MEDICAL RESEARCH COUNCIL TECHNOLOGY

# MRC Technology

## January 2015
## Tokyo

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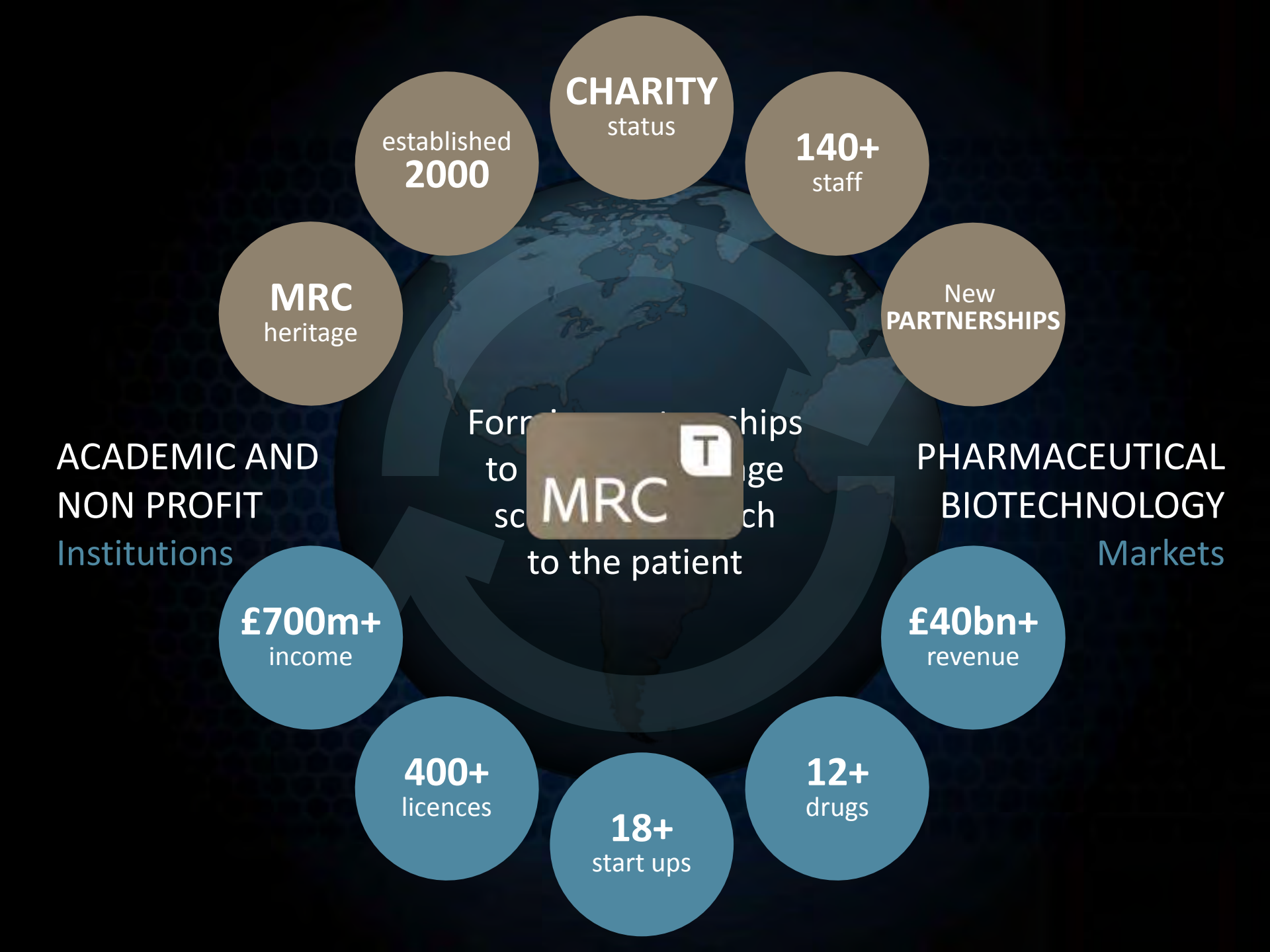
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MRC
heritage
New
PARTNERSHIPS
ACADEMIC AND
NON PROFIT
Institutions
Forr hips
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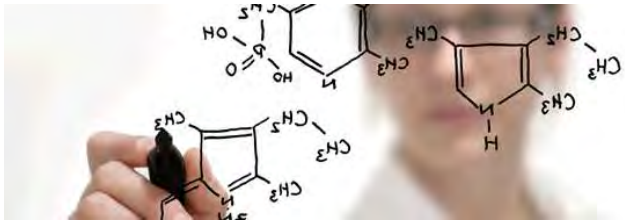
MRC T
PHARMACEUTICAL
BIOTECHNOLOGY
Markets
£700m+
income
£40bn+
revenue
400+
licences
18+
start ups
12+
drugs



# Who are MRC Technology?

- Life Science Specialist Technology Transfer Company
- Main client: UK Medical Research Council
- Founded in mid 1980s
- A UK registered charity
- Expertise in patenting, licensing and drug discovery research
- Collaborating widely

*UK, EC, US, China*

**A partner in antibody engineering**

# FORMING PARTNERSHIPS

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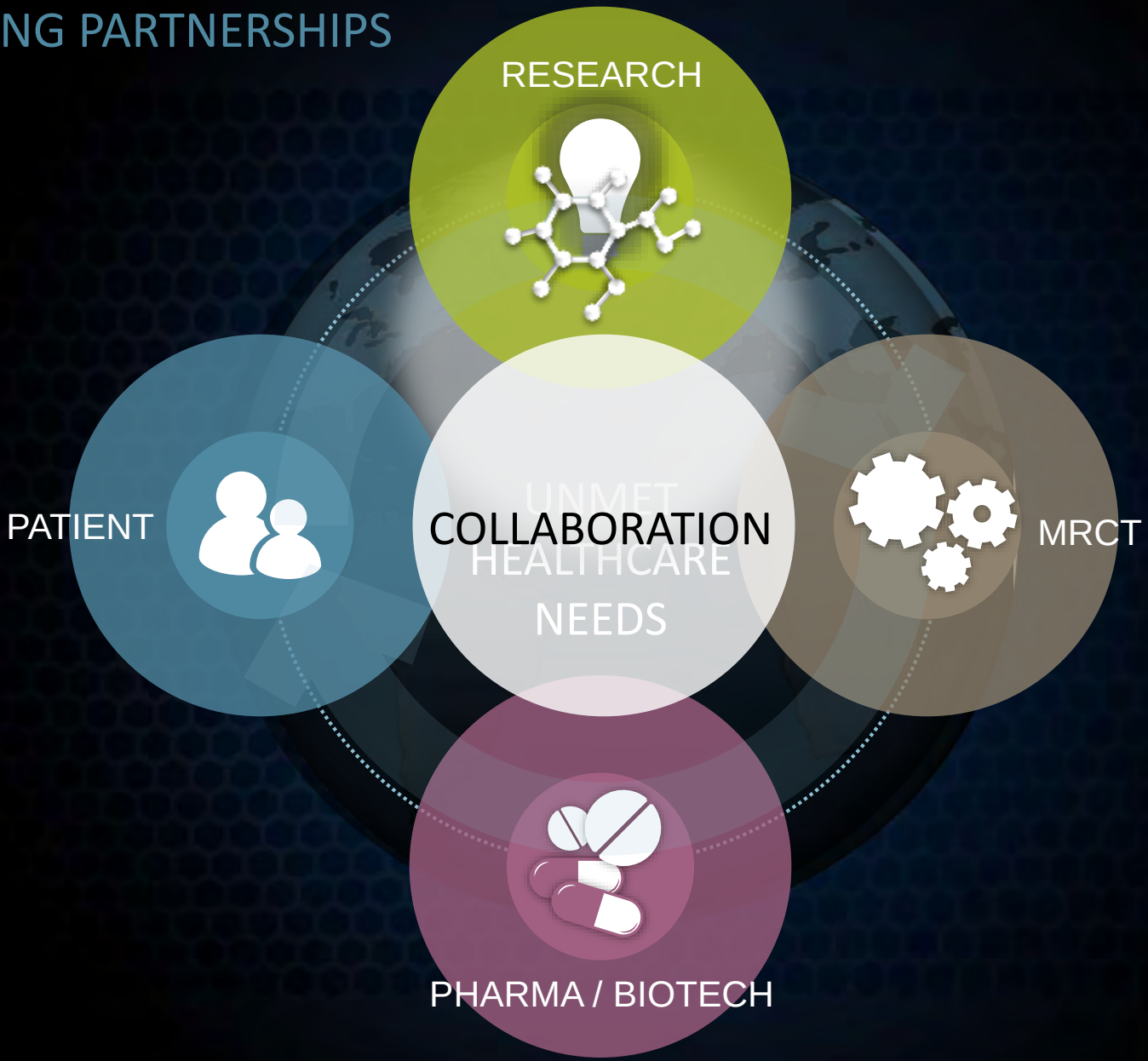


INCREASING PRESSURE ON R&D BUDGETS
ACADEMIC AND
NON PROFIT
Institutions
NEW CHALLENGES
PHARMACEUTICAL
BIOTECHNOLOGY
Markets
GLOBAL PRESSURES


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INCREASING PRESSURE ON R&D BUDGETS
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Institutions
COSTS
RISK
PHARMACEUTICAL
BIOTECHNOLOGY
Markets
GLOBAL PRESSURES

# ADDING VALUE INTELLECTUAL PROPERTY

Identify and evaluate

Protect

Commercialise


MRCT negotiated a royalty buyout of US$265m

ACADEMIC AND NON PROFIT
Institutions

PHARMACEUTICAL BIOTECHNOLOGY
Markets

# ADDING VALUE COMMERCIAL

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Translational funding

Proof of concept

Validation studies

HEPTARES therapeutics

Start-up already signed deals with Novartis worth $200 million

ACADEMIC AND NON PROFIT
Institutions

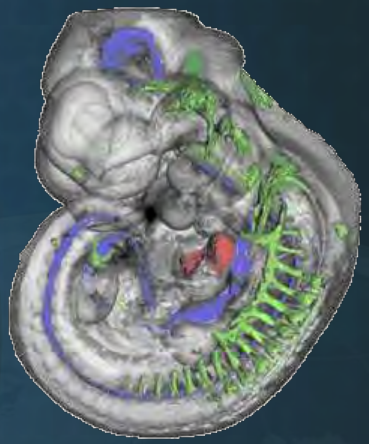
PHARMACEUTICAL BIOTECHNOLOGY
Markets

# ADDING VALUE SCIENTIFIC DEVELOPMENT

Centre for
Diagnostic Discovery
Edinburgh, Scotland
Devices and Diagnostics

Bioptonics

Award winning
Optical Projection
Tomography
(OPT) technology



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# ADDING VALUE SCIENTIFIC DEVELOPMENT

Centre for Therapeutics Discovery

Small Molecule Drug Discovery

Antibody Engineering

4 drugs on market

11 in clinical trials


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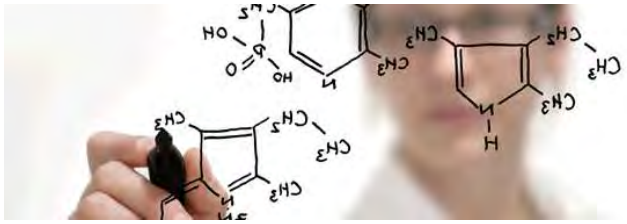
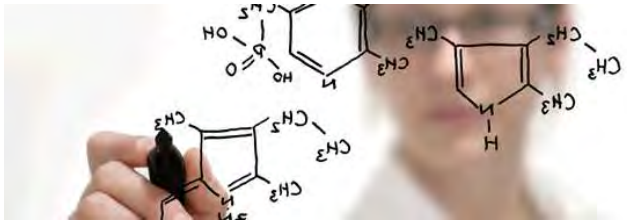


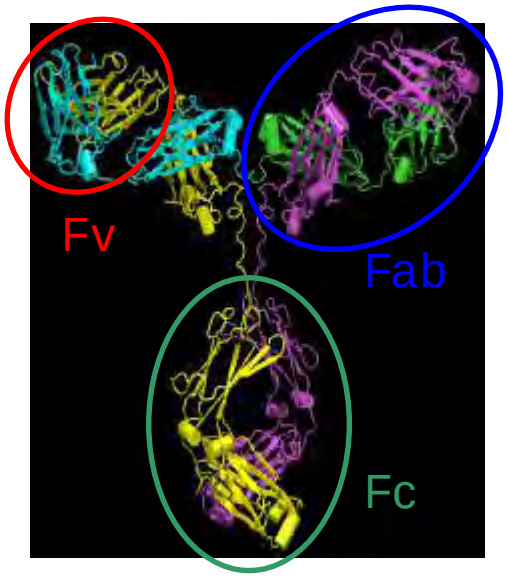
# MRCT: Centre for Therapeutics Discovery

- Own risk research collaboration
  - *Drug Discovery Biology*
  - *Medicinal Chemistry*
  - *BioTherapeutics – antibody engineering*
- Collaborative antibody humanization program with industry
- >75 Research staff
  - *High percentage ex-Industry (GSK, Pfizer, AZ, Merck, etc)*
  - *Annual R&D spend ~£9m*
  - *Laboratories in Mill Hill next to NIMR*

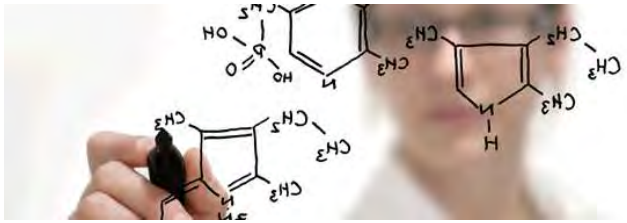


# BioTherapeutics Group

- Capabilities
  - *Generate potentially therapeutic mouse antibodies*
  - *Humanize rodent antibodies (CDR Grafting)*
  - *Antibody engineering*
- Track record
  - *Antibody engineering group established 1988*
  - *55+ antibodies successfully humanized*
  - *12 recombinant antibodies have progressed to clinic*
  - *6 are currently in active clinical development*
  - *4 humanized antibodies secured marketing approval*
- Tysabri: multiple sclerosis (Biogen Idec/Elan)
- Actemra: rheumatoid arthritis (Chugai / Roche)
- Entyvio: Crohn's Disease (Takeda)
- Keytruda: Malignant Melanoma (Merck & Co)

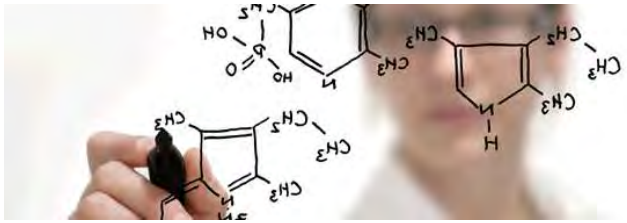




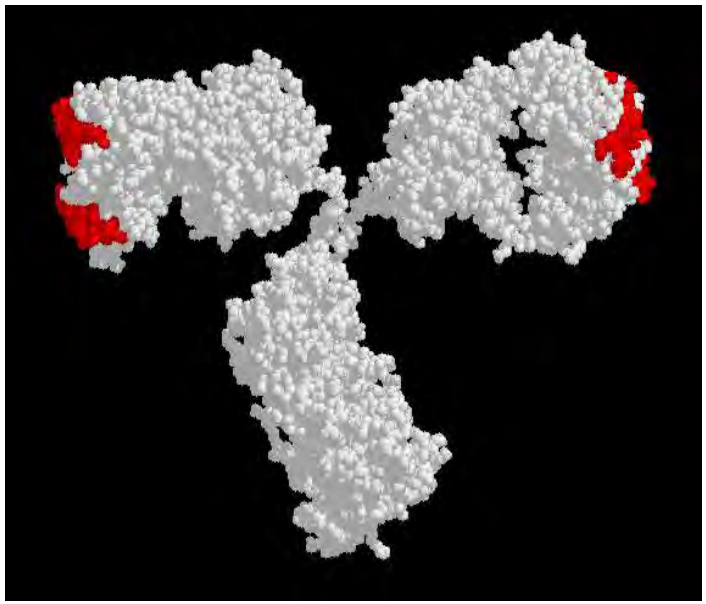


# Selected Collaborations

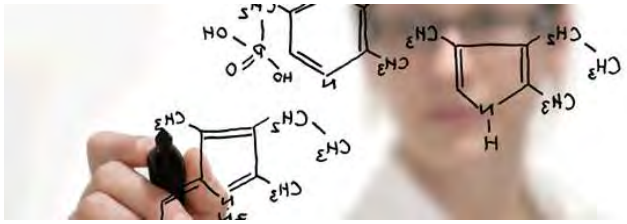
| Company | mAb Number | Status | Name |
|---|---|---|---|
| Biogen/Elan | 2 (1) | Approved | Tysabri |
| Chugai/Roche | 2 (1) | Approved | Actemra |
| Takeda (Leukocyte) | 3 (2) | Approved | Entyvio |
| Merck & Co (Organon) | 1 (1) | Approved | Keytruda |
| Curetech | 1 (1) | Phase II | CT-011 |
| Antisoma | 1 (1) | Phase II | AS1409 |
| Lpath | 1 (2) | Phase II | ISONEP |
| BioArctic | 1 (1) | Phase I | BAN2401 |
| Centocor | 1 (1) | Pre-clinical | not known |



# Advantages of Humanization Mouse Antibodies



- Mouse antibodies accessible
  - *system well characterised and reliable*
  - *High potency achievable*
- Easier to characterise and select mouse Abs in murine models
- Humanization reliable and reproducible process
  - *Significantly reduces risk of immunogenicity*
  - *Validated in clinic and on market*



# Humanization reduces the incidence of adverse reactions

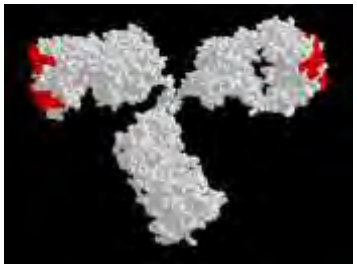
- Marked = >15% patients displayed AAR
- Tolerable = 2-15% patients displayed AAR
- Negligible = <2% patients displayed AAR

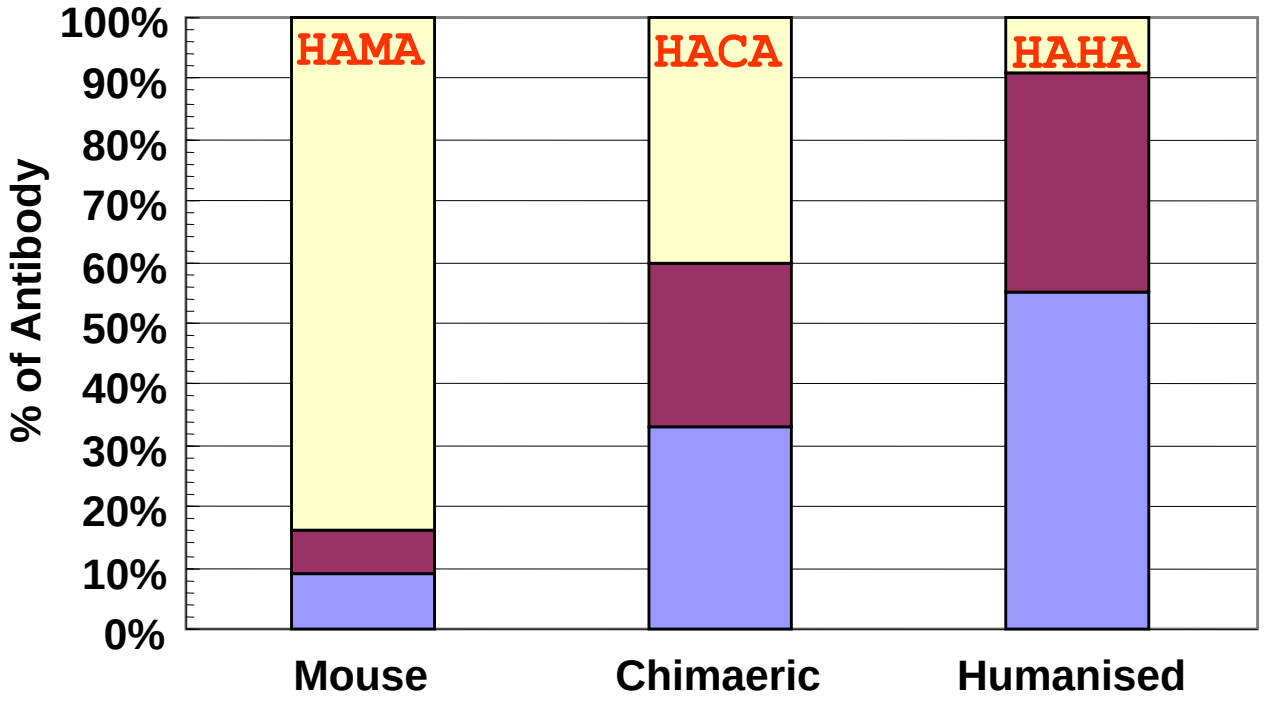
**Study of:**

**Mouse = 44 Abs**

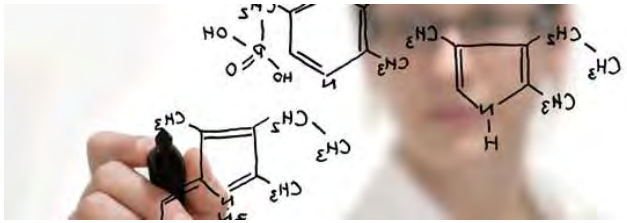
**Chimeric = 15 Abs**

**Humanised = 22 Abs**



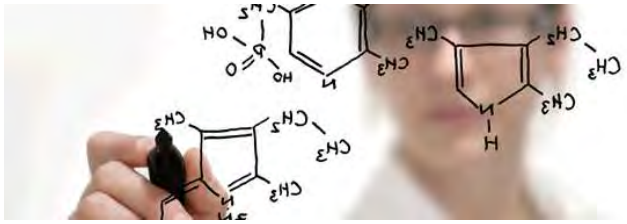



Hwang & Foote (2005)



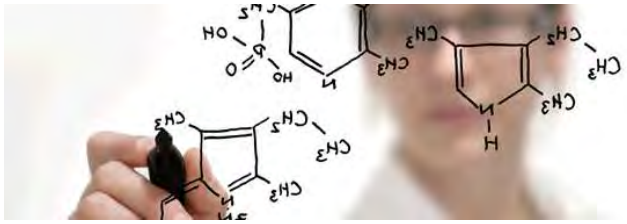
# Antibody Humanization Design Strategy

- Identify panel of similar human acceptor framework regions (FR) from database of >9000 $V_H$ and >2500 $V_L$ human sequences.
- Analyze the amino acid sequences of the mouse antibody
  - *Homology of human/mouse FR residues*
  - *Match CDR loop lengths*
  - *Identify key framework residues - important for CDR structure*
- Select the best human acceptor FR sequences & design several versions of humanized $V_H$ and $V_L$ regions
  - *Mouse donor CDR sequences + human acceptor FW sequences*
  - *Potential sites of mutation in FW sequences – but only where necessary*
- Consider issues such as protein stability, transient expression levels
- Timescale:
  - *Typically ~3 months*



# Case Study: Humanization AP33 for HCV infection

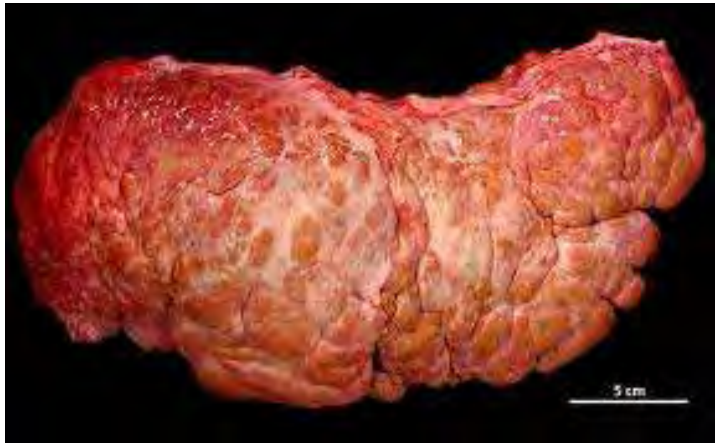
- Humanizing AP-33, an antibody to the E2 protein of HCV
  - *AP33 blocks HCV entry into hepatocytes*
  - *Aim to retain broad specificity of the antibody*
  - *HCV has 6 genotypes plus thousands of sub genotypes*
  - *Genotypes 1, 2 and 3 most prevalent in USA, Europe and Japan*
  - *AP-33 blocks cell entry in vitro across all 6 major genotypes*
- Challenge 1 - retain broad specificity and potency
- Challenge 2
  - *Heavy chain has 8 key framework residue mismatches – an unusually high number*
  - *AP33 had an unusual light chain with no human equivalent*

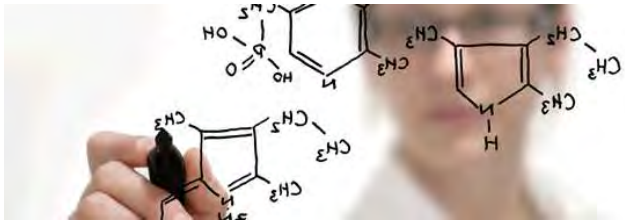


# Case Study: Humanized Antibody for Fibrosis

- Mouse monoclonals created in collaboration with Sheffield University
- Target strongly implicated in the etiology of fibrosis

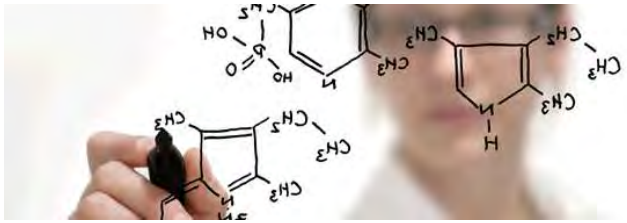
  *Large amount of data in literature*
- Humanized by MRCT
- *In vitro* and *in vivo* PoC established
- Licensed to UCB in December 2013





# Flexible Business Models

- Cash Plus Milestone
  - *Upfront project payment*
  - *Single ‘success’ milestone (IND)*
- Shared Risk
  - *No project payment*
  - *Milestones and small Royalty*



# Why Companies Come to MRC Technology

- Huge experience in antibody engineering

  *Track record of product delivery*

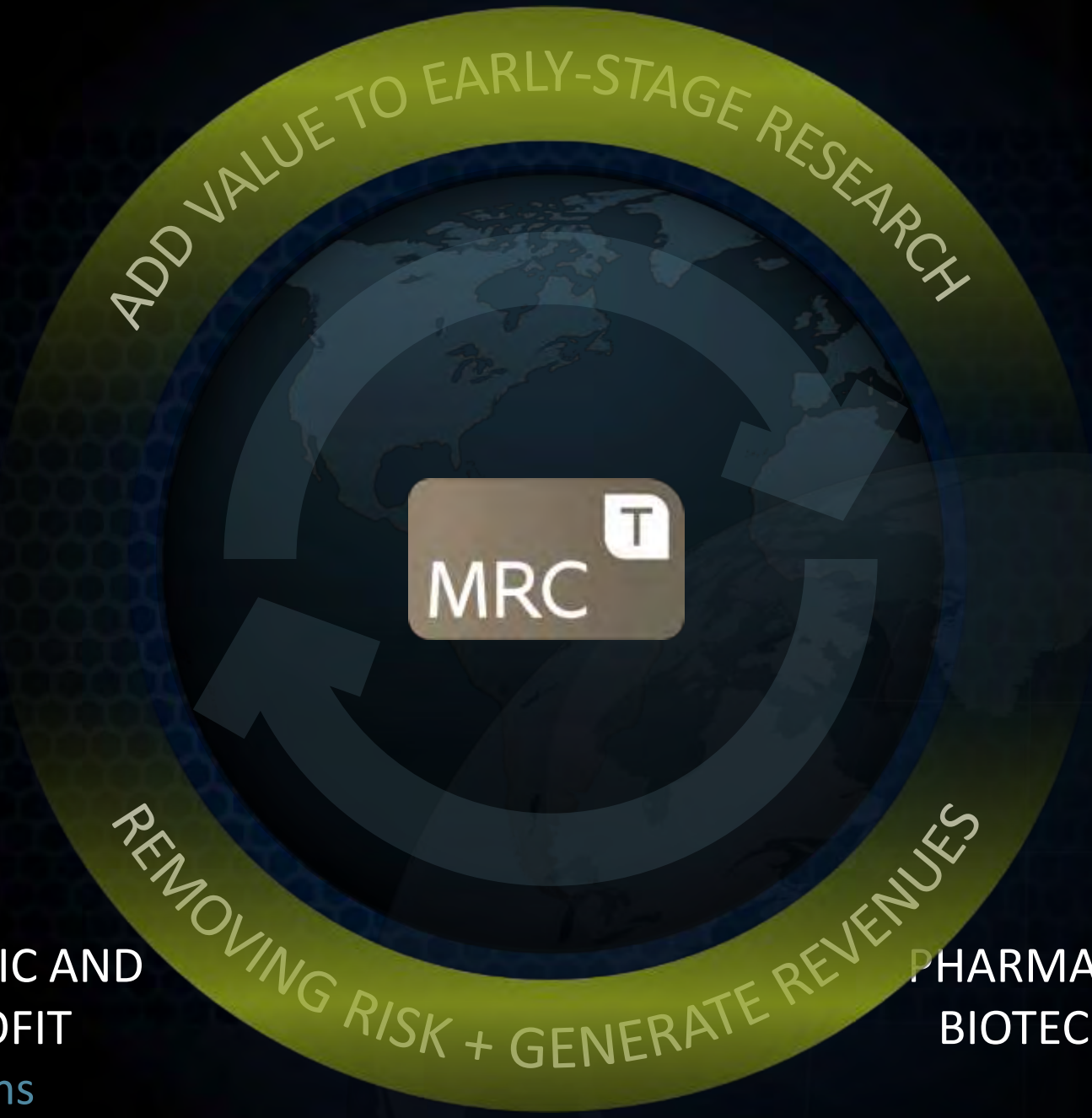
- Not one molecule, not 6 variants but…

  *The best variant we can discover and deliver*

  *Cheaper isn't better, the next stage will cost you 20 times more*

- Not a CRO but a Collaborator

  *Tell us what you want and we'll try to deliver*

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Forming partnerships
to drive early stage
scientific research
to the patient
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