Monoclonal antibodies (mAbs) in Infectious Diseases

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Disclosure

- Nothing to disclose

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Objectives

- Give a brief overview of mAbs
- Highlight the use of mAbs in infectious diseases
- Review the use of mAbs in the SARS CoV-2 pandemic

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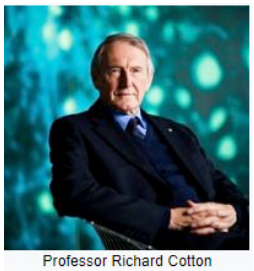
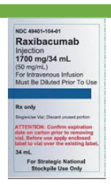
mAb Development Timeline



Professor Richard Cotton

1890 1951 1975 1986 1998 2012 2020



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mAbs - Overview

- A mAb is a pure collection of identical antibody (Ab) molecules with the same specificity.
- mAbs are derived from a unique parent B lymphocyte/plasma cell.
- Most therapeutic mAbs are immunoglobulin (Ig) G

- mAbs actions
  - Antagonism
  - Signalling
  - Ab dependent cellular cytotoxicity (ADCC)
  - Complement dependent cytotoxicity (CDC)
  - Ab dependent cellular phagocytosis

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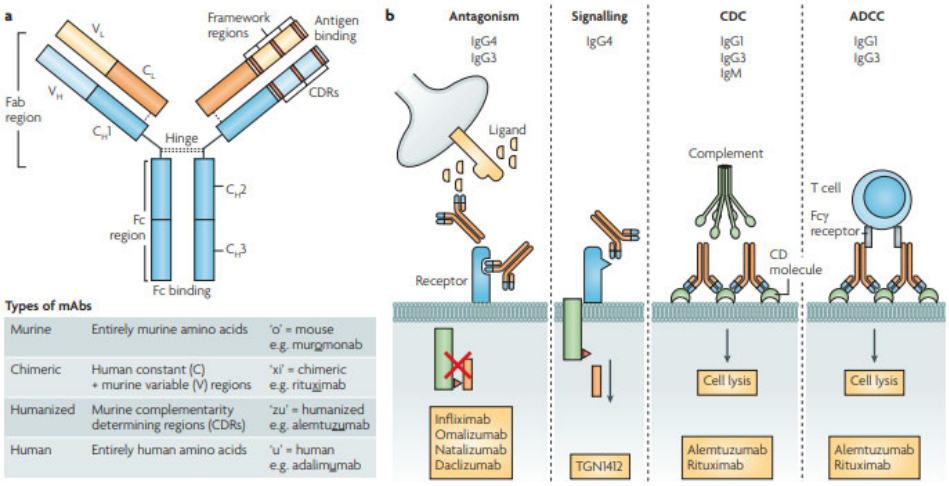
REVIEWS



Types of mAbs

Murine	Entirely murine amino acids	'o' = mouse e.g. murɑmonab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. rituximab
Humanized	Murine complementarity determining regions (CDRs)	'zu' = humanized e.g. alemtuzumab
Human	Entirely human amino acids	'u' = human e.g. adalimumab

Nature Reviews Drug Discovery 2010; 9:325-338

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REVIEWS

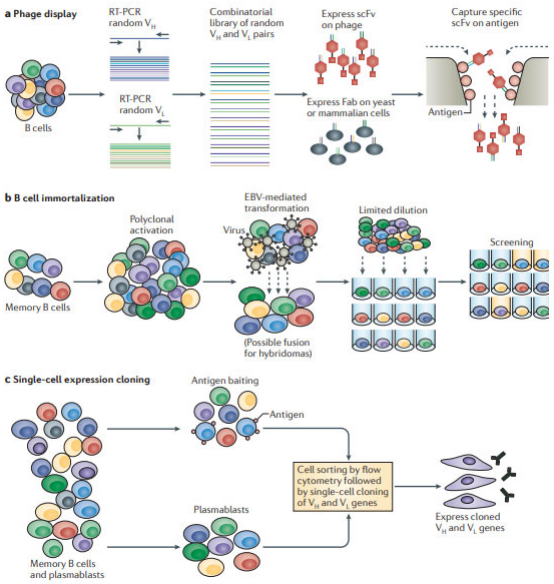

Table 1 | **Advantages and disadvantages of the methodologies commonly used to isolate monoclonal antibodies from humans**

Method	Pros	Cons
Phage display	• High-throughput screening for the desired specificity and functional capacity • Can find B cells that were generated decades earlier and maintained in the memory B cell population • Expressed immunoglobulins can be from multiple B cell types	• No cognate heavy and light chain information • Does not provide information on the relative frequency of B cell specificities • Non-eukaryotic expression of immunoglobulins may bias against certain specificities
In vitro culture and selection usually with B cell immortalization	• High-throughput screening for the desired specificity and functional capacity • Can find B cells that were generated decades earlier and maintained in the memory B cell population	• Typically need to screen thousands of B cells to find a few desired cells • Most amenable to memory B cells
Single-cell expression cloning with antigen baiting	• Can be a highly efficient method to obtain hundreds of B cells with the desired specificity • Amenable to all B cell types expressing a BCR on the cell surface	• Limited to B cells expressing a BCR on the cell surface and by the availability of good antigenic baiting reagents • Difficult to screen for functional characteristics
Single-cell expression cloning of plasmablasts without antigen baiting	• Can be a highly efficient method to obtain hundreds of B cells with the desired specificity, depending on the timing and quality of immunogenic stimulus • Provides information on the specificity of B cells responding directly to recent antigen exposure	• There is only a brief window of time when plasmablasts are present after exposure to the antigen • Works best with fresh PBMC samples

BCR, B cell receptor; PBMC, peripheral blood mononuclear cell.

Nature Reviews Immunology 2012, 12:709-719

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mAbs - Overview

- mAb applications
  - Identification of phenotypic markers unique to particular cells
  - Immunodiagnosis
  - Tumor identification
  - Therapy
  - Functional analysis of cell surface and secreted molecules

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mAbs - Immunodiagnosis

- Radioimmunoassays
  - radioactive decay
- Enzyme linked immunoassays
  - enzyme color conversion
- Immunohistochemical staining
  - labelling and detection of antigens in cells/tissues

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mAbs - Therapeutics

Pros

- Highly specific
- Long half lives
- Amenable to molecular engineering

Cons

- Adverse effects
  - Therapeutic effect
  - Mechanism of action
  - Immunogenicity
- Cost

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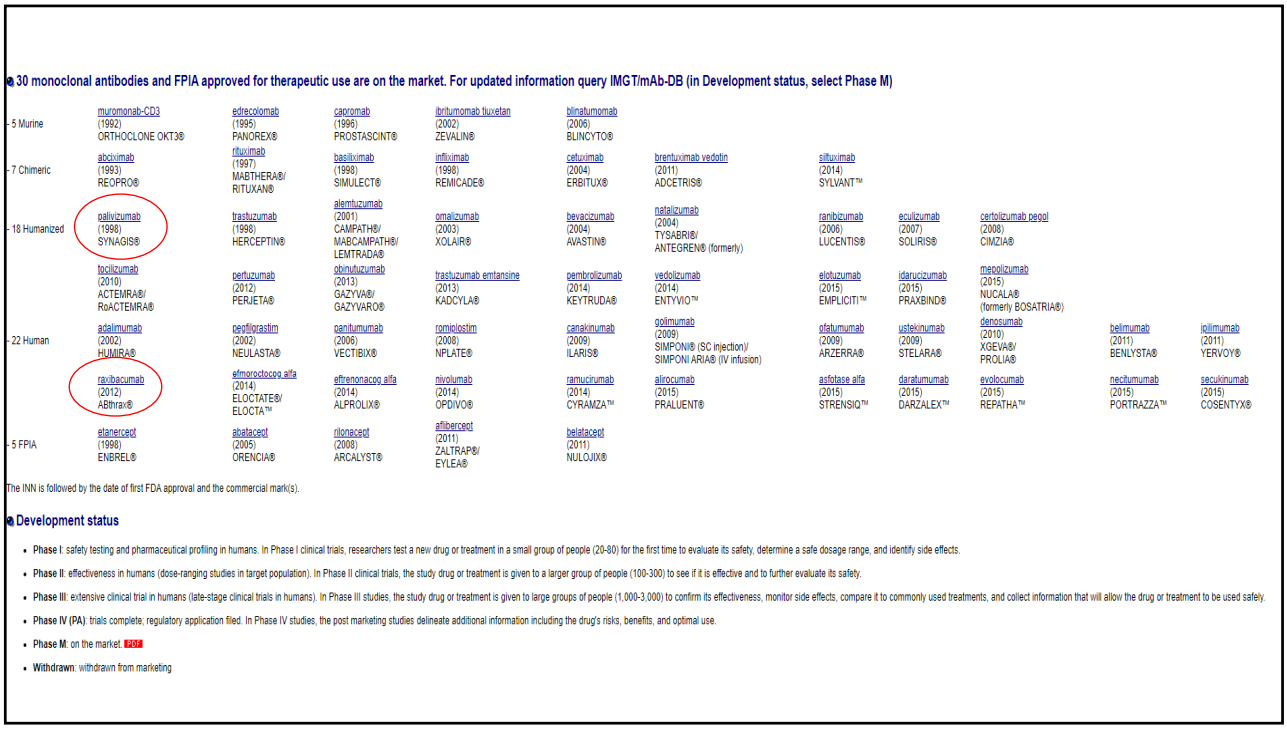

30 monoclonal antibodies and FPIA approved for therapeutic use are on the market. For updated information query IMGT/mAb-DB (in Development status, select Phase M)

- 5 Murine	muromonab-CD3 (1992) ORTHOCLONE OKT3®	edrecolomab (1995) PANOREX®	capromab (1996) PROSTASCINT®	ibritumomab tiuxetan (2002) ZEVALIN®	blinatumomab (2006) BLINCYTO®					
- 7 Chimeric	abciximab (1993) REOPRO®	rituximab (1997) MABTHERA®/ RITUXAN®	basiliximab (1998) SIMULECT®	infliximab (1998) REMICADE®	cetuximab (2004) ERBITUX®	brentuximab vedotin (2011) ADCETRIS®	siltuximab (2014) SYLVANT™			
- 18 Humanized	palivizumab (1998) SYNAGIS®	trastuzumab (1998) HERCEPTIN®	alemtuzumab (2001) CAMPATH®/ MABCAMPATH®/ LEMTRADA®	omalizumab (2003) XOLAIR®	bevacizumab (2004) AVASTIN®	natalizumab (2004) TYSABRI®/ ANTEGREN® (formerly)	ranibizumab (2006) LUCENTIS®	eculizumab (2007) SOLIRIS®	certolizumab pegol (2008) CIMZIA®	
	tocilizumab (2010) ACTEMRA®/ RoACTEMRA®	pertuzumab (2012) PERJETA®	obinutuzumab (2013) GAZYVA®/ GAZYVARO®	trastuzumab emtansine (2013) KADCYLA®	pembrolizumab (2014) KEYTRUDA®	vedolizumab (2014) ENTYVIO™	elotuzumab (2015) EMPLICITI™	idarucizumab (2015) PRAXBIND®	mepolizumab (2015) NUCALA® (formerly BOSATRIA®)	
- 22 Human	adalimumab (2002) HUMIRA®	pegfilgrastim (2002) NEULASTA®	canfumumab (2006) VECTIBIX®	romiplostim (2008) NPLATE®	canakinumab (2009) ILARIS®	golimumab (2009) SIMPONI® (SC injection)/ SIMPONI ARIA® (IV infusion)	ofatumumab (2009) ARZERRA®	ustekinumab (2009) STELARA®	denosumab (2010) XGEVA®/ PROLIA®	belimumab (2011) BENLYSTA®	ipilimumab (2011) YERVOY®
	raxibacumab (2012) ABthrax®	efmoroctocog alfa (2014) ELOCTATE®/ ELOCTA™	eftrenonacog alfa (2014) ALPROLIX®	nivolumab (2014) OPDIVO®	ramucirumab (2014) CYRAMZA™	alirocumab (2015) PRALUENT®	asfotase alfa (2015) STRENSIQ™	daratumumab (2015) DARZALEX™	evolocumab (2015) REPATHA™	necitumumab (2015) PORTRAZZA™	secukinumab (2015) COSENTYX®
- 5 FPIA	etanercept (1998) ENBREL®	abatacept (2005) ORENCIA®	rilonacept (2008) ARCALYST®	aflibercept (2011) ZALTRAP®/ EYLEA®	belatacept (2011) NULOJIX®					

The INN is followed by the date of first FDA approval and the commercial mark(s).

Development status

- **Phase I**: safety testing and pharmaceutical profiling in humans. In Phase I clinical trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- **Phase II**: effectiveness in humans (dose-ranging studies in target population). In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- **Phase III**: extensive clinical trial in humans (late-stage clinical trials in humans). In Phase III studies, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- **Phase IV (PA)**: trials complete; regulatory application filed. In Phase IV studies, the post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.
- **Phase M**: on the market. PDF
- **Withdrawn**: withdrawn from marketing

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mAbs – ID Therapeutics

- competition from other forms of treatment/prevention (esp vaccines)
- complexity of pathology, immunology and epidemiology of infection (e.g. dengue, influenza)
- microbes

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Andy Marlette, USA TODAY Network
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mAbs in the SARS CoV-2 Pandemic

- Emergency use authorizations (EUA)
  - casirivimab/imdevimab (Nov 2020)
  - bamlanivimab/etesevimab (Feb 2021)
  - sotrovimab (May 2021)
  - tixagevimab/cilgavimab (Dec 2021)
  - bebtelovimab (Feb 2022)

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Summary

- mAbs are an important facet of infectious diseases diagnostics as well as vaccine development research
- mAbs for therapeutics in infectious diseases are limited by the availability of effective drugs, prophylactic strategies in addition to the variability and complexity of microbial antigens
- Represent a viable option for bridging treatments in the management of emerging infections.

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References
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