Neurobiology of Disease 130 (2019) 104504

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Editorial

A brief history of antibody-based therapy

ARTICLE INFO

Keywords:
Vaccination
Passive immunization
Active immunization
Cancer
Infectious diseases
Alzheimer's disease
Parkinson's disease
Huntington's disease

ABSTRACT

Active and passive immunization have been used to treat human disease for hundreds of years and improvements in technology and knowledge is only increasing the number of therapeutic applications. The current and future use of immunization to treat neurodegenerative diseases are briefly described herein to serve as an introduction to this special issue.

The very first documented use of immunization arose in the 1700's and culminated in the discovery of the vaccine for small pox (Riedel, 2005). It involved administration of a less virulent form of the small pox virus (Riedel, 2005) to allow the immune system to develop antibodies against the pathogen. This initial foray into antibody therapy was a form of "active" immunization which remained the only described approach until the late 1800's (Graham and Ambrosino, 2015) (Fig. 1). Active immunization entails that the individual is infected with an artificial, attenuated or dead immunogen in order to stimulate the immune system to develop antibodies against a pathogen which can then be used to prevent infection with a more virulent form of the virus, toxin or bacteria. In contrast, passive immunization refers to the administration of pre-formed antibodies that can directly bind the disease-causing agent (McDonagh, 1966). Historically, active immunization has been most commonly used in the prevention of infectious diseases, while passive immunization has been favoured when symptoms were already present. Prior to broad spread vaccination campaigns, passive and active immunizations were often employed in tandem. Passive immunization was given at the first signs of disease to assist in fighting off infection, while attenuated or live infectious agents were injected to induce long-term protection. While the terms have not changed with time, the technology surrounding the production of vaccines and antibodies has significantly evolved. Although active immunization follows much of the same method as initially established, sub-unit vaccines can now be designed, in certain circumstances, to mimic the structure of the toxic agent obviating the need to inject live or attenuated pathogens, which reduces the risk of the immunogen regaining virulence (Moyle, 2015). Sub-unit vaccines tend to result in weaker immune responses and are generally accompanied by immune activating substances known as adjuvants (Apostolico Jde et al., 2016). Newer iterations of active immunizations are refining the immunogens and the cell populations that are activated to increase specificity and thereby reduce side-effects (Moyle, 2015). Historically, standard practice for passive immunization was to find a patient whom had recently recovered from the disease of interest, collect blood and purify gamma globulin, the fraction that contains circulating antibodies (McDonagh, 1966). When convalescent individuals were unavailable, gamma globulin would be collected from healthy subjects, human placentas or from animals exposed to the disease (McDonagh, 1966). Since human serum was often unobtainable, antibodies from other mammalian species exposed to the infectious agent were commonly used, although this clearly increased the risk of serious adverse events (Rubbo and Suri, 1962). From 1975 to 1985, major technological advances allowed for *in vitro* production of large quantities of monoclonal antibodies (Fig. 1). This included the fusion of myeloma cell lines with splenocytes from a mouse exposed to the antigen of interest, the development of a phage selection system where the viral genome was modified such that the phage would externally express the desired antigen and the production of humanized antibodies (Fig. 1). This virus could then be used to generate the antibody by injection into a host (Kaplon and Reichert, 2019; Smith, 1985), while expression systems, such as the fused myeloma cells, allowed the production of large quantities of specific antibodies (Kohler and Milstein, 1975) and development of humanized antibodies reduced the risk of side-effects.

Although infectious diseases resulted in the development of active and passive immunization, both of these immunomodulatory therapies have been extensively explored for other indications, including cancer and immune disorders. Indeed, oncology has one of the highest numbers of approved antibody therapies with more than thirty available or under regulatory review as of 2018 (Carter and Lazar, 2018). This number will continue to expand as an additional thirty compounds are in late stage clinical trials (Kaplon and Reichert, 2019). The first reports of research into the efficacy of passive immunization for cancer arose around the same time as passive immunization for infectious diseases using similar approaches (Fig. 1). Antibodies were generally obtained by injecting tumours into animals, purifying antibodies and injecting this fraction into the person suffering from this disease (Currie, 1972). The experiments related to active immunization of cancer began in the

https://doi.org/10.1016/j.nbd.2019.104504
Received 10 May 2019; Received in revised form 11 June 2019
Available online 16 June 2019

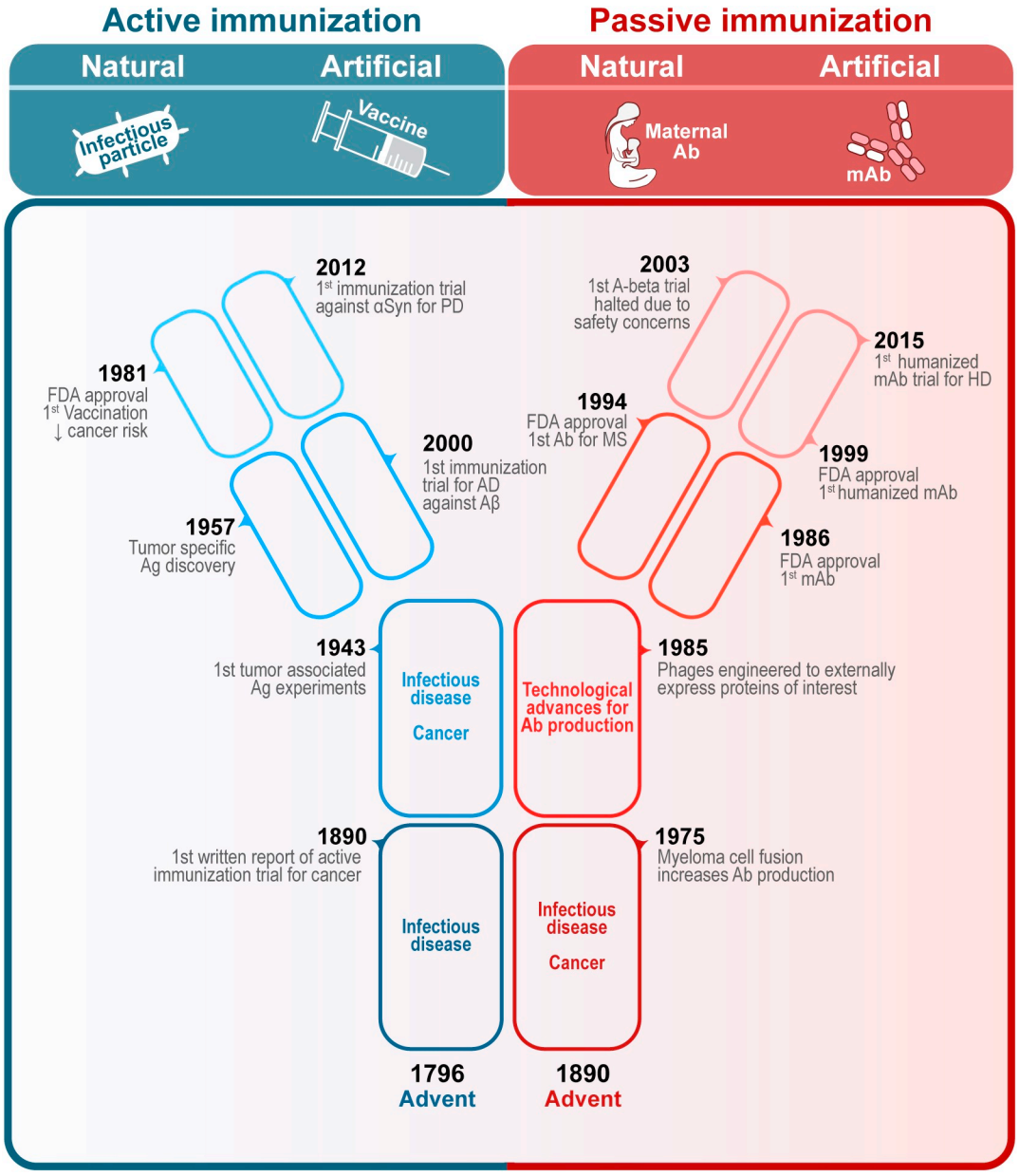

Fig. 1. Timeline of antibody therapy. Abbreviations: Ab; antibody, Aβ; Amyloid-β, Ag; antigen, αSyn; α-Synuclein, FDA; Food and Drug Administration, HD; Huntington's disease, mAb; monoclonal antibody, MS; Multiple Sclerosis, PD; Parkinson's disease.

early 1900's and generally involved direct injection of autologous or allogenic tumours into patients (Currie, 1972). Both active and passive methods were almost invariably ineffective but they regained popularity in the 1950's when strong evidence for the presence of cancer specific antigens was published (Southam, 1960) (Fig. 1). Despite this advancement and the many clinical trials, only two vaccines have been approved as therapies for cancer (Griesenauer and Kinch, 2017). For passive immunization, an improved understanding of cancer biology and better methods of antibody production have greatly diversified the available options which are much more targeted and clinically effective. Since the first approval of antibody therapy by the FDA in 1986, the development of antibodies steadily increased until 2013, after which the number of approvals reached an all-time high (Kaplon and Reichert, 2019) (Fig. 2a). The first approved antibody, Murmomanab, targeted CD3 leading to the inactivation and removal of T-cells within hours of administration (Todd and Brogden, 1989). The approval of Murmomanab represented the start of modern passive immunization as well as the shift from treatment of infectious disease to non-traditional targets.

A new focus of antibody therapy has been on neurological conditions. The first evidence for active and passive immunization as a therapy for neurodegenerative disorders emerged from a series of preclinical studies performed in mouse models of Alzheimer's disease (AD) in the late '90s and early 2000s (Bard et al., 2000; Janus et al., 2000; Schenk et al., 1999). The first of these studies demonstrated a near complete prevention of Aβ plaques and AD-related CNS pathology after vaccination, while subsequent studies showed improved cognition (Janus et al., 2000) and reduced Aβ accumulation in the brain following peripheral antibody administration (Bard et al., 2000). The early preclinical studies quickly led to clinical trials of active, and later passive, immunization in AD (Bayer et al., 2005; Salloway et al., 2009). Although immunization against Aβ as a therapy for AD was the earliest example of targeting neurodegenerative disorders, its history is far from universally positive. Early attempts with both modalities resulted in a

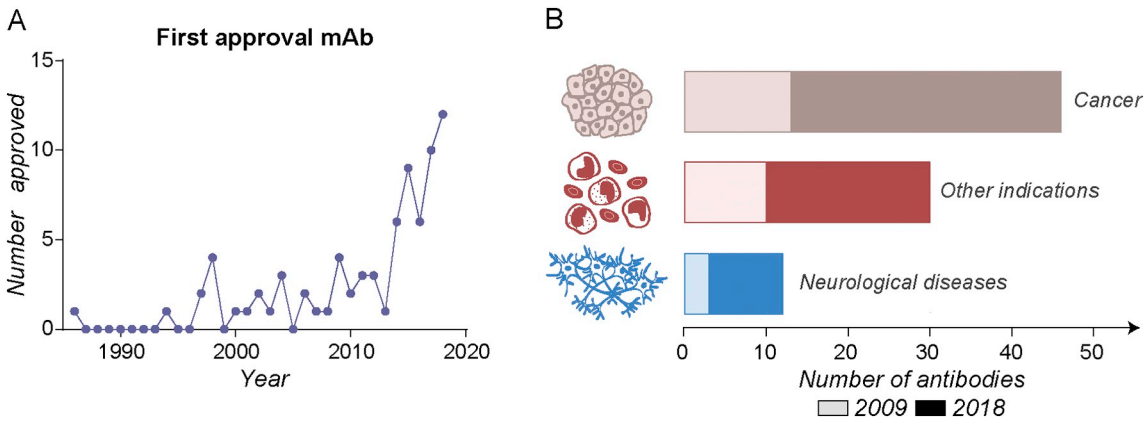

Fig. 2. The increasing popularity of antibody therapy. The number of antibody-based therapies approved by the FDA from 1986 until 2018 (A). The number of ongoing phase III clinical trials financed by pharmaceutical companies in 2009 and 2018 comparing those for cancer, neurological and other indications (B). Abbreviations: mAb; monoclonal antibody.

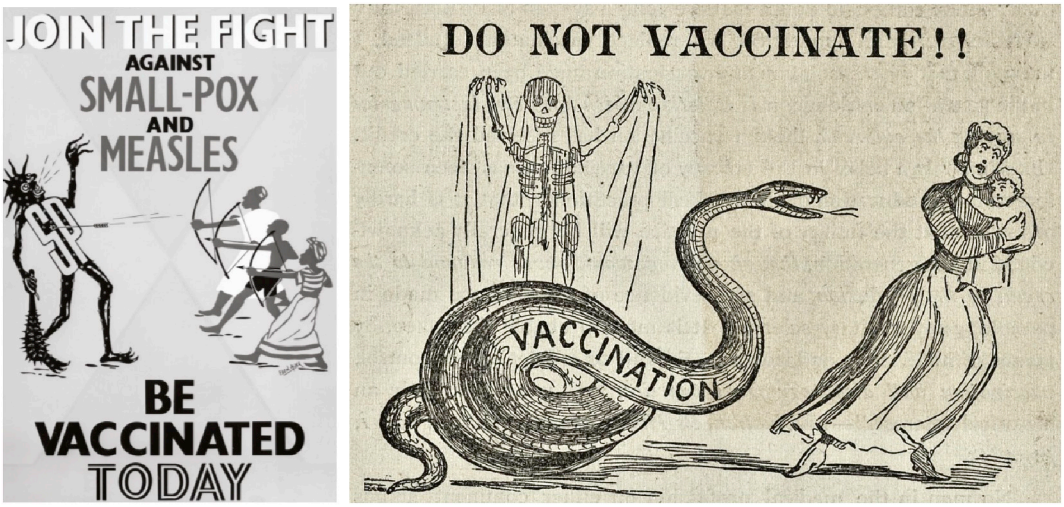

Fig. 3. Vintage advertisements. (Left) Image taken from Pinterest, (right) image from an anti-vaccination publication from 1892 - The Historical Medical Library of The College of Physicians of Philadelphia.

heightened risk of adverse events, including meningoencephalitis, which ultimately led to halted trials (Gilman et al., 2005; Orgogozo et al., 2003). Since then, safety has been improved and phase III trials are ongoing for both passive (Kaplon and Reichert, 2018) and active immunization (Yang and Xiao, 2015). For active immunization, positive results came out of a recent phase I trial, which showed immunogenicity against Aβ, increased plasma serum Aβ concentration and early indications of benefits on cognition in mildAD patients (Wang et al., 2017). Passive immunization trials have been less successful with two of three ongoing phase III trials having been aborted in 2019 for lack of efficacy. Despite the failures and challenges, some interesting successes have benefited other fields. Attempts to target cell death in AD by increasing nerve growth factor led to the development of Tanezumab, an antibody-based therapy that is now in phase III clinical trials with documented positive results for reducing chronic pain (Hefti, 2019).

Building on this, active and passive immunization have now began to be evaluated for Huntington's disease (HD) (Denis et al., 2019), Parkinson's disease (PD) (Savitt and Jankovic, 2019) and prion disorders (Burchell and Panegyres, 2016). Since 2010, the number of phase III clinical trials using monoclonal antibodies to treat neurological disorders has increased at least five-fold (Fig. 2b) (Kaplon and Reichert, 2019; Reichert, 2010). The seven antibodies currently in phase III trials are targeted against immune factors, nerve growth factor and Aβ, demonstrating the diversity of available targets for immunotherapy in neurological disorders (Kaplon and Reichert, 2019). Current candidates include immune modulators such as semaphorin 5D in HD (Denis et al., 2019), but the most common targets are the pathological proteins associated with the disease. Given the recent evidence related to the prion-like properties of these proteins, this trend seems only likely to increase given the analogous nature of pathological proteins with other infectious particles. Indeed, a surge of publications have now consistently reported that the spread of abnormal proteins such as amyloid-β, Tau and α-synuclein (Jucker and Walker, 2013; Soto, 2012) is an underlying pathogenic process in a number of neurodegenerative disorders, including genetic disorders such as Amyotrophic lateral sclerosis (Meyer et al., 2014) and HD (Cicchetti et al., 2014; Masnata et al., 2019). Accordingly, there are multiple active and passive immunization clinical trials ongoing in PD and tauopathies to assess benefits of targeting α-synuclein (Zella et al., 2018) and tau (Medina, 2018; Zella et al., 2018). In addition to multiple targets, several novel forms of immunotherapy for both passive and active immunization are also beginning to surface. For passive immunization, important innovations include intrabodies and nanobodies which use very small cell permeable antibodies (Messer and Joshi, 2013). For active immunization, new methodologies include DNA vaccinations

(Okura and Matsumoto, 2008) and activation of specific patient cell populations *in vitro* prior to administration into the body (Brezovakova et al., 2018). This continued research, which is highlighted in this special issue, illustrates the most recent discoveries which will allow for the development of more effective vaccines, antibodies and antibody conjugates in the context of neurodegenerative disorders.

Immunizations and antibody-based therapies have been part of medical practice for more than two centuries and they have led to critical improvements in human healthcare. Despite the favorable outcomes, vaccination has raised serious concerns and provoked, on occasions, hostile criticism. While it may seem as if the anti-vaccination movement is a modern invention, publicity describing the dangers of vaccination appeared as early as advertisements for this approach (Fig. 3). Indeed, the perceived risk of vaccination is high, considering that it involves, at times, injecting a disease-causing agent into the body. Improvements in technology have greatly reduced the hazards associated with such practice but vaccination with live or attenuated pathogens still carries a chance of infection (Moyle, 2015). Whether the discussed improvements will be able to further mitigate risk is yet to be seen, however, if immunization could be developed to the point we have reached for infectious disease, perhaps neurodegenerative disease may also become a story from the past.

Declaration of Competing Interests

The authors declare no competing interests.

Acknowledgments

FC is a recipient of a Researcher Chair from the Fonds de Recherche du Québec en Santé (FRSQ) providing salary support and operating funds and MA holds a post-doctoral fellowship from the same agency. The authors are very grateful to Ms. Hélèna L. Denis for producing the artwork included in this manuscript.

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