Bringing new biologicals to patients: the mission of the research-based pharmaceutical company

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I3H Inaugural Conference
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OVERVIEW

- **Impact of biologicals on patient care**
  - Have transformed the market
  - Target a wide variety of diseases
- **Monoclonal antibodies are currently front and center in the development of new biologics**
  - EU played a key role in this process and is still a technology leader in this field
  - Our technology allows us to test science based hypotheses
- **Finding new targets: technological advances**
  - Technological advances in genetics present new opportunities to identify new targets
  - Pharma industry picking up this new trends
  - Informatics: uncovering signals in data to bring value to patients
- **Future of Pharma and Biologicals**
  - Large needs
  - Technology
  - Pharma

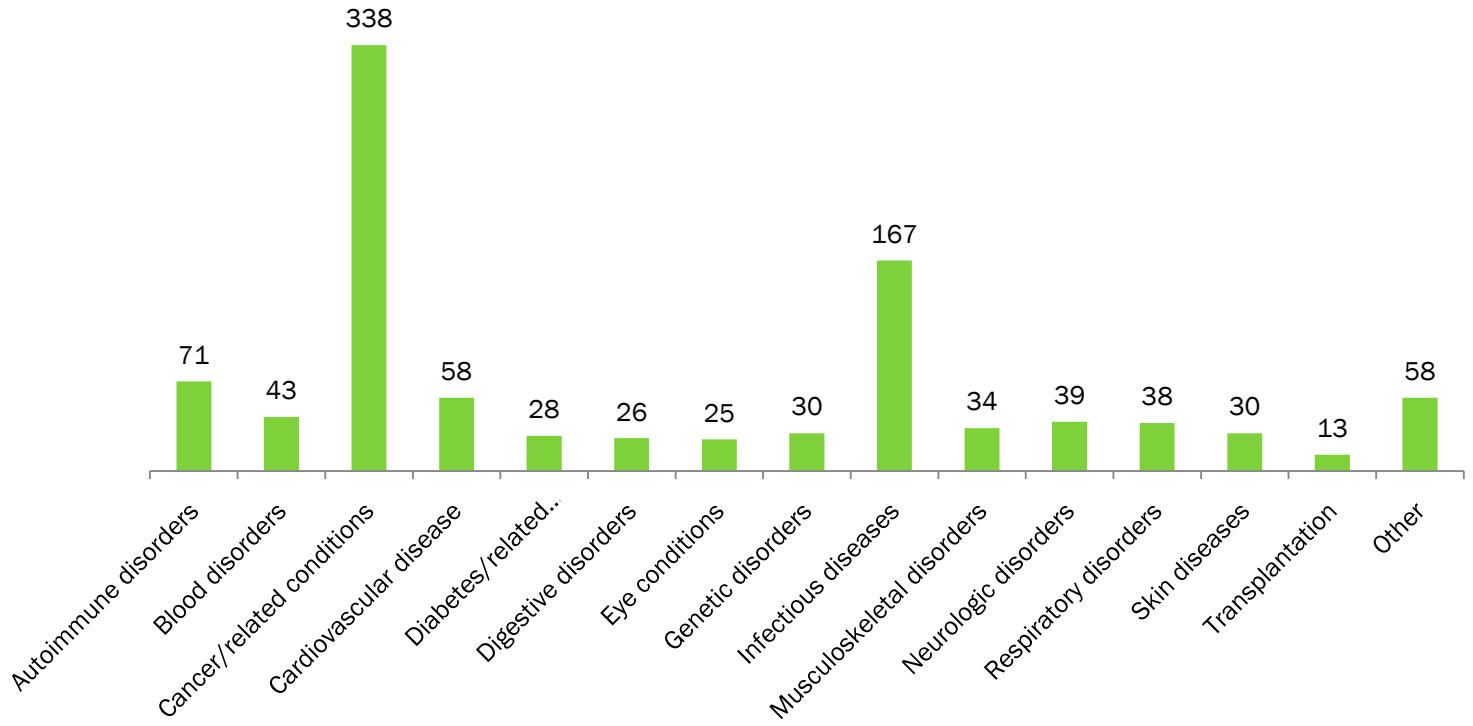
BIOLOGICALS HAVE TRANSFORMED PATIENT CARE

- Biological Medicine sales have been increasing significantly more than stagnant pharma markets
- In 2013, 6 of the top 10 best selling human drugs were biologics (5 mAbs and 1 fusion protein), which collectively amounted to a worldwide sales of $49.1 billion.
- By 2020, biological products are projected to account for more than 50 percent of sales within the top 100 prescription products
- Currently, most of the sales derived from biologicals is made in developed economies as their price and cold chain remains an issue in the developing world

BIOLOGICS ARE TARGETING A WIDE VARIETY OF DISEASES

Biologic Medicines in development – by therapeutic category

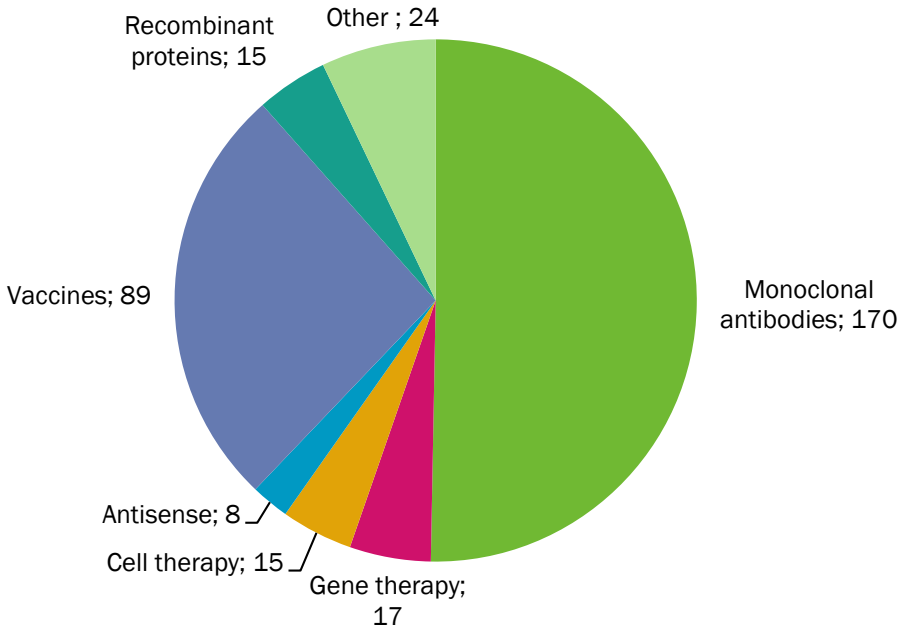
Some medicines are listed in more than one category



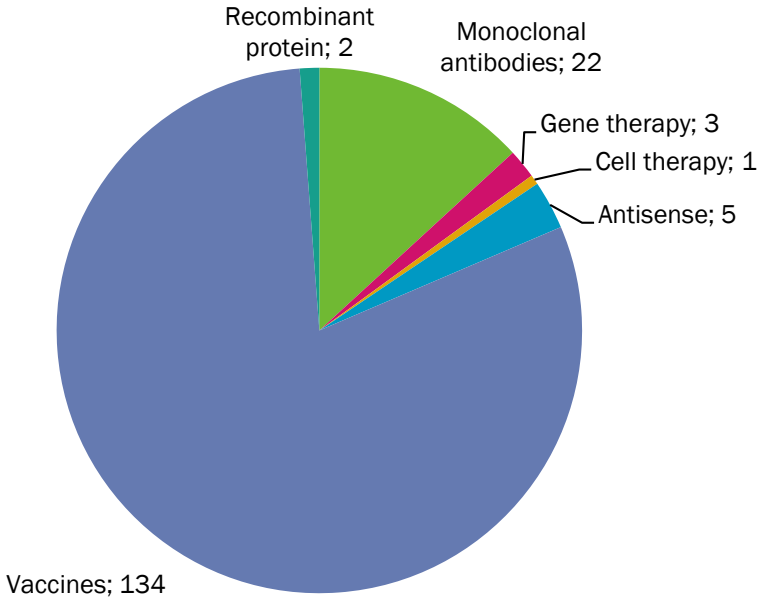
BIOLOGICS ARE USING SEVERAL TECHNIQUES AND TECHNOLOGIES TO TREAT AND PREVENT DISEASE

Biologic Medicines in development – by technique and technology

Cancer/related disorders

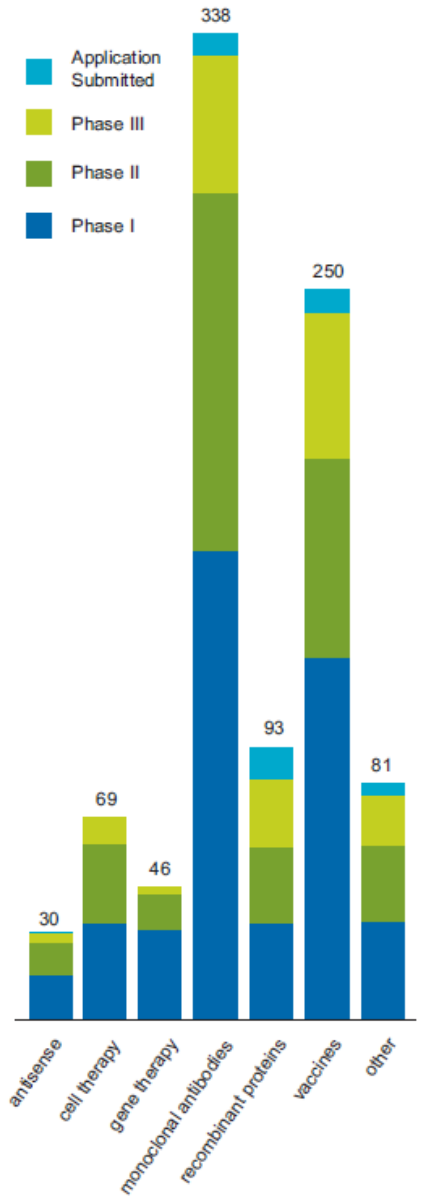


Infectious diseases



MONOCLONAL ANTIBODIES ARE CURRENTLY THE MAIN FOCUS OF BIOLOGICALS DEVELOPMENT

- In 2013, US pharmaceutical companies accounted for 80% of the world's R&D in health care biotechnology
- Together these companies are developing 907 medicines and vaccines using biological processes
- 65% of these products are either monoclonal antibodies (37%) or vaccines (28%).



EUROPE AT THE FOREFRONT OF THE DEVELOPMENT OF MABS AS A NEW TREATMENT

- In 1975, Köhler and Milstein (Cambridge university, UK) developed the hybridoma technique for the production of monoclonal antibodies. In 1984 they received the Nobel Prize for Physiology and Medicine

- After this discovery two additional steps were needed before mAbs could be used as a treatment:

  1. Make them look more human: Humanization of Abs was first made possible in the 1986 by CDR grafting, developed by Greg Winter at the Cambridge University, UK.

  2. Make enough of them: Several recombinant techniques have been developed in the 1990's to achieve this. Celltech, now UCB, described the first recombinant antibody expression.

UCB CELLTECH LEADING IN BOTH HUMANIZATION OF ABS …

0022-1767/92/1489-2756$02.00/0
THE JOURNAL OF IMMUNOLOGY

Vol. 148, 2756–2763, No. 9, May 1, 1992
Printed in U.S.A.

HUMANIZED OKT3 ANTIBODIES: SUCCESSFUL TRANSFER OF IMMUNE MODULATING PROPERTIES AND IDIOTYPE EXPRESSION

E. STEVE WOODLE,[1]* J. RICHARD THISTLETHWAITE,* LINDA K. JOLLIFFE,† ROBERT A. ZIVIN,† ALEXANDER COLLINS,† JOHN R. ADAIR,† MARK BODMER,† DILJEET ATHWAL,† MARIA-LUISA ALEGRE,§ AND JEFFREY A. BLUESTONE[2]*

*From the *Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, IL 60637; the †R. W. Johnson Pharmaceutical Research Institute, Ortho Pharmaceutical Corporation, Raritan, NJ; ‡Celltech Limited, Celltech Research Division, Slough, Berkshire, UK; and the §Ben May Institute, Committee on Immunology, University of Chicago, Chicago, IL 60637*

Antibodies that possess the Ag-binding regions of OKT3 within the context of a human framework (Hu-OKT3 Ab) offer distinct advantages for optimizing anti-CD3 mAb therapy. First, manipulation of Ab genes to produce humanized Ab that retain Ag-binding activity may circumvent antigenicity problems. Second, Ab gene engineering provides a means

OKT3. In conclusion, these studies indicate that gOKT3–5 and cOKT3 Ab possess immune modulating properties similar to murine OKT3 and thus offer attractive alternatives to murine OKT3 for in vivo therapy.

Development of the hybridoma technique of Kohler and

Woodle ES et al (1992), J. Immunol, 148, 2759-2763

… AND HIGH LEVEL EXPRESSION OF ABS

HIGH-LEVEL EXPRESSION OF A RECOMBINANT ANTIBODY FROM MYELOMA CELLS USING A GLUTAMINE SYNTHETASE GENE AS AN AMPLIFIABLE SELECTABLE MARKER

C.R. Bebbington, G. Renner, S. Thomson, D. King, D. Abrams and G.T. Yarranton
Celltech Ltd., 216, Bath Road, Slough Sl1 4EN, U.K.

We report a method for introducing a glutamine synthetase (GS) selectable marker into myeloma cells in which transfectants are selected by growth in a glutamine-free medium. Vector amplification can subsequently be selected using the specific inhibitor of GS, methionine sulphoximine (MSX). Using this system, DNA sequences encoding a chimeric B72.3 IgG4 antibody were expressed from hCMV-MIE promoters in NSO myeloma cells. A cell line was isolated after a single round of selection for

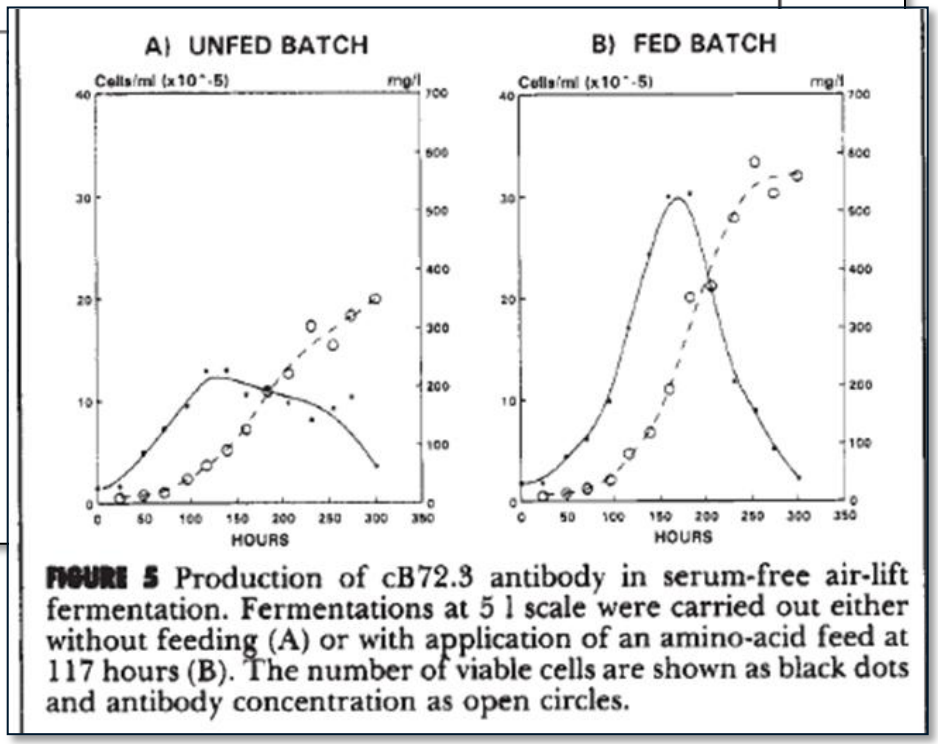
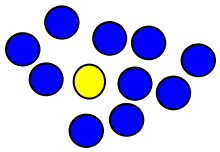


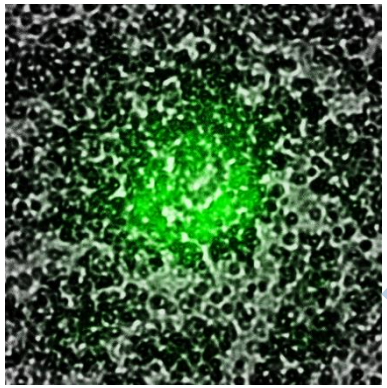
FIGURE 5 Production of cB72.3 antibody in serum-free air-lift fermentation. Fermentations at 5 l scale were carried out either without feeding (A) or with application of an amino-acid feed at 117 hours (B). The number of viable cells are shown as black dots and antibody concentration as open circles.

Bebbington, CR et al (1992), Nature Biotechnology, 10, 169-175

UCB IS A TECHNOLOGY LEADER FOR AB SCREENING AND DESIGN …

3,000,000,000 Immune B Cells → **Very High Quality Antibodies**



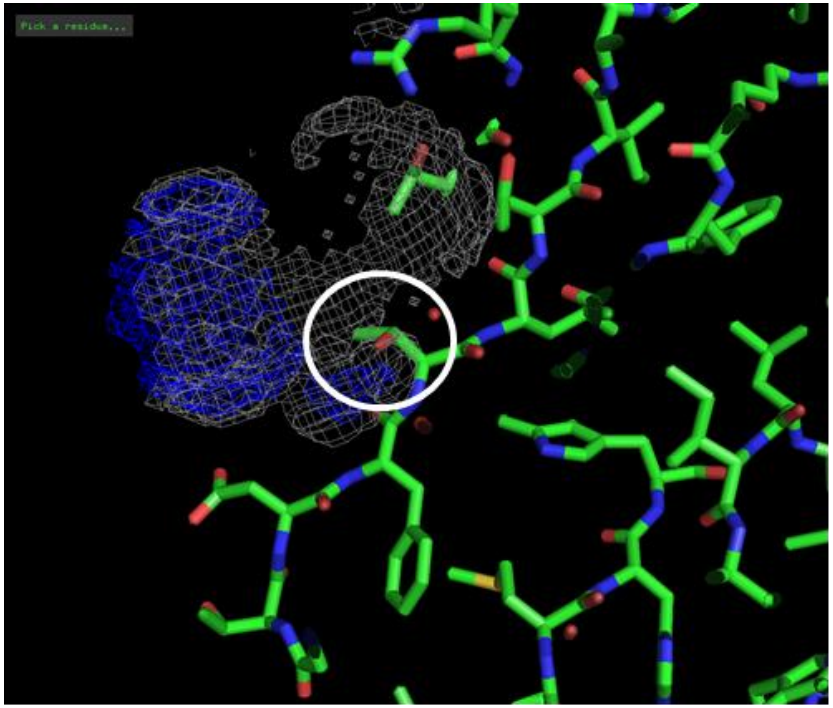


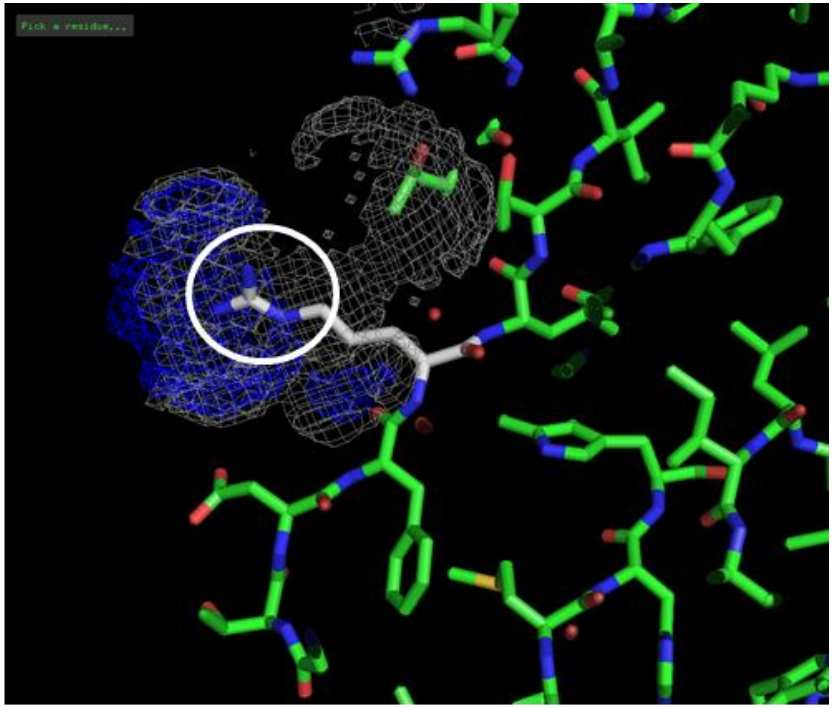
Identification and isolation of single, specific B Cells

US7993864
EP1570267B1

… AND ATOMIC INSIGHT

IOTA – A Proprietary UCB Tool for Rational, Structure-based Antibody Design





Threonine → Arginine

Terry Baker and Jiye Shi

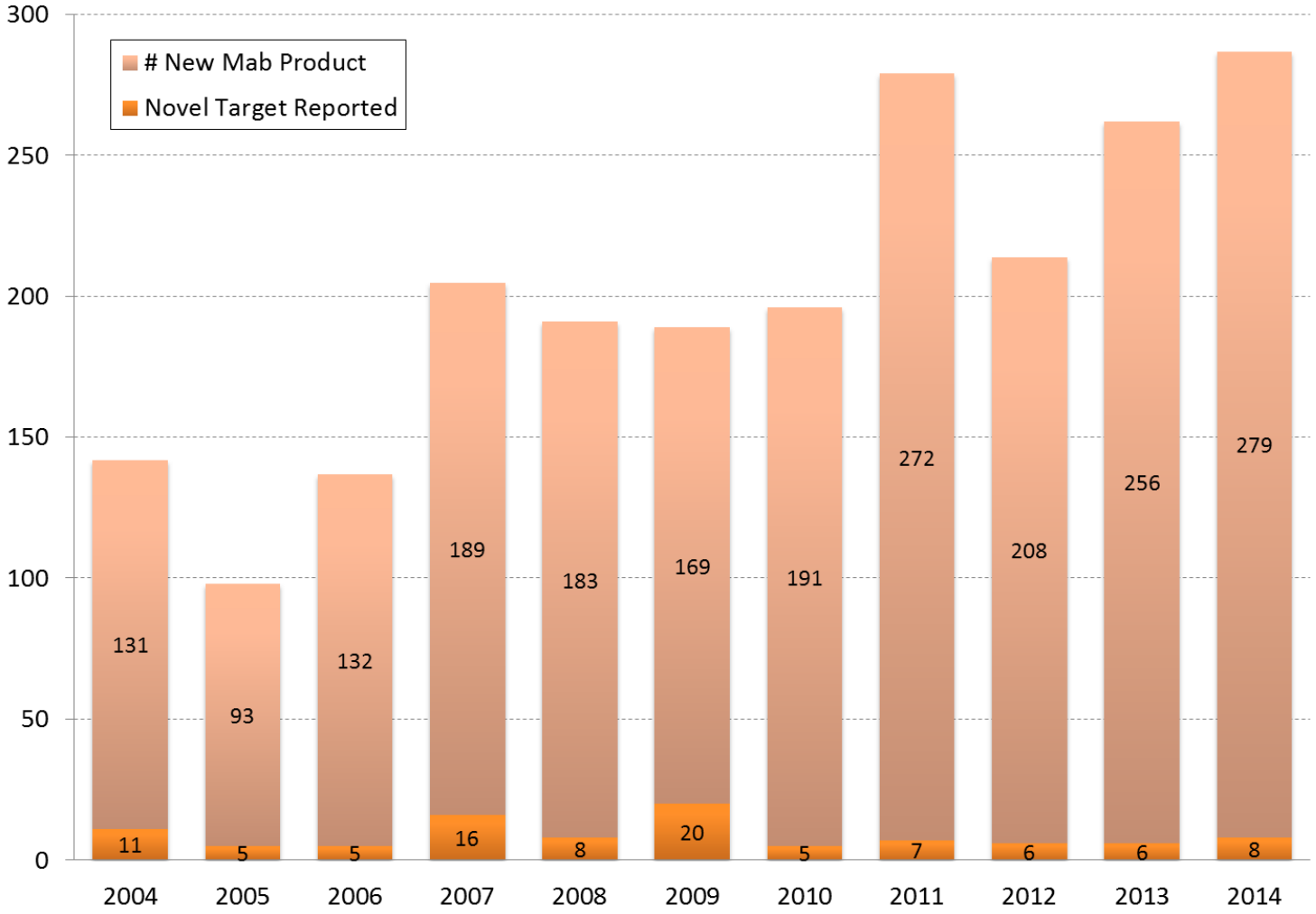
UCB TECHNOLOGY OPEN TO ACADEMIC AND BIOTEC PARTNERS

Screening billions of B cells increases the probability of finding:

- very rare, function-modifying antibodies binding at specific epitopes
- variable region sequences readily amenable to humanisation and engineering
- variable region sequences with appropriate biophysical characteristics simplifying downstream processing

UCB's new state of the art antibody discovery facility

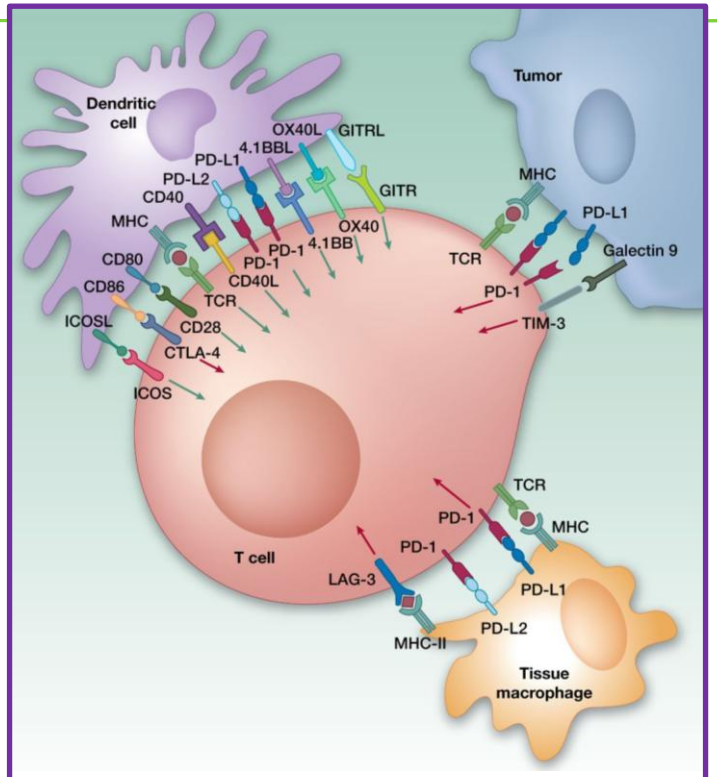
THE TECHNOLOGY TO DEVELOP NEW MABS IS IN PLACE, WHAT ABOUT FINDING NEW TARGETS?



Source: Pharmaprojects, Novel Targets by year, New Products by year, therapeutic class: antibodies

Cancer Immunotherapy: Starting to make a Real Impact

- Immune 'check point' inhibitors have demonstrated dramatic effects on survival in some difficult to treat cancers
  - Number of checkpoint inhibitors will expand to treat a broader range of patients
- In the future, alternate ways activate tumor directed T-cells will complement checkpoint inhibitors and further increase patient responses
  - Tumor associated macrophage immune activation
  - Enhance dendritic cell presentation of tumor antigen
- Stromal cells also regulate the immune status within the tumor microenvironment. It is highly likely that inhibitors of these cells will lead to breakthroughs in some patients
- Recent successful examples of this new generation of drugs are Keytruda (PD-L1, Merck) and Yervoy (CTLA-4, BMS)



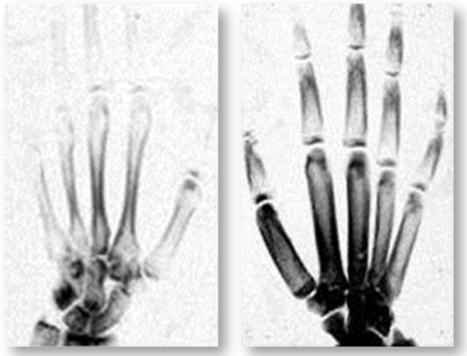
The ability of T-cells to kill tumor cells can be turned on and off. They are regulated by signals coming from other immune cells and even the tumor itself. If a T-cell has been turned off, it may be switched back on by a checkpoint inhibitor or activator.

TECHNOLOGICAL ADVANCES IN GENETICS PRESENT NEW OPPORTUNITIES TO IDENTIFY NOVEL TARGETS MORE EFFICIENTLY THAN EVER

THEN – 1990s

What is the genetic basis

of Sclerosteosis?



Human high bone mass disorder allowed identification of gene that regulates bone formation (Brunkow et al Am J Hum Genetics 2001)

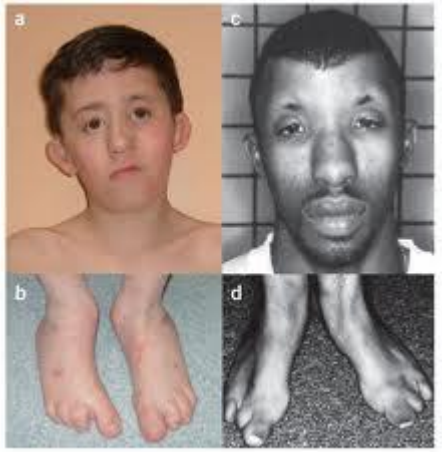
How was the gene identified?

Work on characterising sclerostin pedigree began in 1975 (Baton)

A team of Celltech scientists worked for 2 years to identify the mutation before publishing in 2001

NOW

Discovery of the causative mutation in Millar syndrome Ng et al (Nature Genetics 2009).



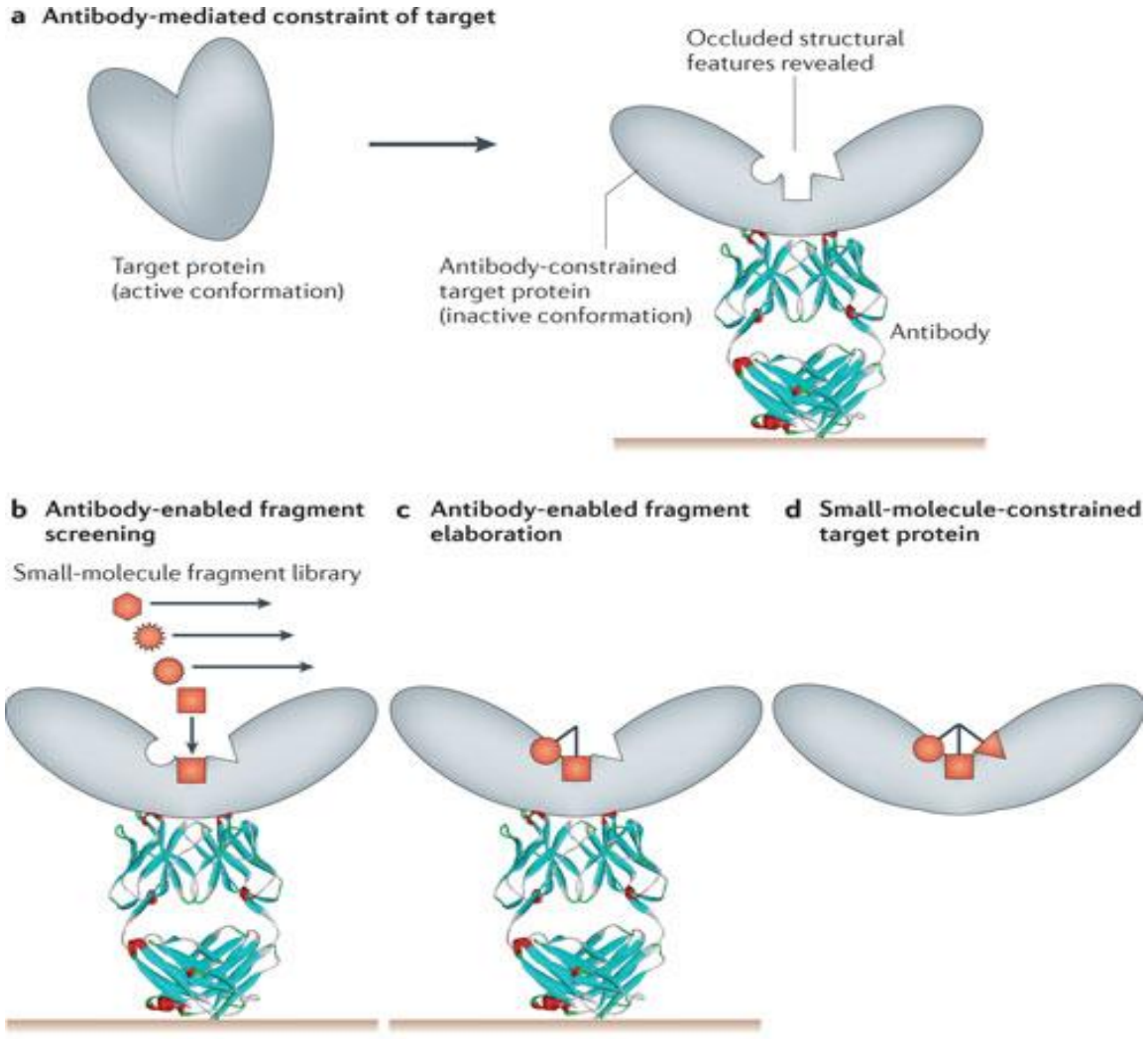
How was the gene identified?

Exome sequencing of 4 Millar Syndrome patients

Exome sequencing can now be completed in around one week, at a cost of ~ $1500

Small Molecule Fragment Screening against an Antibody-Stabilised Target Conformation

July 2012



Lawson, A.D.G. 2012 Nature Reviews Drug Discovery 11: 519-525

PHARMA INDUSTRY PICKING UP NEW OPPORTUNITIES?

- **Greater availability of human genetic information …**
  - Cost of sequencing has decreased by 4,000 fold[1] in 10 years
- **… Opens the door to a new paradigm of drug discovery …**
  - Unprecedented availability of genetic data: new drug discoveries (gene proteins, RNA)
  - Big data: uncovering signals
  - Academia and Pharma discovering together
- **… US and EU are ahead of the curve, but needs to continue differentiating itself**
  - Personalizing treatments: stratification, companion diagnostics
  - Rebound in R&D productivity

[1] Based on cost of sequencing 1 genome, 2 As of 2014

Source: National Human Genome Research Institute, http://www.genome.gov/sequencingcosts/; MIT Technology Review

FDA Approved Antibody Therapeutics in 2014

Murine monoclonal antibodies			
OKT3	CD3	transplant rejection	Ortho
Bexxar	CD20	non-Hodgkin's lymphoma	Corixa GSK
Zevalin	CD20	NHL	Biogen IDEC
Chimeric antibodies			
ReoPro	gpIIb/IIIa	percutaneous coronary intervention	Centocor J&J
Rituxan	CD20	NHL, RA	Biogen IDEC
Remicade	TNFα	Crohn's, RA, PsA, AS	Centocor J&J
Simulect	CD25	transplant rejection, UC	Novartis
Erbitux	EGFR	colorectal cancer	Imclone BMS
Humanised / human antibodies			
Zenapax	CD25	transplant rejection	PDL
Synagis	RSV	paediatric infection	MedImmune
Herceptin	HER2	breast cancer	Genentech
Mylotarg	CD33	AML (calicheamicin conjugate)	UCB Wyeth
Campath	CD52	CLL	Ilex Millennium
Xolair	IgE	asthma	Genentech
Raptiva	CD11a	psoriasis	Genentech
Avastin	VEGF	colorectal, lung cancer	Genentech
Tysabri	α4β1	MS	Biogen IDEC
Soliris	C5	haemolytic anaemia	Alexion
Lucentis	VEGF	AMD	Genentech
Humira	TNFα	RA, Crohn's, PsA, AS	Abbott
Vectibix	EGFR	colorectal cancer	Amgen
Cimzia	TNFα	Crohn's, RA, PsA, AS	UCB
Simponi	TNFα	RA, PsA, AS	Centocor J&J
Ilaris	IL-1β	CAPS	Novartis
Arzerra	CD20	CLL	GSK/Genmab
Stelara	IL-12/23	Psoriais	J&J
Actemra	IL-6R	RA	Roche/Chugai
Prolia/Xgeva	RANKL	Osteoporosis/Bone metastases	Amgen
Benlysta	BLyS	Lupus	HGS GSK
Yervoy	CTLA-4	Metastatic melanoma	BMS
Adcetris	CD30	Hodgkin lymphoma	Seattle Genetics
Perjeta	HER2	breast cancer	Genentech/Roche
ABThrax	Bacillus	anthrax	HGS
Kadcyla	HER2	metastatic breast cancer (emtansine conjugate)	Genentech/Roche
Gazyva	CD20	chronic lymphocytic leukemia	Genentech/Roche

FDA Approved Antibody Therapeutics 1985

Future: Pharma and Biologicals

- **Large needs**
  - Ageing of population
  - Epidemic risk
  - Patient empowerment/social media
  - Payor and population request value

- **Technology**
  - Convergence biology, physics, big data, digital
  - Patient insights: genetics, stem cells, antigen specifics

- **Pharma**
  - Accountable to find new solutions
  - Measurable value to patients