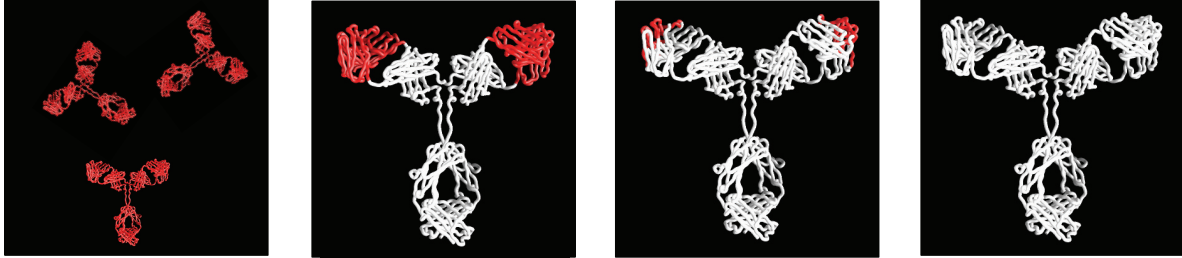


The antibody revolution: turning inventions into medicines and companies



Foundation Lecture, Royal Society
7 March 2011

Therapeutic antibodies today

Used for treatment of:

Cancer. Breast, bowel, head and neck cancer, bone, leukaemias (NHL, AML, CLL).

Immune disorders. Paroxysmal nocturnal haemoglobinuria (PNH), transplantation rejection, rheumatoid arthritis, osteoporosis, Crohn's disease, psoriasis, ankylosing spondylitis, asthma, multiple sclerosis.

Others. Acute macular degeneration

Infections. Respiratory syncytial virus.

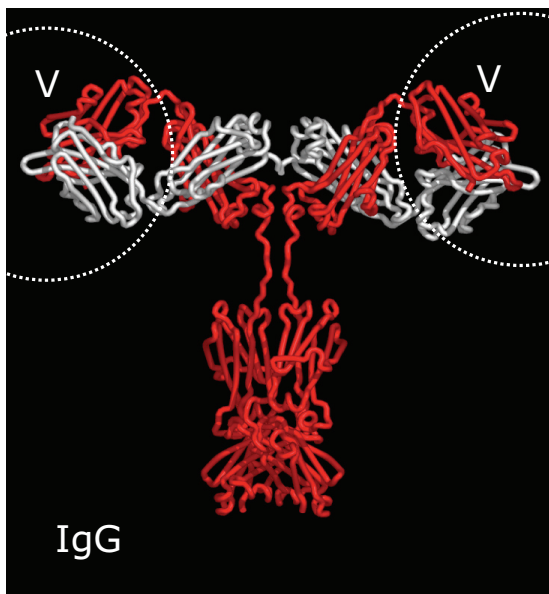
Pharmaceuticals 2010

<u>Brand name</u>	<u>Systematic name</u>	² <u>Sales (USD\$)</u>
Lipitor	atorvastatin	10.7
(Lantus, Humulin)	insulins	9.7
Advair	fluticasone/salmeterol	7.9
¹ Enbrel	etanercept	6.8
¹ Humira	adalimumab	6.5
Avastin	bevacizumab	6.2
Rituxan	rituximab	6.1
¹ Remicade	infliximab	5.8
Crestor	rosuvastatin	5.7
Herceptin	trastuzumab	5.2

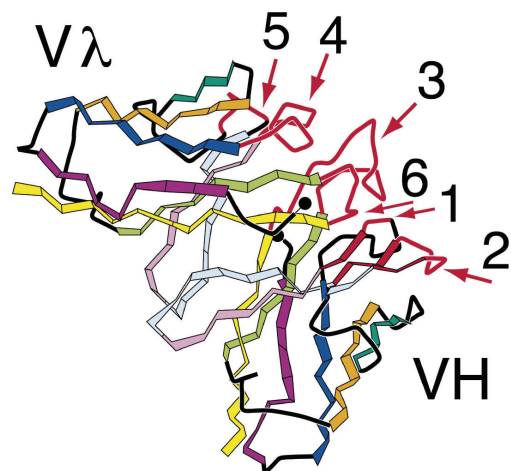
¹anti-TNF mAbs. ²mAbs were \$41 bn market, CAGR 11%, 6 mAbs in top 10, each >\$USD 5 bn pa.

Cancer. Breast, bowel, head, neck and bone cancer, leukaemias (NHL, AML, CLL). **Immune disorders.** PNH, transplantation rejection, rheumatoid arthritis, Crohn's disease, psoriasis, ankylosing spondylitis, asthma, multiple sclerosis. **Others.** Acute macular degeneration, osteoporosis. **Viral infections.** Respiratory syncytial virus.

Structure of antibodies

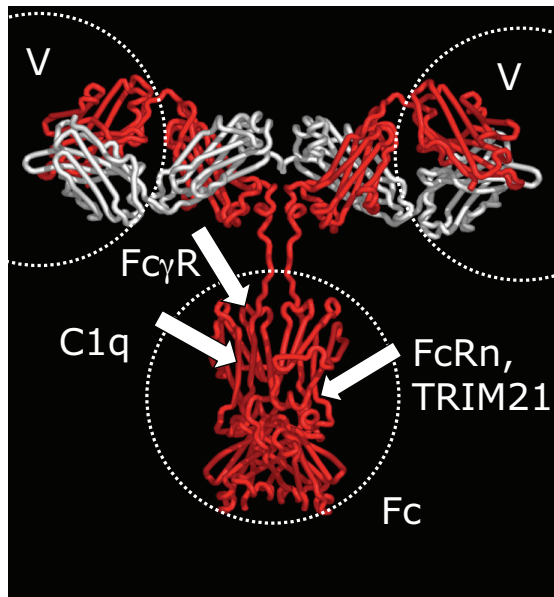


Four chains, two heavy and two light; domain structure, variable and constant domains



Variable domains provide scaffold with Ag-binding loops

Mode of action of antibodies

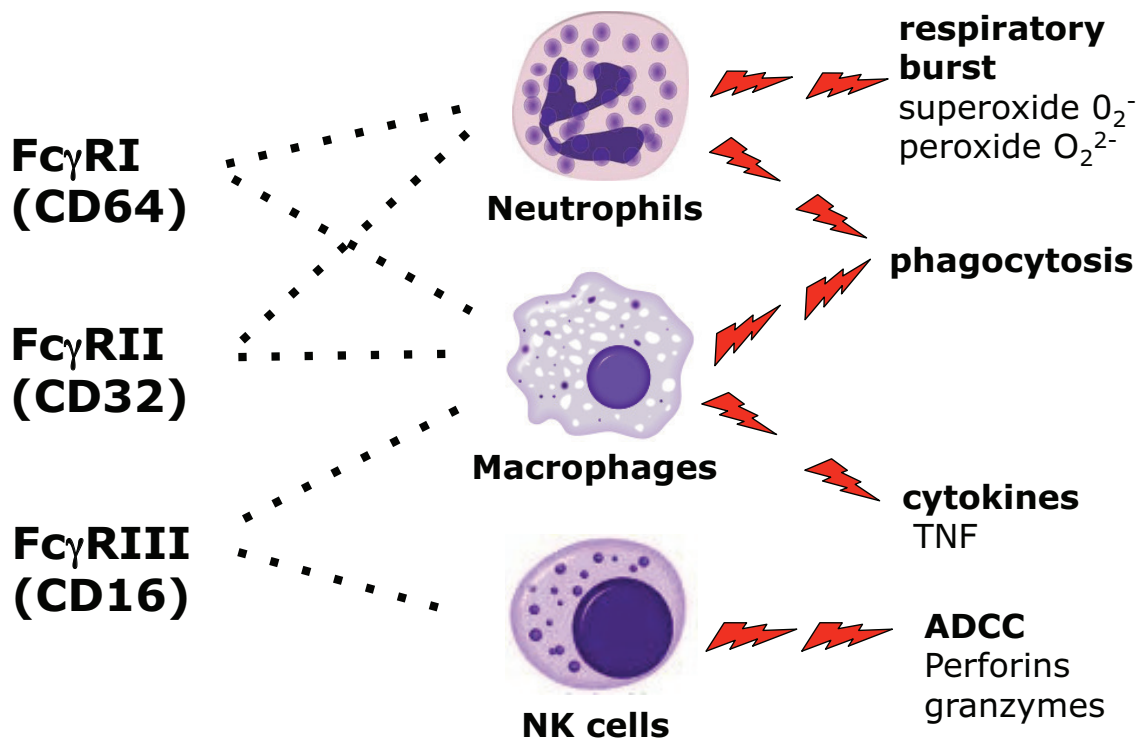


Binds antigen. Variable domains bind antigen, blocking its action; may also lead to apoptosis of cells.

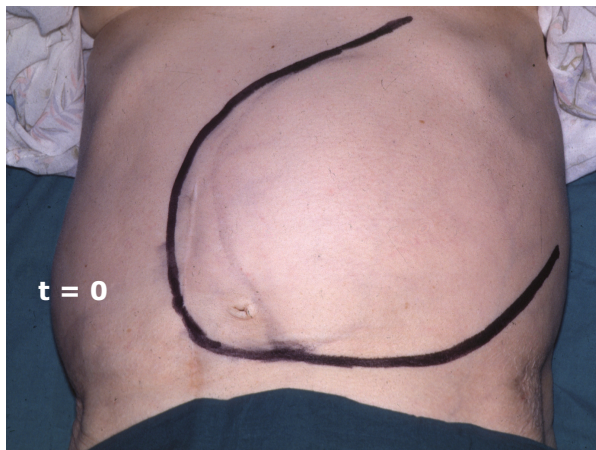
Long serum half-life (PK), Ab escapes filtration (150 kD) and pinocytosis (recycling FcRn).

Killing. The other end (Fc) acts as flag to the immune system leading to killing (Fc receptors on neutrophils, macrophages & NK cells; serum C1q; TRIM21).

Fc γ R effector mechanisms

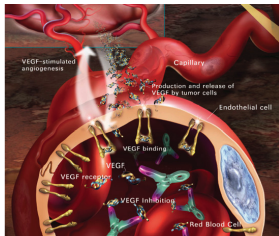


Campath-1H on non-Hodgkin lymphoma



Hale G., Dyer M.J., Clark M.R., Phillips J.M., Marcus R., Riechmann L., Winter G. & Waldmann H. (1988). Remission induction in non-Hodgkin lymphoma with reshaped human monoclonal antibody CAMPATH-1H. *Lancet* 2, (8625) 1394-1399.

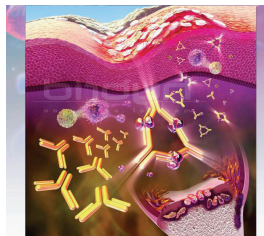
Mode of action of therapeutic mAbs



Bevacizumab
(Avastin -Genentech/
Roche)

IgG1
Target: VEGF.
Treat: colorectal
cancer

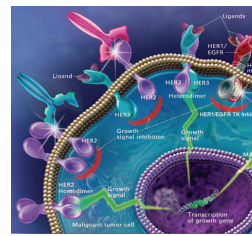
Blocking



Adalimumab
(Humira-Abbott)

IgG1
Target: TNF
Treat: rheumatoid
arthritis

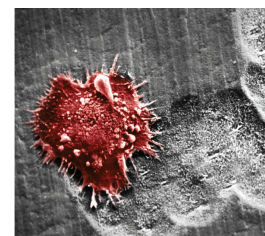
Blocking>>killing



Trastuzumab
(Herceptin-Genentech/
Roche)

IgG1
Target: HER2
Treat: HER2+
breast cancer

Killing>> blocking



Denosumab
(Prolia-Amgen/GSK)

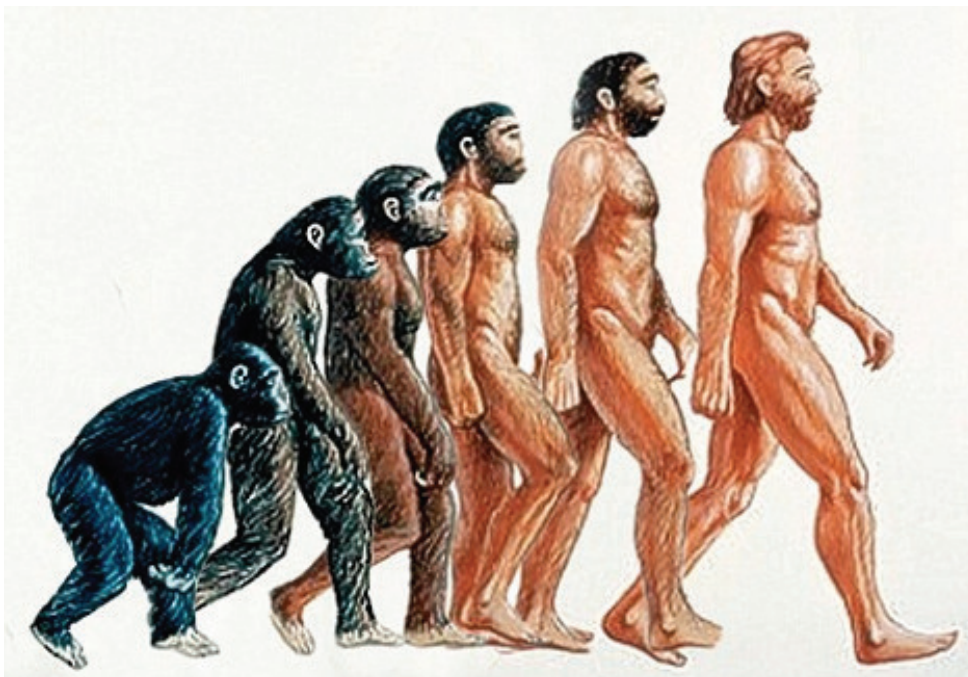
IgG2
Target: RankL
Treat: Osteoporosis

Blocking

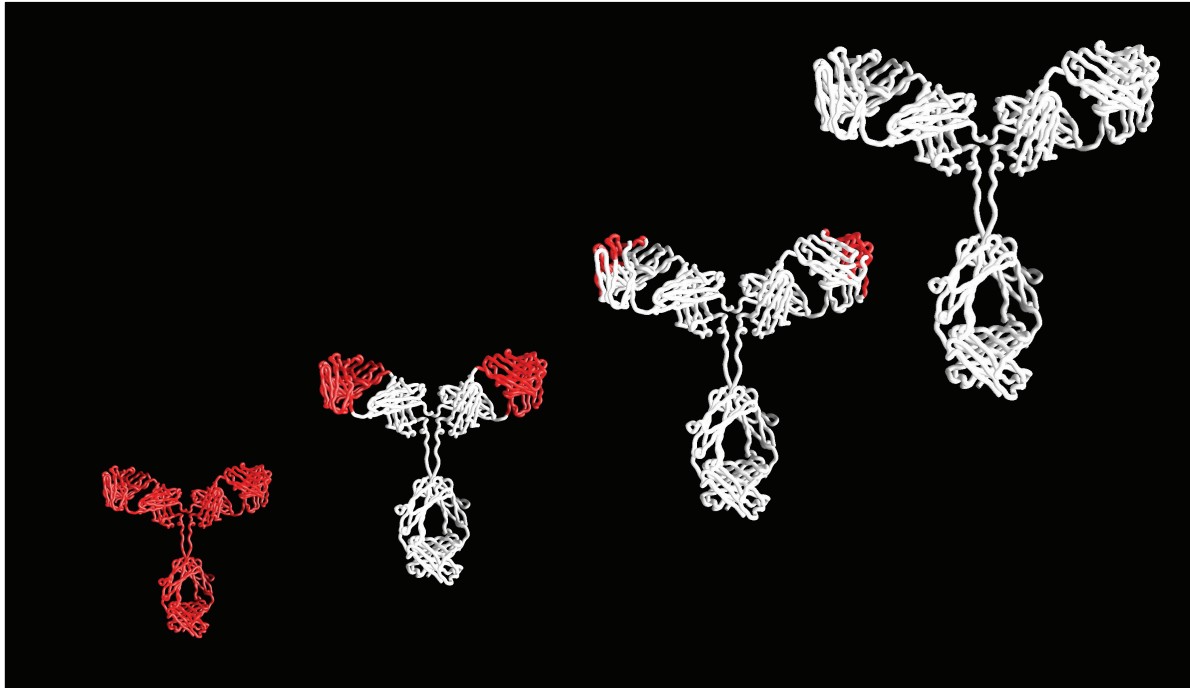
Pharmaceutical drug classes

	Antibodies	Chemicals
High target affinity	Green	High target affinity (Red)
High target specificity	Green	High target specificity (Red)
Low off-target toxicity	Green	Low toxicity (Red)
Blocks protein-protein	Green	Blocks protein-protein (Red)
Long serum half-life	Green	Long serum half-life (Red)
Killing mechanisms	Green	Effector mechanisms (Red)
Access to small sites	Access to small sites (Red)	Green
Extravascular targets	Extravascular targets (Red)	Green
Intracellular targets	Intracellular targets (Red)	Green
Oral route	Oral route (Red)	Green
Immunogenicity	Immunogenic (Red)	Green

The ascent of Man



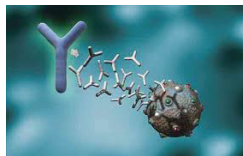
The ascent of the human therapeutic antibody



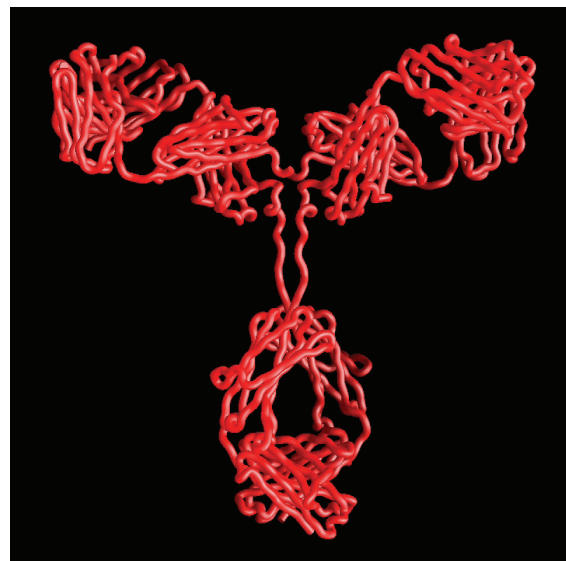
Rodent monoclonal antibodies

1975. Milstein and Kohler (MRC)

Immunize mice with antigen (Ag), fuse antibody-producing cells from spleen (mortal) with myeloma cell line (immortal) to give a cell line hybridomas (immortal and produces a monoclonal antibody (mAb)).



PLUS. Magic bullets: immunize mice with human tumours, find mAbs that kill Tu but not normal cells.
MINUS. Poor killing activities in humans
MINUS. Immunogenic, blocking of therapy / anaphylaxis with prolonged treatment.

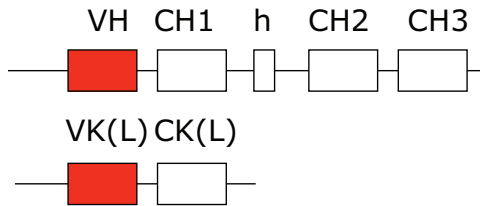


Mouse-human chimaeric antibodies

1983. Cabilly

1984. Morrison and Oi.

Protein engineering; join mouse variable region genes (will bind Ag) to human constant region genes (will trigger human effector functions)

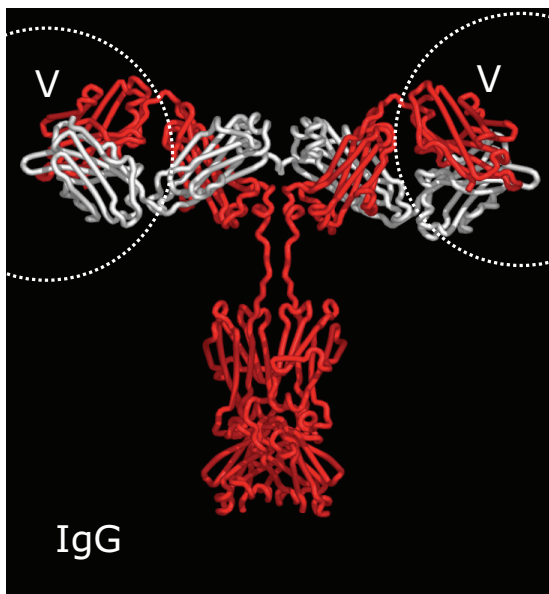


PLUS. 2/3 human and less immunogenic than rodent mAbs

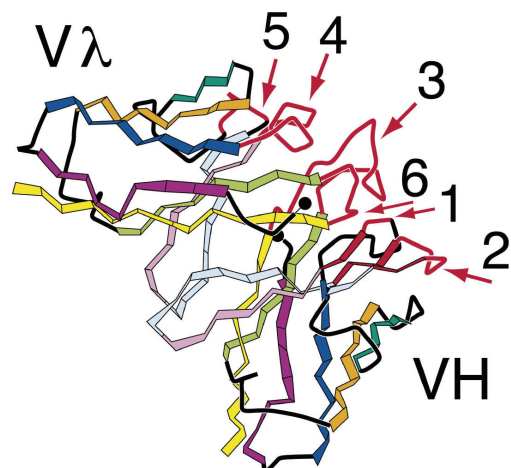
PLUS. powerful human effector functions



Structure of antibodies



Four chains, two heavy and two light; domain structure, variable and constant domains

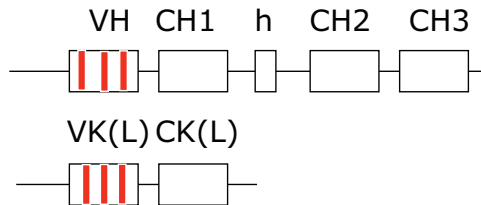


Variable domains provide scaffold with Ag-binding loops

Humanized antibodies

1986. Winter (MRC).

Protein engineering; transfer only the Ag-binding loops into human antibody



PLUS. Humanized mAbs 95% human and less immunogenic than rodent mAbs

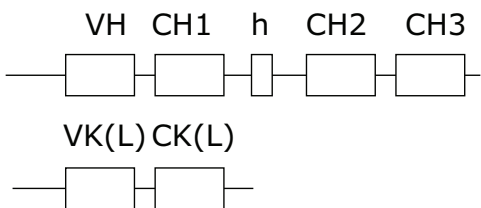
PLUS. Powerful human effector functions and killing.



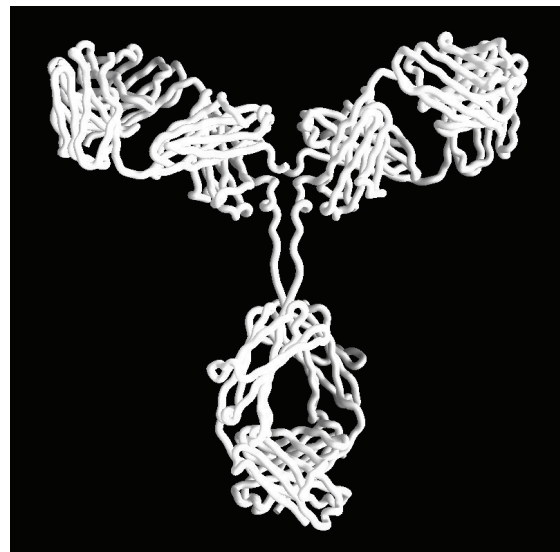
Human antibodies – from repertoires

1989. Winter (MRC)/Lerner (Scripps).

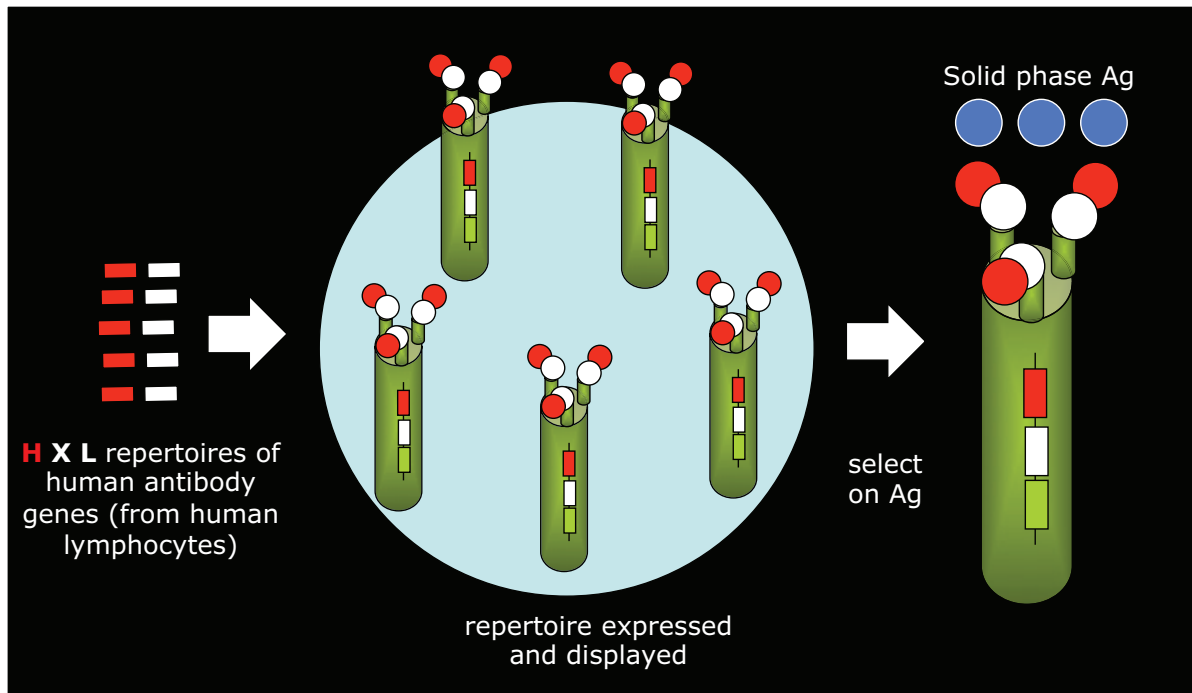
Protein engineering; repertoires of human antibody genes/phage display to build human antibodies directly.



PLUS. Fully human antibodies



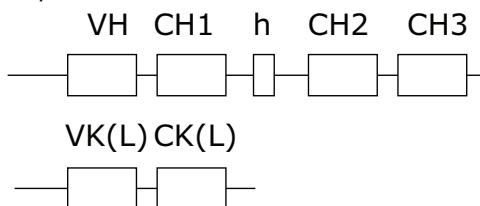
Human antibodies – reduction to practice



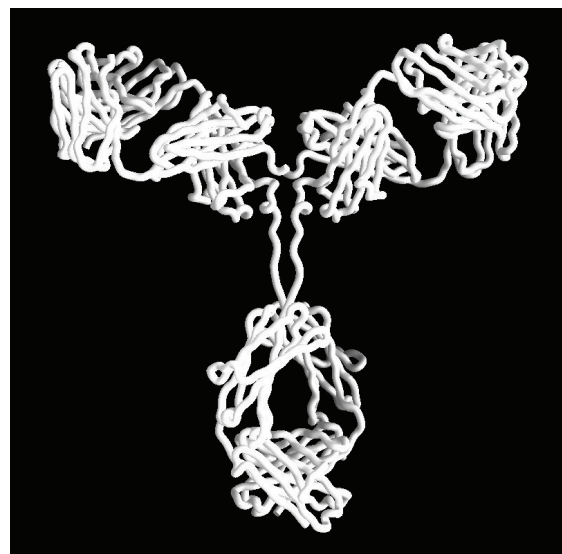
Human antibodies – from mice

1989. Neuberger/Bruggemann (MRC/AFRC).

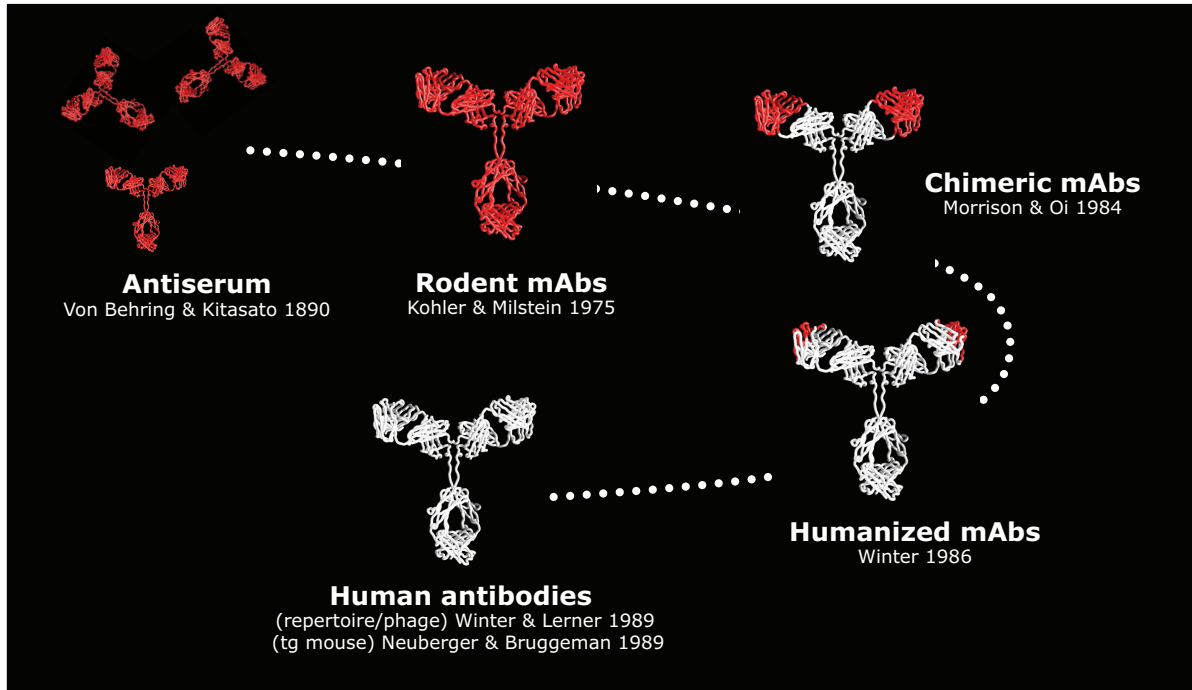
Mouse engineering, transgenic mice with human antibody genes, then immunize and make hybridomas.



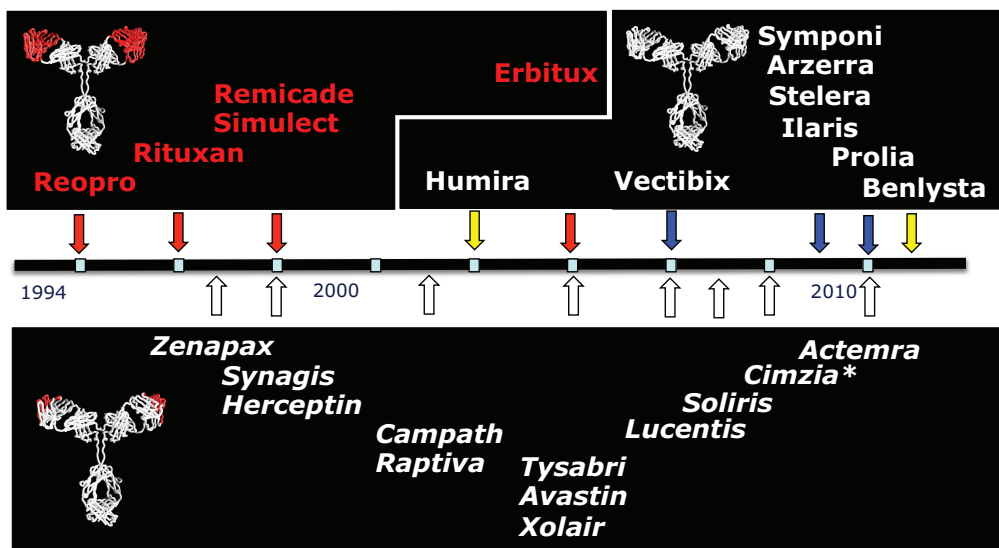
PLUS. Fully human antibodies



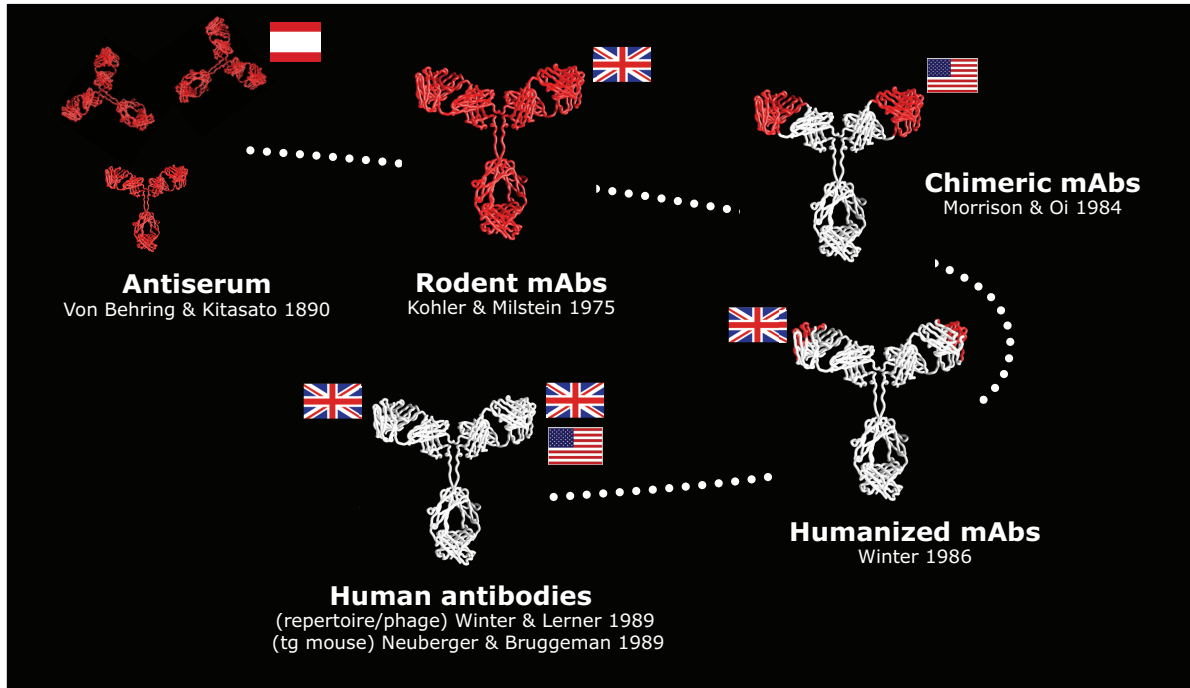
Antibody technology



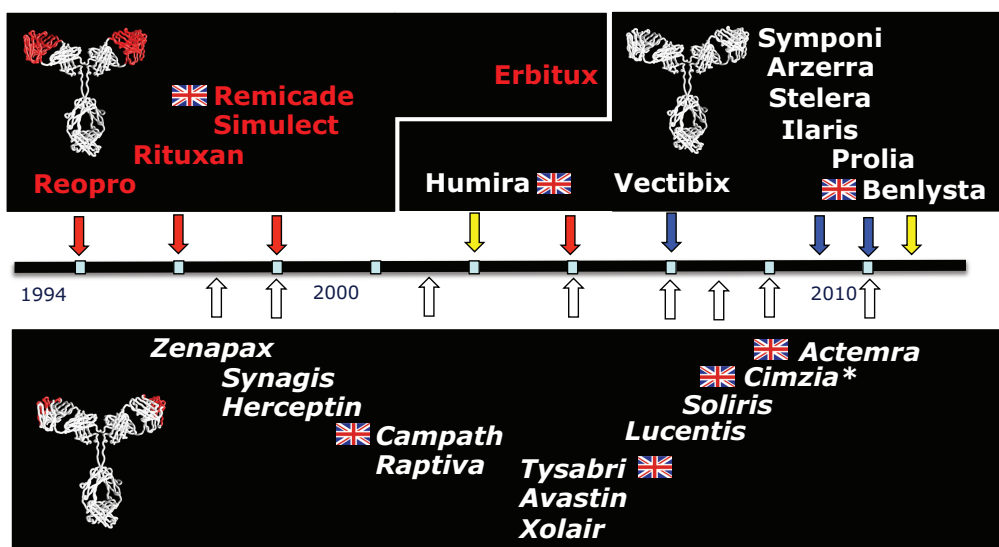
Antibody products



Antibody technology – UK role



Antibody products – UK role



- ***Remicade**; Kennedy Institute of Rheumatology > Centocor/J&J
- ***Campath**: Cambridge University/MRC-LMB > Wellcome Biotech > LeukoSite > Millenium > Genzyme > Sanofi
- Tysabri**: MRCT > Biogen/IDEC
- Cimzia**: Celltech > UCB-Celltech
- Actemra**: MRCT > Chugai
- Humira**: CAT > Abbott
- Benlysta**: CAT > HGS [GSK]

Translation process

Patents

None

Single

Multiple

Improvements

Licensing strategy

Exclusive

Non-exclusive

Co-licensing

Rights to future IP

Commercial exploitation

Research collaboration

Development

Start-up

Biotech

Pharma

Outcomes

Research impact

Clinical impact

UK impact (companies/jobs)

Royalties

Sales

Translation process (MRC) - mouse mAbs

Patents

None

X

NRDC

Single

Multiple

Improvements

X

Rat hybridomas/BTG

Licensing strategy

Exclusive

Non-exclusive

Co-licensing

Rights to future IP

X

MRC/Celltech

Commercial exploitation

Research collaboration

Development

X

Blood group reagents

Start-up

Biotech

X

Celltech

Pharma

Outcomes

Research impact

X

research reagents

Clinical impact

X

diagnostic tests

UK impact (companies/jobs)

X

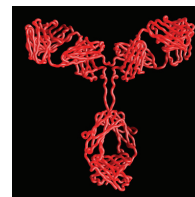
Celltech, Unipath

Royalties

Sales

X

>\$10 bn pa worldwide [2008]



Failure to patent mouse mAbs

Letter from NRDC to MRC

“It is certainly difficult for us to identify any immediate practical applications which could be pursued as a commercial venture...and it is not immediately obvious what patentable features are at present disclosed in the Nature paper”

Translation process (MRC) - mouse mAbs

Patents		
None	X	NRDC
Single		
Multiple		
Improvements	X	Rat hybridomas/NRDC
Licensing strategy		
Exclusive		
Non-exclusive		
Co-licensing		
Rights to future IP	X	Celltech
Commercial exploitation		
Research collaboration		
Development	X	Blood group reagents
Start-up		
Biotech	X	Celltech
Pharma		
Outcomes		
Research impact	X	research reagents
Clinical impact	X	diagnostic tests
UK impact (companies/jobs)	X	Celltech, Unipath
Royalties		
Sales	X	>\$10 bn pa worldwide [2008]



Translation process (MRC) - humanised mAbs

Patents

None

Single

X

Multiple

Improvements

X

Licensing strategy

Exclusive

X

Non-exclusive

X

Co-licensing

X

Rights to future IP

Commercial exploitation

Research collaboration

X

Development

X

Start-up

X

Biotech

X

Pharma

X

Outcomes

Research impact

Clinical impact

X

UK impact (companies/jobs)

X

Royalties

X

Sales

X

TNF exclusive to Celltech

>40 companies licensed

with key patent from Celltech

Celltech, Behringwerke

MRCC [Chugai, Elan, LeukoSite]

Scotgen, Protein Design Laboratories

Celltech, Genentech

Wellcome

several diseases

Celltech

>\$500M

>\$20 bn pa worldwide [2010]



Patent landscape late 1980s

Patents

1. H/L co-expression
2. Chimeric Abs
3. Humanised Abs



Genentech
Celltech

Genentech

2

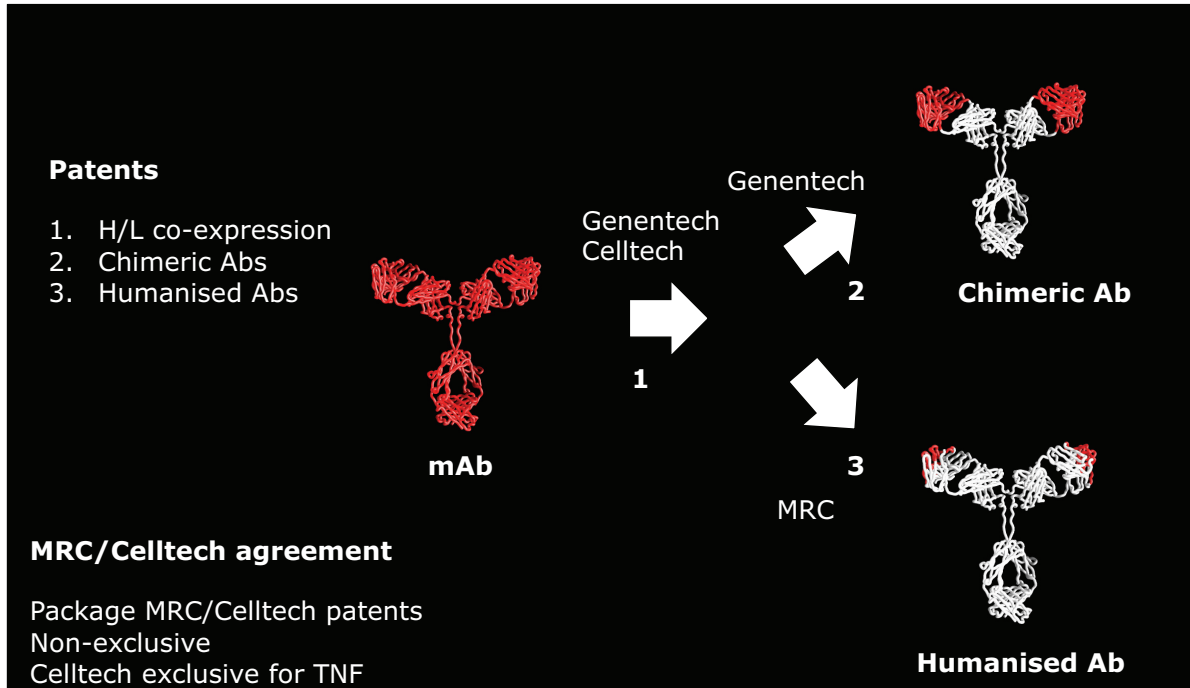


MRC

3



Patent landscape late 1980s



Translation process (MRC) - humanised mAbs

Patents

None	
Single	X
Multiple	
Improvements	X

Licensing strategy

Exclusive	X
Non-exclusive	X
Co-licensing	X
Rights to future IP	

Commercial exploitation

Research collaboration	X
Development	X
Start-up	X
Biotech	X
Pharma	X

Outcomes

Research impact	
Clinical impact	X
UK impact (companies/jobs)	X
Royalties	X
Sales	X

TNF exclusive to Celltech
>40 companies licensed
with key patent from Celltech

Celltech, Behringwerke
MRCC [Chugai, Elan, LeukoSite]
Scotgen, Protein Design Laboratories
Celltech, Genentech
Wellcome

several diseases
Celltech
>\$500M
>\$20 bn pa worldwide [2010]



MRC Collaborative Centre

Antibody
Diseases treated
Company partners
Patients treated
Sales

Actemra (tocilizumab)
 Rheumatoid arthritis
 Chugai (Roche)
 >100,000
 US \$435M (2010)

Tysabri (natalizumab)
 MS, Crohn's disease
 Elan (Biogen-IDEC)
 59,000
 > US \$ 1000M



Translation process (MRC) - humanised mAbs

Patents

None
 Single X
 Multiple
 Improvements X

Licensing strategy

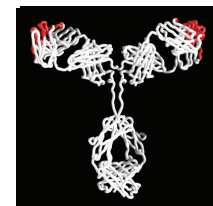
Exclusive X TNF exclusive to Celltech
 Non-exclusive X >40 companies licensed
 Co-licensing X with key patent from Celltech
 Rights to future IP

Commercial exploitation

Research collaboration X Celltech, Behringwerke
 Development X MRCC [Chugai, Elan, LeukoSite]
 Start-up X Scotgen, Protein Design Laboratories
 Biotech X Celltech, Genentech
 Pharma X Wellcome

Outcomes

Research impact
 Clinical impact X several diseases
 UK impact (companies/jobs) X Celltech
 Royalties X >\$500M
 Sales X >\$20 bn pa worldwide [2010]



Translation process (MRC) - human mAbs

Patents

None	
Single	X
Multiple	X
Improvements	X

Licensing strategy

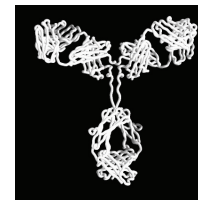
Exclusive	X	CAT
Non-exclusive		
Co-licensing	X	MRC/CAT/Scripps
Rights to future IP	X	

Commercial exploitation

Research collaboration	X	CAT
Development		
Start-up	X	CAT (HGS, BASF, Abbott, Pfizer, Genentech)
Biotech		
Pharma		

Outcomes

Research impact		
Clinical impact	X	several diseases
UK impact (companies/jobs)	X	GSK, Astrazeneca
Royalties	X	>\$250M
Sales	X	>\$6 bn worldwide [2010]

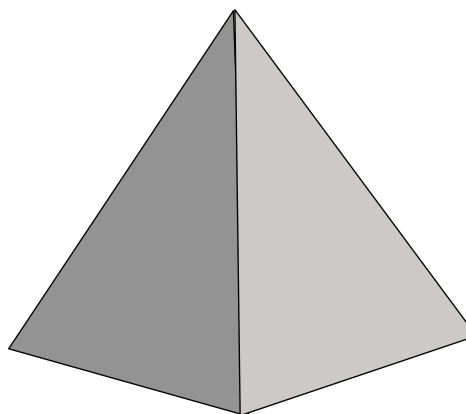


Start-up companies

BUSINESS PLAN

(for deals, pipeline of preclinical & clinical leads)

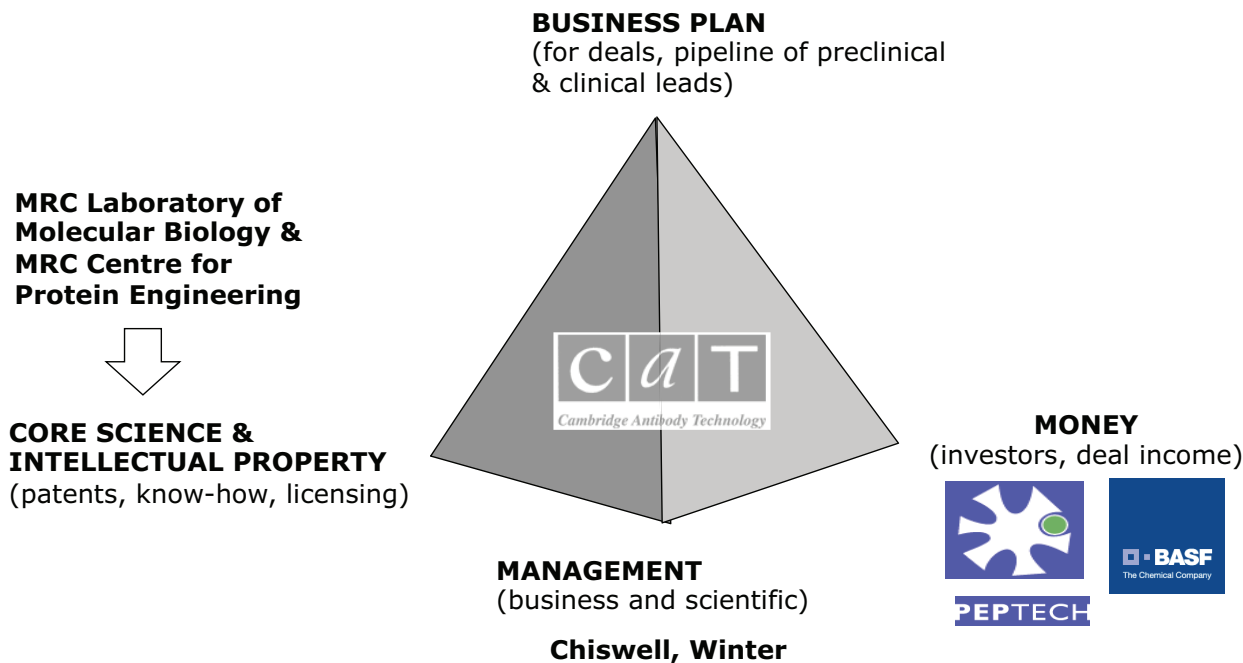
CORE SCIENCE & INTELLECTUAL PROPERTY
(patents, know-how, licensing)



MONEY
(investors, deal income)

MANAGEMENT
(business and scientific)

Cambridge Antibody Technology



Translation process (MRC) - human mAbs

Patents

None

Single

X

Multiple

X

Improvements

X

Licensing strategy

Exclusive

X

CAT

Non-exclusive

Co-licensing

X

MRC/CAT/Scripps

Rights to future IP

X

Commercial exploitation

Research collaboration

X

CAT

Development

Start-up

X

CAT (HGS, BASF, Abbott, Pfizer, Genentech)

Biotech

Pharma

Outcomes

Research impact

Clinical impact

X

several diseases

UK impact (companies/jobs)

X

GSK, Astrazeneca

Royalties

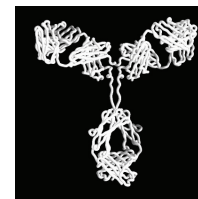
X

>\$250M

Sales

X

>\$6 bn worldwide [2010]



Summary & Comments

Translation

Work emerged from blue skies research

Three different models of translation, mostly successful

Long times lines to product

Biggest value for UK captured by working the technology in association with industry

No VCs

No interactions with UK large pharma

Public/private money used for translation.