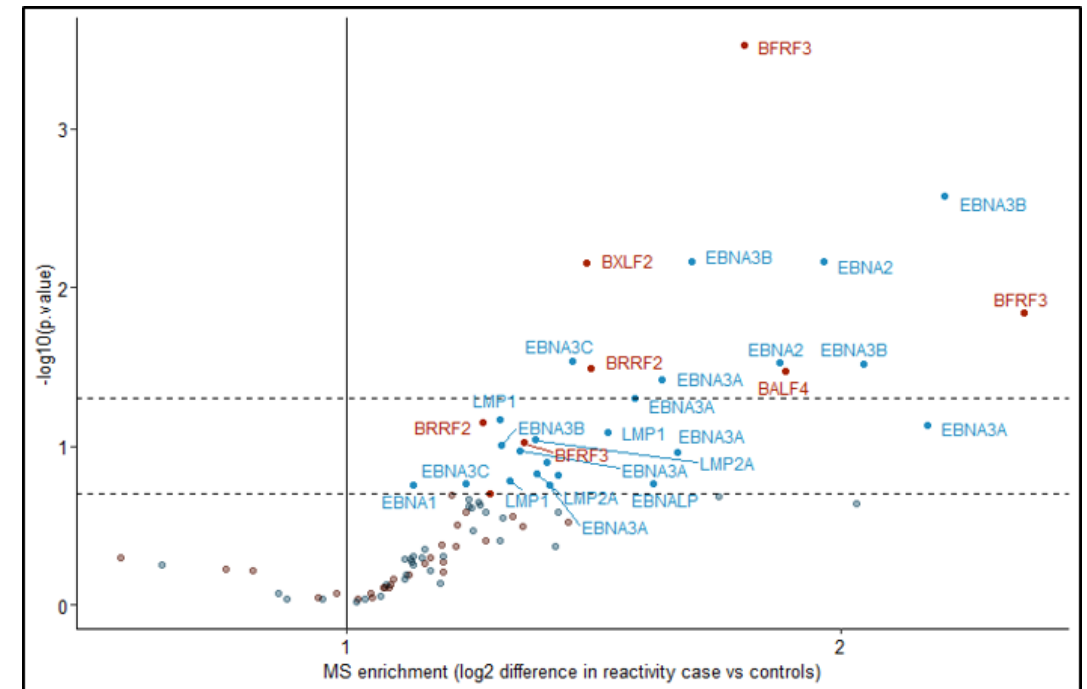


<sup>1</sup>IP:EP 4 444 741 A1



# SARS-CoV-2 Membrane Protein Dimer

## EBV targets in multiple sclerosis



# The Platform Identifies Novel Targets

# The two kinds of drug



**Doxorubicin  
(1 nm)**

**Antibody IgG  
(10 nm)**

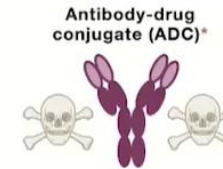
Property	Small molecules	Antibodies
Size	500 daltons	150,000 daltons
Oral bioavailability	Yes	No
Intracellular distribution	Yes	No
Inhibit enzymes	Yes	Yes
Cytotoxic	Yes	Yes
Block protein-protein interactions	No	Yes
Half-life	Short (hours)	Long (weeks)
Off target toxicity	Yes	Less



**Fragment  
(Fab)**



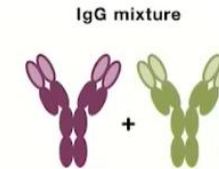
**Bispecific IgG\***



**Fragment  
(bivalent nanobody)**



**Bispecific  
fragment (TCE)\***



**Fragment  
(scFv)**



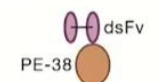
**Fusion protein  
(ImmTAC)\***



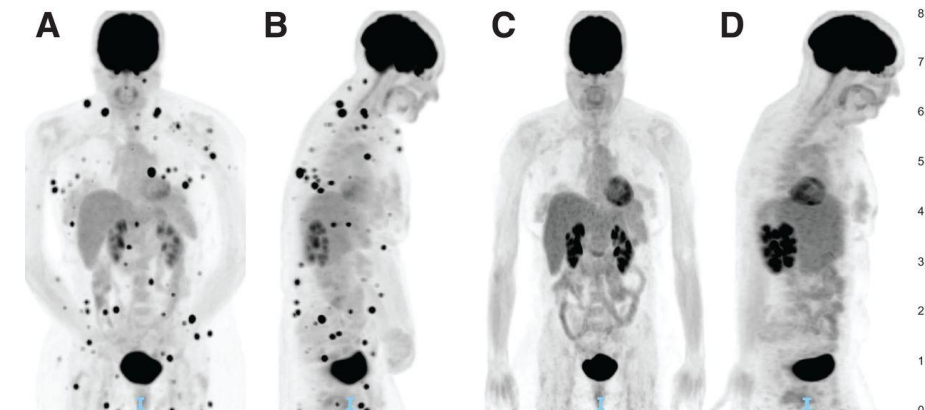
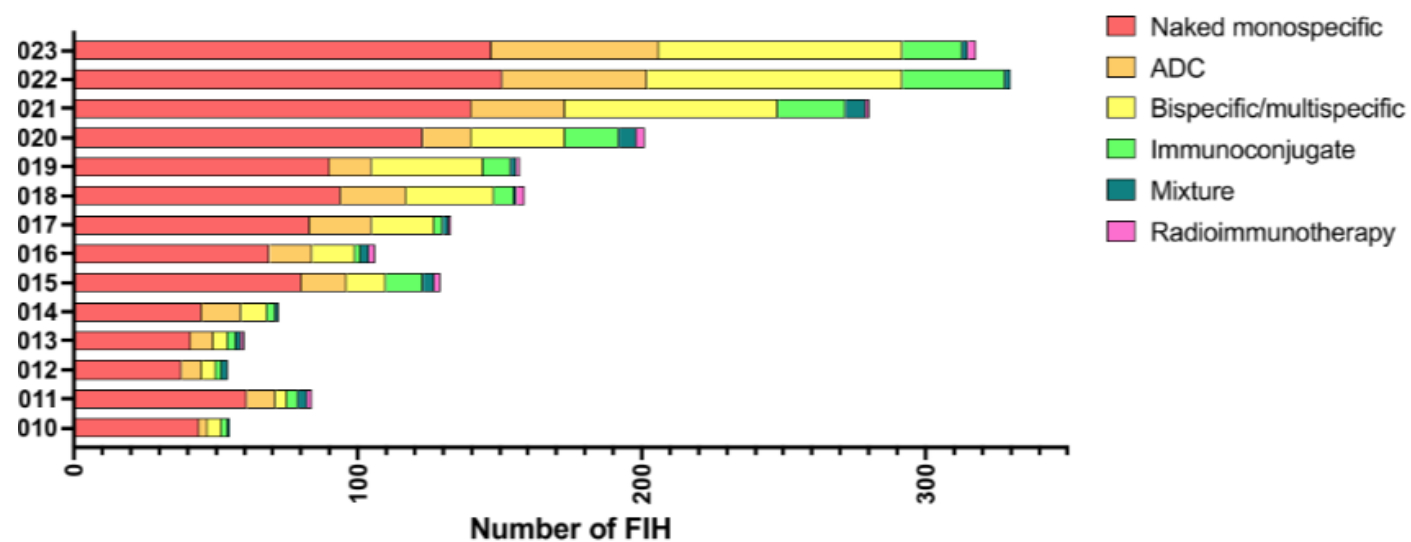
**Fragment  
conjugate**



**Fusion protein  
(Immunotoxin)\***

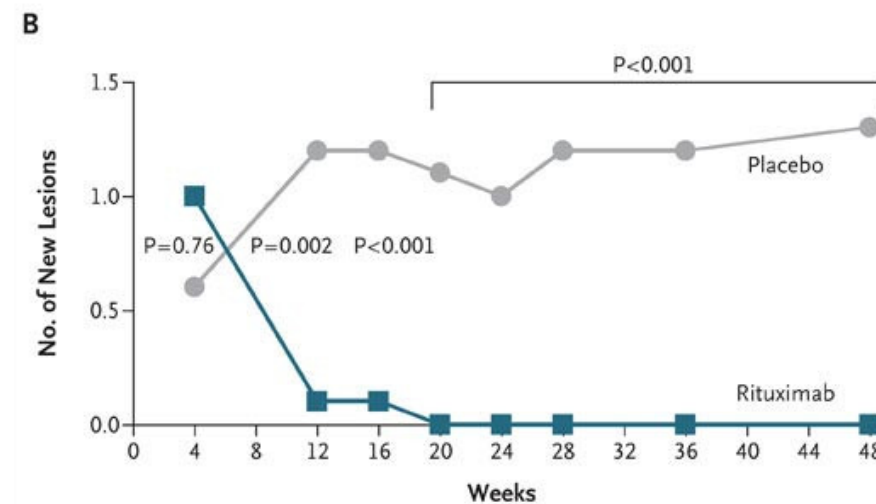
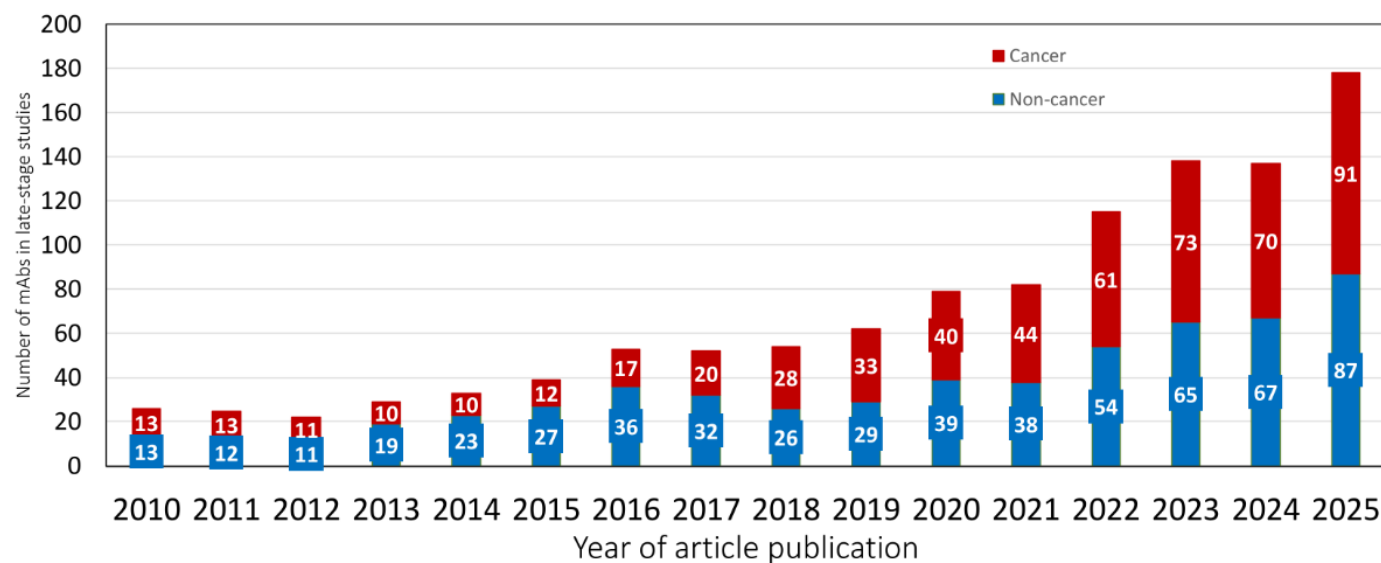


## Antibodies entering clinical study

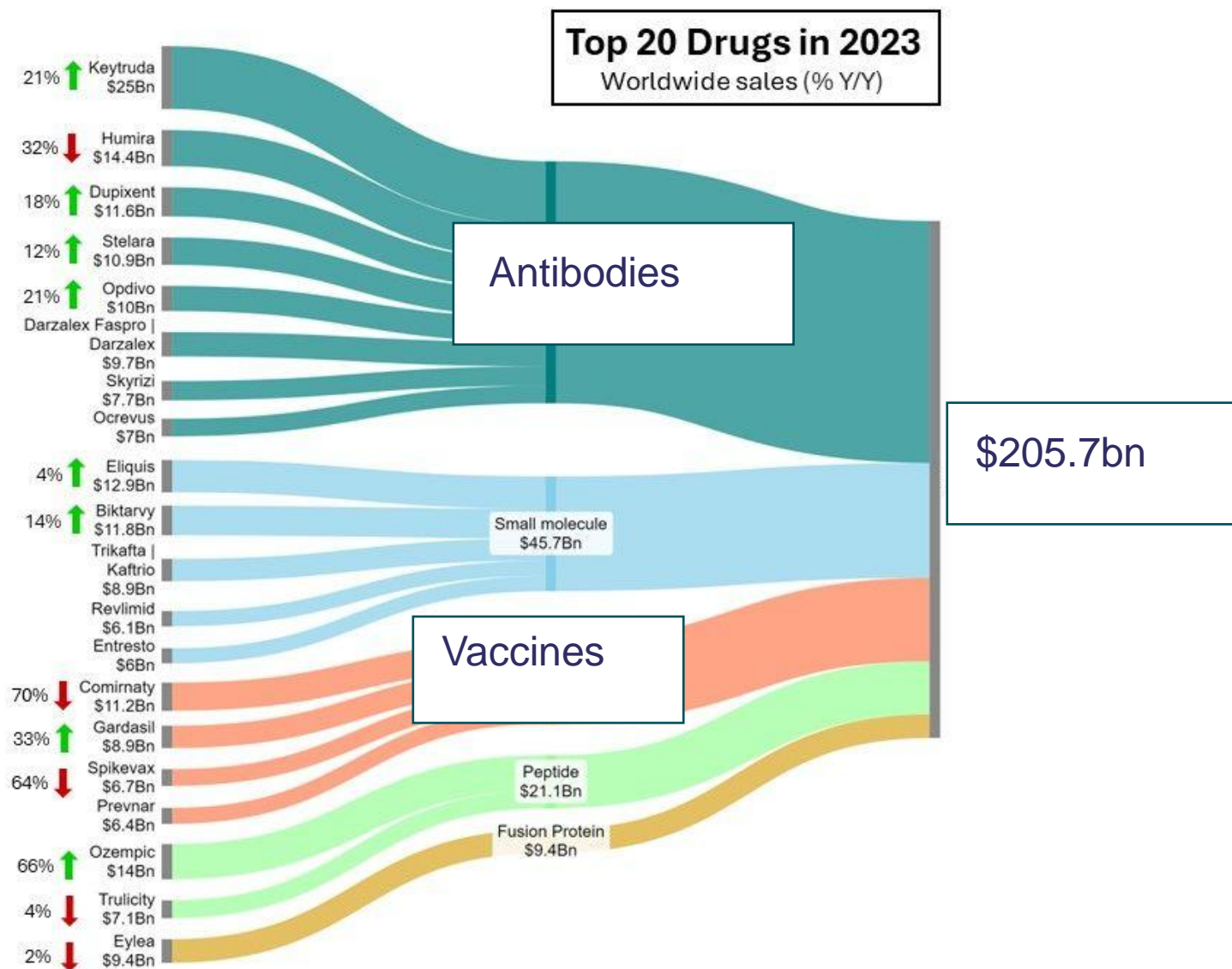


Dougherty et al. J Nuc Med, 2024

## Antibodies in late-stage clinical study

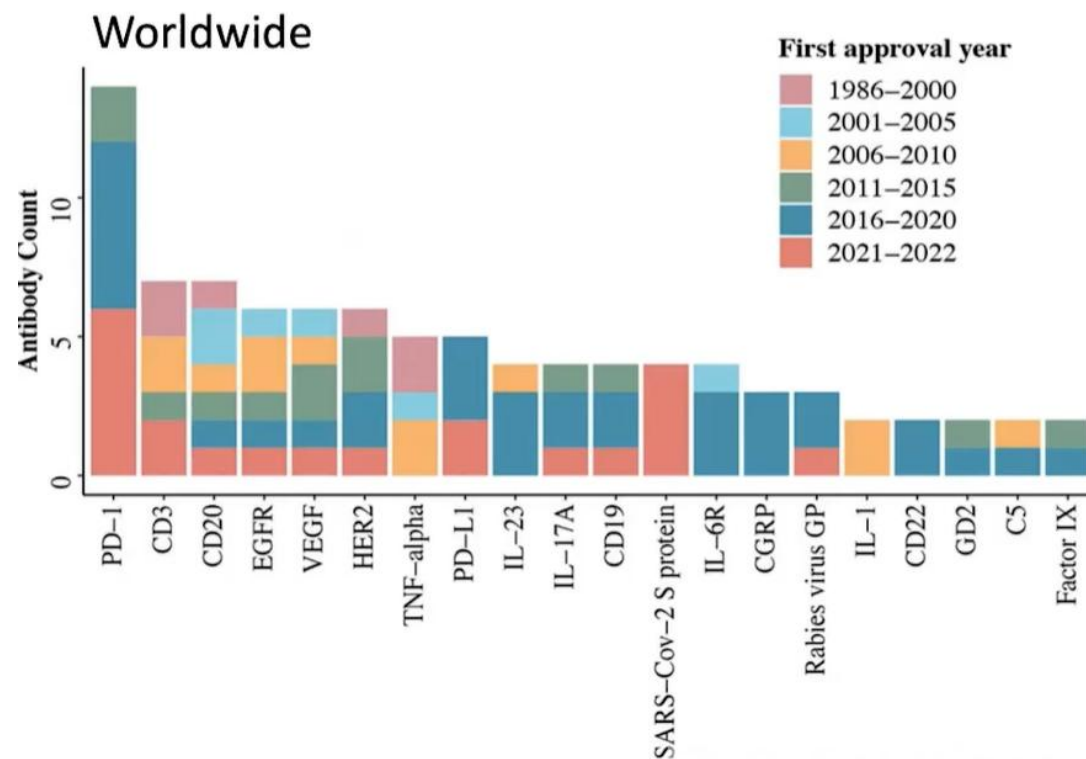
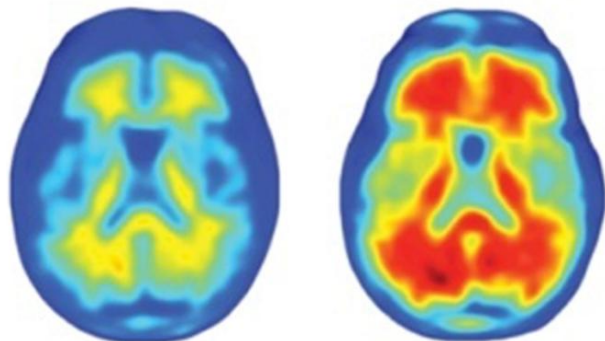


Hauser et al. NEJM. 2008



- 12/20 and 46/100 top selling drugs by revenue are antibody therapies or vaccines.
- Antibody market in 2024 is estimated to be worth \$236bn and growing to **\$660bn** by 2032 (CAGR of 11.8%).
- Vaccine market in 2024 is estimated at \$83.98bn and growing to **\$139.17bn** by 2032 (CAGR of 6.5%).

# The Problem



Filed a PCT patent application for the thermodynamic method. Dec 2021.



## ICURE Explore

A fast-paced, full-time, 12-week market exploration programme. Up to £35,000 for Entrepreneurial Lead's salary and costs.

University proceeded to Full patent filing  
July 2024 after success on ICURE.

### Find your market

ICURE gives researchers the chance to turn ground-breaking research into investment-ready spin-out companies and licence agreements. We provide funding and personalised support to test the commercial potential of an idea.

### Find your customers

ICURE has helped create hundreds of investible spin-outs and licence agreements. Key to this is the training and support that helps founders identify customers and build traction with them. ICURE-supported projects have received around £500 million of additional investment through private investors, licensing agreements, follow-on funding and research grants.

### Find yourself

ICURE helps researchers develop the skills, confidence and entrepreneurial mindset needed to transition successfully into the commercial world. Many participants go on to lead innovative UK spin-out companies, turning their research into impactful ventures.



*"It all starts with antigen, no-one has cracked that yet. B cell epitope prediction tools are still in their infancy" – Vinodh Kurella, Takeda*



*"We need someone to storm the beachhead" – Daniel Chen MD/PhD, CSO Synthetic Design Lab*



*"Everybody would agree we need new targets" – Mitchell Ho, Deputy Chief and Senior Investigator, NIH NCI*



*"Epitope discovery is the high hanging fruit" – Andrew Waight, Snr Director of ML engineering*

## Our Route to market

**Revenue stream 1:** B2B computational service  
– Selling a computational antigen design service to pharmaceutical and biotechnology companies

**Revenue stream 2:** Licensing our IP generated through our work

**Revenue stream 3:** Milestone based royalties for products developed using our method. (E.g. at the point of IND)

### High Growth Spinout Programme

Draft a business plan to negotiate a license with the University for the IP.

Two core activities with  
opportunity for expansion

Profits



Developing our own  
mAbs therapeutics



Performing Target  
Discovery  
For Customers

Investors

Johnson  
& Johnson

MERCK

sanofi

GSK

GILEAD

novo nordisk

AstraZeneca

Roche

Pfizer

# Therapeutic Portfolio

	Area	Target Optimization	Drug Discovery	Preclinical	Phase 1	Phase 2	Phase 3
SARS-CoV-2	Long COVID						
EBV	MS						
EBV	ME/CFS						
HCMV	Autoimmune Disease						



**Thank You**

**Gilbert Lab:**

**Nick Gilbert**

Charles Dixon

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Rafal Czapiewski

Olivia Fleming

**Immunology**

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**Kim Lee**

David Kavanagh

Graeme Cowan

**Marsh Lab:**

Joe Marsh

Mihaly Badonyi

Lukas Gerasimavicius

**Rowling Clinic**

Siddharthan Chandran

David Hunt

Niall MacDougall

Dawn Lyle

**Waldman Lab (Neuroimaging)**

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Daisy Mollison

Rozanna Meijboom

Beth York

**UCSF**

Sergio Baranzini

Yihui Sun

**McGill University**

Adil Harroud

**Scottish National Blood  
Transfusion Service**

Rachel Cooper

Mark Turner

Stuart Imlach

**FutureMS Participants**