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352 How can monoclonal antibodies be harnessed against
353 neglected tropical diseases and other infectious diseases?

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370 **Highlights**

- 371 1. Therapies based on monoclonal antibodies against bacterial and viral agents have already
372 entered the clinic, while no monoclonal antibodies against parasites, animal envenoming, or
373 mushroom poisonings have been tested in the clinical setting
- 374 2. Neglected tropical diseases represent a golden opportunity for antibody developers, as there
375 are many scientifically low-hanging fruits in this field
- 376 3. An increasing number of therapeutic monoclonal antibody discoveries has been reported for
377 neglected tropical diseases and other infectious diseases
- 378 4. Monoclonal antibodies may be particularly useful for developing therapies against
379 intoxications caused by both animals and bacteria
- 380 5. Low cost of manufacture and selective cross-reactivity are key challenges for developing
381 monoclonal antibodies against neglected tropical diseases and other infectious diseases
- 382 6. Treatment against snakebite envenoming and bacterial and viral infections will likely
383 require the use of oligoclonal antibodies for multi-target neutralization

384

385

386 **Abstract**

387 **Introduction:** Monoclonal antibody-based therapies now represent the single-largest class of
388 molecules undergoing clinical investigation. Although a handful of different monoclonal antibodies
389 have been clinically approved for bacterial and viral indications, as well as rabies, therapies based on
390 monoclonal antibodies are yet to fully enter the fields of neglected tropical diseases and other
391 infectious diseases.

392 **Areas covered:** This review presents current state-of-the-art in the development and use of
393 monoclonal antibodies against neglected tropical diseases and other infectious diseases, including
394 viral, bacterial, and parasitic infections, as well as envenomings by animal bites and stings.
395 Additionally, a short section on mushroom poisonings is included. Key challenges for developing
396 antibody-based therapeutics is discussed for each of these fields.

397 **Expert opinion:** Neglected tropical diseases and other infectious diseases represent a golden
398 opportunity for academics and technology developers for advancing our scientific capabilities within
399 the understanding and design of antibody cross-reactivity, use of oligoclonal antibody mixtures for
400 multi-target neutralization, novel immunization methodologies, targeting of evasive pathogens, and
401 development of fundamentally novel therapeutic mechanisms of action. Furthermore, a huge
402 humanitarian and societal impact is to gain by exploiting antibody technologies for the development
403 of biotherapies against diseases, for which current treatment options are suboptimal or non-existent.

404

405 **1. Introduction**

406 For millions of years, viruses, bacteria, parasites, and natural toxins have represented a daily threat
407 and disease burden for humankind. Although many diseases caused by these pathogens are now under
408 control, particularly due to improved hygiene, effective vaccination programs, and the development
409 of antibiotics, many diseases remain untreatable or have reemerged as a result of development of
410 resistance towards therapy [1,2]. Some of these diseases are infectious diseases, whereas others are
411 non-communicable. A special cross-category of diseases are the “neglected tropical diseases”, which
412 are tropical diseases (most of them infectious) that mostly affect impoverished communities having
413 little political voice, and thus perpetuate poverty and vulnerability. In general, these diseases have
414 received little attention from health authorities, research agendas, and the pharmaceutical industry.
415 The World Health Organization currently lists 20 diseases as category A neglected tropical diseases
416 that are of the highest importance. These include viral, bacterial, parasitic diseases, and snakebite
417 envenoming ([Table 1](#)) [3]. These and other infectious diseases are caused by foreign agents, and
418 antibody-based therapies may therefore present many benefits to their prevention or cure, as
419 antibodies are inherently evolved to fight off foreign threats.

420 The lion’s share of antibody-based therapies that are already in clinical use or in clinical
421 development are against indications in the areas of oncology, autoimmune diseases, and other chronic
422 diseases [4–6]. To a large extent, this trend is driven by financial incentives and the reality that
423 enterprises operating in the pharmaceutical industry typically must deliver a monetary return on
424 investment to their shareholders. With the traditional business and reimbursement models for
425 pharmaceuticals, achieving financial success may be challenging for antibody-based therapies against
426 many neglected tropical diseases and other infectious diseases, despite the existence of a huge unmet
427 humanitarian need for better therapies in areas such as infectious and parasitic diseases [1,7–11],
428 envenomings by animal bites and stings [12–14], and mushroom poisonings [15]. In these areas,

existing therapeutic options are either suboptimal, or resistance towards therapy is developing. Although only a few indications within these disease areas are supplied with effective biologics that have reached the clinic, a growing number of studies on the discovery and development of both conventional and advanced antibody-based experimental biotherapeutics have been reported. Moreover, with the general increase in global wealth and the decreasing cost of therapeutic antibody manufacture, it is speculated that antibody-based therapies may become sufficiently cost-competitive to be employed against challenging neglected tropical diseases, such as snakebite envenoming [16,17]. In this review, prominent examples of antibody-based therapeutic developments within the areas of viral infections, bacterial infections, parasitic infections, envenomings, and poisonings are reviewed. These examples are followed by an opinion on how novel antibody technologies can better be integrated in the development of a new generation of effective and affordable biotherapies against indications within these disease areas.

441

2. New antibody-based therapeutics for neglected tropical diseases and other infectious diseases

2.1 Viral pathogens

For decades, researchers have worked on developing monoclonal antibodies against a large number of viral pathogens [18], and with the recent Ebola outbreaks, the search for antibody-based therapeutics against viral indications has gained increased momentum. One of the key challenges with viral pathogens is their ability to undergo rapid mutation and retain their infectivity. Therefore, focus in the viral antibody field is often directed towards development of broadly-neutralizing antibodies against which it is difficult for viruses to create escape mutants [18]. In this relation, human immunodeficiency virus (HIV) has in particular been a challenging indication, although researchers

452 have recently reported promising results on the generation of broadly-neutralizing efficacious
453 monoclonal antibodies targeting key epitopes on glycoproteins on the HIV particle [19–22]. Another
454 challenge with viral pathogens is that it can be difficult to predict *in vivo* efficacy for therapeutic
455 monoclonal antibodies targeting the virus, as *in vitro* efficacy is not always predictable due to the
456 complex pathogenesis involved in viral infections. This is well exemplified by recent studies on the
457 development of monoclonal antibodies against the alphaviruses, Western equine encephalitis virus
458 (WEEV) [23,24] and Venezuelan equine encephalitis virus (VEEV) [25]. In these studies, human-
459 like antibodies were developed by phage display technology using scFv antibody libraries derived
460 from macaque monkeys immunized with the viruses. Promising macaque scFvs were selected and
461 genetically fused with fully human Fc regions to create scFv-Fc antibody constructs. Upon
462 expression, several of these antibodies were demonstrated to be able to prevent WEEV or VEEV
463 particles from infecting Vero cells using an *in vitro* neutralizing peroxidase-linked antibody assay, as
464 well as the antibodies provided protection *in vivo* in a murine model employing BALB/c mice
465 challenged with virus particles by the airborne route. However, other antibodies, such as ToR67-3B4
466 and ToR68-2C3, failed to protect *in vitro*, yet exhibited efficacious neutralizing properties *in vivo*,
467 possibly due to effective complement-mediated lysis or antibody-dependent cell-mediated lysis of
468 infected cells [23–25]. Despite such challenges for prediction of *in vivo* efficacy, some antiviral
469 monoclonal antibodies have already reached the market, including Pavilizumab for prevention of
470 respiratory syncytial virus (RSV) infections [26], the recombinant human monoclonal antibody,
471 known as Rabishield, for prevention of rabies [27], and Ibalizumab against HIV [28]. In the future, it
472 is likely that even more antiviral monoclonal antibodies will pass regulatory approval, as a large
473 number of antiviral monoclonal antibodies are currently undergoing evaluation in clinical trials [18].

474 The discovery and evaluation of therapeutic monoclonal antibodies and antibody fragments has
475 been reported against a number of highly infectious viral tropical diseases, including Sudan Ebola

476 virus [29], Zaire Ebola virus [30–33], Nipah virus [34], Hendra virus [35], Dengue virus [36,37], Zika
477 virus [37–40], rotavirus [41], norovirus [42], and Marburg virus [43] (Figure 1). Different antibody
478 discovery methodologies were successfully used in these studies, including hybridoma-based and
479 phage display-based approaches, and the antibodies generated were shown to have efficacy in
480 different preclinical models, including rodents and monkeys, with some antibodies displaying
481 efficacy in clinical trials [41]. Moving on from the discovery and development phase, other important
482 challenges for therapeutic monoclonal antibodies against viral tropical diseases is the high cost of
483 clinical development and the limited market sizes and accessibility [18]. These barriers complicate
484 business planning, which may be one of the reasons why much of the work performed in this field
485 has been undertaken by academics or military research units, sometimes working in collaboration
486 [24,29,43]. Finally, therapies based on monoclonal antibodies compete with alternative therapeutic
487 strategies, including vaccination, which is often a more cost-effective approach to achieving patient
488 survival and viral containment [18].

489

490 2.2 Bacterial pathogens

491 Before the introduction of antibiotics in the 1930s, bacterial infections were treated with animal-
492 derived antisera comprising polyclonal antibodies [44]. These medicines presented a number of
493 drawbacks, including a propensity to elicit adverse reactions due to the immunogenic disposition of
494 the animal antibodies and other proteins present in the antisera, as well as difficulties in standardizing
495 their manufacture and distribution [7]. The treatment of bacterial infections underwent a medical
496 paradigm shift with the advent of antibiotics, such as penicillin, saving millions of lives for both
497 humankind and livestock [2,45]. However, with the surge in antibiotic usage in the last many decades,
498 emergence of antimicrobial resistance now represents one of the major threats to human health [1,2].

499 Many of the bacterial pathogens, for which antimicrobial resistance has developed, are not strictly
500 classified as neglected tropical diseases. However, a large number of these disease-inflicting bacteria
501 thrive in the tropics and share many commonalities with more classical neglected tropical diseases,
502 including poor treatment options for patients. The pathogenicity exerted by bacteria responsible for
503 infectious diseases is often facilitated by the colonization of bacteria and production of toxic
504 compounds that disturb homeostasis of the host. Therefore, antibody-based therapies that target key
505 virulence factors (toxins and adhesion/colonization factors) have successfully been developed and
506 approved to combat bacterial infections, such as the human monoclonal antibodies Bezlotoxumab
507 against *Clostridium difficile* toxin B [44,46], Raxibacumab and Obiltoxaximab against *Bacillus*
508 *anthracis* protective antigen (co-administered with antibiotics) [47,48], and Atidortoxumab against
509 *Staphylococcus aureus* alpha toxin [49]. Common for these therapies is that they all involve
510 intravenous administration of monoclonal immunoglobulin G (IgG) type antibodies. In the future,
511 other antibody formats and other routes of administration, as well as the use of DNA vaccines, may
512 find their way to the market, both for human and veterinary indications [50–55].

513 Within the areas of neglected tropical diseases and bacterial infections, a range of different
514 monoclonal antibody formats have been investigated for therapeutic applications. These include
515 humanized IgG, murine IgG, and single-domain monoclonal antibodies against Shiga toxins type 1
516 and 2 (Stx1 and Stx2) and Shiga-like toxins [56–59], bispecific human monoclonal antibodies against
517 pertussis toxins [60], human monoclonal immunoglobulin A (IgA) antibodies against tuberculosis
518 [61], chimeric IgG antibodies targeting the conserved core/lipid A region of lipopolysaccharide of
519 *Vibrio cholerae* [62], and human IgM antibodies against endotoxins (lipopolysaccharides, LPS) from
520 gram-negative bacteria involved in sepsis and septic shock [63] (Figure 2). These studies, and many
521 others, demonstrate the applicability of utilizing various different therapeutic approaches to either
522 target the pathogenic bacteria or to neutralize their symptom-inflicting toxins [1]. In this relation,

523 there is a hypothetical benefit to targeting key epitopes of the toxins, such as their functional toxic
524 site, instead of targeting the bacteria themselves. Mutants that are able to escape therapeutic
525 intervention are known to evolve for many pathogenic bacteria [2,64]. However, from an evolutionary
526 perspective, it seems less likely for toxins to undergo mutations in their functional site that allow the
527 toxins to avoid recognition by a therapeutic antibody, while still retaining their toxic functionality,
528 than for bacterial escape mutants to evolve. More studies on bacterial and toxin evolution are needed,
529 though, to confirm such a hypothesis.

530

531 *2.3 Parasites*

532 Twelve of the 20 diseases recognized by the World Health Organization as category A neglected
533 tropical diseases are caused by parasites ([Table 1](#)) [3]. Additionally, although not included in the
534 category A list of neglected tropical diseases (alongside tuberculosis and HIV, due to substantial and
535 sustained international funding), malaria continues to claim a high number of human lives [65].
536 Although treatment options are available for some of these diseases, no approved antibody-based
537 therapies currently exist against these indications, and only few reports on therapeutic monoclonal
538 antibodies against parasitic pathogens exist in the scientific literature. Some efforts have, however,
539 been reported on the development of monoclonal IgG antibodies and single-domain antibodies with
540 therapeutic potential against human African trypanosomiasis [9,54]. The challenge with parasitic
541 infections is often their ability to evade the mammalian immune response by different mechanisms,
542 which include entering and multiplying within cells, shedding/varying their protein coat, and
543 modulating the immune response of their host [66–68]. For trypanosomiasis, as an example, the
544 parasite achieves this evasion by shedding its VSG coat proteins, followed by expression of other
545 VSG proteins with different antigenic disposition [69,70]. However, in the most recent study on

antibody-based therapeutics against trypanosomiasis, researchers circumvented this challenge. Here, the development was reported of an antibody-drug conjugate (ADC) targeting the trypanosome haptoglobin-haemoglobin receptor, which was shown to be efficacious against *Trypanosoma brucei* in a murine infection model [9] (Figure 3). In comparison, the malaria parasite avoids the human immune system by infecting red blood cells and hiding intracellularly. Nevertheless, in a recent study, the discovery of monoclonal human antibodies directed against the *Plasmodium falciparum* circumsporozoite protein was reported [71]. These antibodies were isolated from several human subjects that had been immunized with an attenuated Pf whole-sporozoite vaccine, and the antibodies were demonstrated to provide *in vivo* protection in two different mouse models of malaria infection [71].

In contrast to the therapeutic field, the field of parasite diagnostics has seen the development of a range of monoclonal antibodies against many of the neglected tropical diseases caused by parasites, including schistosomiasis [72], echinococcosis [73], taeniasis [74], leishmaniasis [75], lymphatic filariasis [76], and onchocerciasis [77]. These and other diagnostic developments may indeed help improve patient stratification, clinical diagnosis, and overall patient care within parasitology. However, monoclonal antibodies for diagnostic purposes seldom fulfill the requirements for therapeutic monoclonal antibodies that are used invasively, and a need thus remains for more research and development of antibody-based therapies against parasitic diseases.

564

2.4 Envenoming by animal bites and stings

Envenomings are caused by animals that possess venoms, which are mixtures of protein-based toxins. These toxins are typically evolved for predation purposes, although some animal venoms have also evolved to have a defensive function [12,78]. Classical signs of envenoming from venomous animals,

569 such as snakes, scorpions, spiders, bees, fish, centipedes, jellyfish, and other creatures may include
570 neurotoxicity, hemotoxicity, nephrotoxicity, cytotoxicity, myotoxicity, and other less common
571 toxicities. These toxicities may clinically manifest themselves as ptosis, flaccid paralysis,
572 coagulopathies, hemorrhage, necrosis, acute kidney injury, rhabdomyolysis, edema, blistering,
573 inflammation, pain, and shock [12,13,79,80]. Venoms may also induce anaphylaxis due to their
574 proteinaceous and sometimes immunogenic dispositions [81–83]. The clinical manifestations of
575 envenomings caused by venomous animals may share some similarities with the clinical
576 manifestations caused by infectious diseases. However, there are several essential differences
577 between these pathophysiologies that have a large impact on what therapeutic strategies may be viable
578 for treating envenoming. Five highly important differences exist:

579 Firstly, there is no incubation period for amplification of the disease-causing agent, as the entire
580 dose of venom is injected instantaneously. There may, however, be a delay in pathogenesis, if the
581 venom toxins are systemically-acting and need to leave the bite/sting site to exert their toxic actions
582 (e.g. neurotoxins and hemotoxins), known as the depot effect. This has the implication that
583 intervention is exceptionally urgently needed, and that envenomings must be treated as critical
584 emergencies. Secondly, the toxin loads from envenomings by larger venomous animals are delivered
585 immediately and can be pharmacologically enormous. As an example, larger snakes can deliver up
586 to 2.5 gram (dry weight) of venom toxins with molecular weights of 5-100 kDa. This has the
587 implication that exceptionally high amounts of antitoxin (up to 15+ gram dry weight antibody protein)
588 may be needed for successful treatment [84]. This further has the consequence that cost of
589 manufacture has a high impact on what therapeutic modalities are economically feasible, as most
590 animal envenomings occur in poor communities in the rural tropics [17,85,86]. Thirdly, animal
591 venoms are highly complex, comprising tens to hundreds of different toxins. This has the implication
592 that mixtures of antitoxins are likely to be needed against most envenomings, and that antivenom

593 developers should carefully consider which venom components are medically important to neutralize,
594 and which are not, to minimize the complexity of the therapeutic intervention [87–89]. Fourthly,
595 envenomings are not infectious and therefore only carry a risk to the envenomed victim. This has the
596 implication that the utility of vaccination is limited, if at all existent, as there is no benefit of herd
597 immunity and no risk of uncontrollable epidemic outbreaks. Finally, animals evolve significantly
598 slower than microorganisms and viruses. This has the fortunate implication that medically relevant
599 toxin mutations and the development of resistance against treatment is unlikely to occur for thousands
600 of years.

601 Animal envenomings are currently still treated using polyclonal antibodies derived from the
602 plasma of hyper-immunized animals (horses, sheep, donkeys, and occasionally rabbits)
603 [12,13,79,90]. When properly manufactured, these life-saving medicines are effective in neutralizing
604 animal venoms. However, due to their heterologous nature, they have a propensity to cause
605 immunological reactions in human recipients [90]. To circumvent this challenge of immunogenicity,
606 and to improve other therapeutic properties, such as enhancing efficacy and reducing batch-to-batch
607 variation, researchers worldwide have started to embrace different antibody technologies with the
608 goal of developing recombinant antivenoms [89,91,92]. Recently, the discovery of the first fully
609 human oligoclonal IgGs against animal toxins was reported [93]. Here, it was demonstrated that
610 phage display selection employing naïve human antibody libraries could be exploited to discover
611 mixtures of human monoclonal IgGs that could abrogate dendrotoxin-mediated neurotoxicity of black
612 mamba (*Dendroaspis polylepis*) whole venom *in vivo* [93]. Also, other researchers have recently
613 reported the discovery of human monoclonal scFvs that can broadly neutralize toxins from multiple
614 scorpion species [94,95], as well as it has been shown that experimental antivenoms based on
615 nanobodies and nanobody-constructs can be used to effectively neutralize snake toxins and venoms
616 [96,97]. These and other recent results in antibody discovery within animal envenomings [90,98]

617 (Figure 4) now warrant further development efforts within envenoming therapy. However, the path
618 towards the approval and marketing of fundamentally novel antivenom products is likely to be long,
619 complicated, and require significant support and international collaboration [14,84], as the field of
620 next-generation envenoming therapeutics is still in its infancy.

621

622 2.5 Mushroom poisonings

623 Mushroom poisonings occur across tropical, subtropical, and temperate climates, but share some
624 similar characteristics with animal envenomings and neglected tropical diseases and have thus been
625 included in this review. About 5000 different species of mushrooms exist, with about 50 species being
626 poisonous to humans [15]. In contrast to venom toxins that due to their size and proteinaceous nature
627 are unable to be absorbed in the gastrointestinal tract, mushroom poisons comprise small
628 oligopeptidic toxins that can be readily absorbed in the gastrointestinal tract and are thus toxic when
629 ingested [91]. Most of the mushroom species involved in lethal poisonings are found in the genus
630 *Amanita*, which produces amatoxins, phallotoxins, and virotoxins [99]. Of these toxins, the amatoxins
631 are of highest medical concern, and they retain their potent hepatotoxicity even upon boiling. Their
632 mode of action involves inhibition of the RNA polymerase II, responsible for transcription of mRNA
633 [100]. Even today, the treatment options for mushroom poisonings caused by amatoxins remain
634 inadequate and severe cases of poisoning can necessitate liver transplantation [101–105]. Despite
635 their small size, amatoxins may invoke an immune response, and researchers have reported the
636 development of both IgG and Fab-based monoclonal antibodies using hybridoma technology [106].
637 Interestingly, when these two different antibody formats were assessed for their ability to neutralize
638 amatoxins in a murine model, it was discovered that instead of neutralizing the toxins, both antibody
639 types enhanced toxicity. Particularly, the Fab antibody was shown to dramatically enhance toxicity

640 50-fold, as the Fab antibody increased accumulation of the toxin in the kidneys, causing major
641 nephrotoxicity [106]. More than a decade ago, it was reported that attempts to use antibody-based
642 therapies against mushroom poisonings had not been successful [15], and to the best of my knowledge
643 this finding remains the status quo. It is thus uncertain whether effective antibody-based therapeutics
644 may ever find their way into the field of mushroom poisoning, however, the possibility cannot be
645 entirely excluded. Some of the many recently developed advanced antibody formats, such as
646 bispecifics and novel binding protein scaffolds, may offer improved or entirely different mechanisms
647 of action and pharmacokinetics that might find their utility in mushroom poisoning therapy.

648

649 **3. Conclusion**

650 A number of therapies against infectious diseases based on monoclonal antibodies have found their
651 way to the market in recent years [18,44,46–49]. These approved therapies all fall within the areas of
652 bacterial and viral infections [1,8]. In contrast, the development of therapeutic monoclonal antibodies
653 against parasitic diseases, animal envenomings, and mushroom poisonings is far behind, although
654 recent reports within trypanosomiasis therapy and recombinant antivenoms against snakebite and
655 scorpion envenoming demonstrate potential and utility of employing antibody technologies in these
656 fields [9,93,95]. The reason for the disparity in the development stages between these two groups
657 (bacterial and viral infectious diseases vs. parasitic diseases, animal envenomings, and mushroom
658 poisonings) may possibly be found in their potential for causing uncontrollable epidemic outbreaks
659 coupled to the limited commercial prospects that may exist for the latter group of diseases.

660

661 **4. Expert opinion**

662 Public interest and increased institutional focus on the United Nation's Sustainable Development
663 Goals has brought renewed attention to the global challenges for humankind. Combined with the
664 rapid development of antibody discovery and manufacturing technologies, this may create an opening
665 for bringing antibody-based therapies against neglected tropical diseases and other infectious diseases
666 to life. The antibody developer may piggy-back on the many scientific and technological
667 achievements from the fields of oncology and autoimmune diseases [85], which can be exploited to
668 reap the many technologically low-hanging fruits that exist in the field of neglected tropical diseases
669 due to the lack of prior art. This creates an opportunity for the academic scientist who is evaluated
670 more on his or her ability to perform and publish high impact science than on his or her ability to
671 drive scientifically incremental, yet profitable, development. Specifically, the field of antibody-based
672 therapies against neglected tropical diseases may constitute a possibility for countries in the
673 developing tropics to establish scientific environments and build research capacity and excellence in
674 "blue ocean" fields, allowing them to become global leaders in certain scientific areas that are not
675 already dominated by countries and institutions in the US, Europe, or elsewhere. Neglected tropical
676 diseases and other infectious diseases, as well as envenomings and poisonings caused by animals and
677 mushrooms, are in many ways fundamentally different than oncology and autoimmune diseases with
678 endogenous disease targets. These differences include the therapeutic targets being exogenous and
679 numerous in numbers for given indications (due to hypermutability and presence of multitudes of
680 toxins), as well as the target markets being less profitable and difficult to enter. Antibody discoverers
681 within these fields may therefore be forced to be creative and develop entirely new antibody-based
682 therapeutic approaches and pharmacological mechanisms of action. In turn, this may open up for the
683 possibility of treating currently untreatable diseases or developing next-generation therapies of
684 unprecedented efficacy in fields with suboptimal treatment options. The fields of neglected tropical
685 diseases, other infectious diseases, and intoxications may even represent a scientific Eldorado for

686 areas such as understanding and designing cross-reactivity for monoclonal antibodies [107], use of
687 oligoclonal antibody cocktails for multi-target neutralization [1,17,108], novel immunization
688 approaches [109], targeting of evasive pathogens [9,10], and exploitation of novel therapeutic
689 mechanisms of action [41]. Such potential developments will likely be further catalyzed by advances
690 in antibody production technologies that may enable low cost of antibody manufacture [17,110] and,
691 in turn, better affordability of antibody-based therapies on a global scale. Despite their currently
692 overlooked status, neglected tropical diseases, other infectious diseases, and intoxications may one
693 day find themselves in the limelight of antibody developers, who may recognize the potential for
694 improving therapies for victims worldwide, while simultaneously experimenting with innovative
695 antibody-based approaches and elucidating fundamentally novel antibody properties.

696

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969

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977 **Author contributions**

978 The author was singly involved in all aspect of preparing the manuscript.

979

980 **Conflict of interest**

981 The author declares no conflict of interest.

982

983 **Table 1. The 20 diseases listed as Category A Neglected Tropical Diseases by the World Health**
984 **Organization.**

Viral diseases	Bacterial diseases	Parasitic diseases	Other
Dengue	Buruli ulcer	Chagas disease	Snakebite envenoming
Chikungunya	Leprosy	Dracunculiasis	
Rabies	Mycetoma*	Echinococcosis	
	Trachoma	Foodborne trematodiasis	
	Yaws	Human African trypanosomiasis	
		Leishmaniasis	
		Lymphatic filariasis	
		Onchocerciasis	
		Scabies	
		Schistosomiasis	
		Soil-transmitted helminths	
		Taeniasis and cysticercosis	

985 *It is unknown whether mycetoma is caused by bacterial or fungal infection.

986

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988

989 **Figure legends**

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991

992 **Figure 1**

993 Conceptual overview of different monoclonal antibody formats that have been reported against
994 selected viral indications. **A)** IgG-like antibody discovered against Marburg virus. **B)** V_HH antibody
995 fragment discovered against rotavirus. **C)** IgG antibodies discovered against Dengue and Zika (only
996 one example shown). **D)** IgG-like antibodies discovered against Sudan and Zaire Ebola virus (only
997 one example shown). **E)** IgG antibodies discovered against Hendra and Nipah virus (only one
998 example shown). **F)** IgA and IgG antibodies discovered against norovirus.

999

1000

1001 **Figure 2**

1002 Conceptual and schematic representation of a bacterial cell with a zoom-in on the cell wall. Different
 1003 antibody formats (scFv, IgG, and IgM) targeting various therapeutic targets, including
 1004 lipopolysaccharides and bacterial toxins are depicted.

1005

1006

1007 **Figure 3**

1008 Schematic representation of the mechanism of action of how an antibody drug conjugate (ADC)
 1009 targeting a *Trypanosoma brucei* parasite. **LEFT:** Upon binding to the haptoglobin-haemoglobin
 1010 receptor (HpHbR) on the surface of the parasite, the ADC is internalized, whereby the
 1011 pyrrolobenzodiazepine (PBD) toxin payload is liberated to exert its toxic action, ultimately leading to
 1012 death of the parasite. **RIGHT:** The normal function of the HpHbR is to initiate internalization of the
 1013 haptoglobin-hemoglobin complex for scavenging of heme from the environment, which is further
 1014 utilized for generation of intracellular hemoproteins.

1015

1016

1017 **Figure 4**

1018 Conceptual and schematic representation of selected monoclonal antibody formats that have been
 1019 discovered against toxins from venomous animals. **A)** Human IgG, scFv, and V_HH antibodies are
 1020 shown binding to selected snake toxins (cytotoxin-1 (5NQ4), dendrotoxin 1 (1DEM), and alpha-
 1021 cobratoxin (2CTX)). **B)** scFv, V_HH, and divalent V_HH construct antibodies are shown binding to
 1022 selected scorpion toxins (AahII (1PTX), Cn2 (1CN2), and Css2 (2LI7)). **C)** Murine IgG antibodies
 1023 are shown binding to a selected spider toxin (phospholipase D, (4Q6X)). **D)** scFv antibodies are
 1024 shown binding to selected bee toxins (mellitin (2MLT) and bee venom phospholipase A₂ (1POC)).
 1025 PDB IDs were obtained from the Protein Data Bank (<https://www.rcsb.org>).