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Current Opinion in Microbiology

Antibacterial monoclonal antibodies: the next generation?

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There is a clear need for renewed efforts to combat the increasing incidence of antibiotic resistance. While the antibiotic resistance epidemic is due in part to the misuse of antibiotics, even proper empiric antibiotic therapy increases the selective pressure and potential for drug-resistance and spread of resistance mechanisms between bacteria. Antibiotic resistance coupled with the detrimental effects of broad-spectrum antibiotics on the healthy microbiome, have led the field to explore pathogen specific antibacterials such as monoclonal antibodies (mAbs). Medical need along with advances in mAb discovery, engineering, and production have driven significant effort developing mAb-based antibacterials. If successful, they will provide physicians with precision weapons to combat bacterial infections and can help prevent a return to a pre-antibiotic era.

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Current Opinion in Microbiology 2015, **27**:78–85

This review comes from a themed issue on **Antimicrobials/Microbial systems biology**

Edited by **Paul M Dunman** and **Andrew P Tomaras**

http://dx.doi.org/10.1016/j.mib.2015.07.014

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Introduction

Antibiotics have been a cornerstone of modern medicine since their first development. Effective antibiotics have enabled major medical advances in the treatment of trauma, routine invasive surgery and the care and treatment of immunosuppressed populations, including organ transplant recipients and patients undergoing cancer chemotherapy, thus improving the quality of life and increasing the lifespan for countless people worldwide. Antibiotics have become such an integral part of medicine that their availability, efficacy, and low cost are taken for granted. Most people no longer remember a time when what are now considered minor bacterial infections were largely untreatable. Soon after antibiotics became available, resistance emerged in the pathogens these molecules were meant to treat. This was not particularly problematic as antibiotic development largely kept pace with resistance into the 1960s [1]. However, after many decades of empiric broad-spectrum antibiotic use and misuse, and failure to develop new antibiotics with alternate mechanisms of action, resistance has become an epidemic that threatens a return to the pre-antibiotic era. In addition to the effects of antibiotics on resistance rates, there is mounting evidence that broad-spectrum antibiotics perturb our normal and beneficial microbiome [2]. These microbiome perturbations or dysbioses have been linked not only to a substantial increase in *Clostridium difficile* associated diarrhea but also diabetes, obesity, immune defects, and antibiotic resistance spread through horizontal gene transfer [2,3,4••,5]. Whether the broad implications of microbiome dysbiosis will bear out in future clinical research is unknown, however it is clear that there must be a fundamental change in how bacterial infections are treated.

Monoclonal antibody technology

As the resistance epidemic continues, the need for novel strategies to address this problem has led many to consider single-pathogen antibacterial agents [6,7]. One approach being explored is the use of pathogen specific monoclonal antibodies (mAbs) to prevent infections or to treat an infection adjunctively with antibiotics. Antibodies are natural proteins produced by the adaptive immune system. Passive immunization of individuals with mAbs selected for superior functional activity may both neutralize bacterial virulence and harness the power of the host immune response against the pathogen. The concept of antibody-mediated passive immunization to prevent or treat bacterial infections is not new; it was successfully employed before the discovery of antibiotics in the form of serum therapy [8]. However, due to the high cost and toxicity associated with these products, they were largely replaced with cheaper and safer broad-spectrum antibiotics. Nonetheless, antitoxins are still used in modern medicine to treat some bacterial diseases (*i.e.* diphtheria, botulism) [9,10]. Following the discovery of murine hybridoma technology in 1970s, the pharmaceutical and biotech industries have seen increasing numbers of mAbs in their portfolios [11,12]. The growth and promise of mAb-based therapies have driven many advances in mAb technology and production. Technologies now exist to isolate fully-human mAbs which elicit less immunogenicity and toxicity when administered to patients than previously observed with mAbs isolated from other species. For example, phage libraries expressing fully human antibodies or

antibody fragments are available [13,14]. Traditional hybridoma technology has also been applied to mice genetically engineered to express a fully human antibody repertoire or human Fab fused to a mouse Fc [15,16]. Techniques have also been developed to isolate immunoglobulin directly from human B cells from infected patients or following immunization [17–19]. Advances in mAb technology, coupled with high quality screening assays, have led to the isolation of unique mAbs not previously available for the prevention or treatment of bacterial infections. Many of these are currently in or poised to begin clinical testing (Table 1). In this review, some of the most recent advances in antibacterial mAbs are discussed.

Bacterial surface targets

Bacterial capsular polysaccharides have been successfully targeted as vaccine antigens (*e.g. Streptococcus pneumonia*, *Hemophilus influenza*) [20,21]. Consequently, surface antigens have been a popular target for antibacterial antibody discovery. The key activities of bacterial surface-specific mAbs are engagement of the host immune system through complement fixation and opsonophagocytic killing (OPK). However, clinical trials with mAbs targeting *Staphylococcus aureus* cell surface antigens lipoteichoic acid (pagibaxumab) and ClfA (aurexis) were unsuccessful. The reasons for this are not clear but, pagibaxumab and aurexis were not reported to exhibit OPK activity or to bind bacteria *in vivo*. Also, a Phase II clinical trial in ventilated ICU patients with the opsonic mAb SAR279356 targeting the bacterial surface polysaccharide poly-N-acetylglucosamine (PNAG) was recently terminated due to difficulty enrolling patients [[22], www.clinicaltrials.gov]. More recently, Hazenbos *et al.* isolated a human IgG1 (rF1) from peripheral B-cells of *S. aureus* infected people [23]. rF1 recognizes a highly conserved epitope in the serine aspartate repeat sequence found in several *S. aureus* and *S. epidermidis* cell-wall anchored proteins and binds both bacterial species. Importantly, rF1 mediated OPK and bound bacteria recovered from different infection models,

Table 1

Antibacterial mAb development programs

Organism	Phase	Molecule	Sponsor	Target	Molecule	Discovery platform	Ref.
Staphylococcus aureus	IIb	MEDI4893	MedImmune	Alpha toxin	Human IgG	VelocImmune mice	[39]
	IIa	Tosatoxumab (AR-301)	Aridis	Alpha toxin	Human IgG	Convalescent patient B-cell	[a]
	Phase IIa, study terminated	SAR279356	Alopexx/Sanofi	Anti-PNAG	Human IgG	Convalescent patient B-cell	[22], [a]
	Preclinical	1C11	Univ. of Rochester	Glucaminidase subunit of autolysin	Humanized mouse IgG	Mouse	[24]
	Preclinical	LTM14	Pfizer	Alpha toxin	Human IgG	Phage display	[35]
	Preclinical	ASN100	Arsanis	Alpha toxin + four leukocidins	Human IgG	Human IgG yeast display	[43•]
	Preclinical	rF1	Genentech	Cell-surface protein serine aspartate repeat	Human IgG	Human B-cell	[23]
	Preclinical	Unnamed	IBT	Enterotoxin B	Human IgG	Phage display	[51]
Pseudomonas paeruginosa	IIa	Panobacumab	Aridis	O-antigen (serotype O11)	Human IgM	Human B-cell	[25]
	Discontinued development	KB001-A	Kalobios	PcrV	Humaneered® Pegylated-Fab	Mouse hybridoma	[b]
	I	MEDI3902	MedImmune	Psl and PcrV	Human bispecific IgG	Phage display and VelocImmune mouse	[30••]
Bacillus anthracis	Licensed	Raxibacumab	Glaxo Smithkline	Protective antigen	Human	Phage display	[45]
	III	Anthim® (ETI-204)	Elusys	Protective antigen	Human chimeric	Mouse hybridoma	[49]
Clostridium difficile	III	Actoxumab + bezlotoxumab	Merck	Toxins A and B	Human IgG	HuMab mice	[52•]
Escherichia coli	II	Shigamab®	Bellus Health	Anti-shigatoxin	Chimeric mAb	Mouse hybridoma	[53]

[a] www.clinicaltrials.gov.
[b] kalobios.com.

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