HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 2, e2028517 (3 pages)
https://doi.org/10.1080/21645515.2022.2028517

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Special focus issue: passive immunization

Larry Zeitlin[a] and Richard A. Cone[b]

[a]Mapp Biopharmaceutical Inc and ZabBio, Inc; [b]The Johns Hopkins University and Mucommune, Inc

ARTICLE HISTORY Received 22 December 2021; Accepted 7 January 2022

Introduction

Section 1. Systemic passive immunization

Larry Zeitlin, Ph.D.

Antibodies (Abs) comprise roughly 1.5% of our blood.[1] This is a very significant metabolic commitment and underscores the importance of these molecules for human survival. An adaptive antibody response first appeared in cartilaginous fish 400 million years ago and this defense mechanism continued to evolve within this branch of the evolutionary tree.[2] With the appearance of mammals some 200 million years later, antibodies became important not just for protecting the host, but also for protecting newborns via passive immunization with Abs in the mother's milk. Nursing provides newborns with Abs elicited in the mother – *by the very pathogenic threats present in the local environment* – to protect them while their immune systems mature. Another 200 million years later, von Behring and Kitasato[3] described the first experimental use of passive immunization in 1890 and began successfully treating diphtheria patients with convalescent plasma in 1894. Passive immunization with polyclonal antibody (*e.g.* human convalescent plasma or plasma from immunized animals) became a common clinical tool during the first third of the 20th century.[4] Due to adverse reactions in recipients of plasma from non-human species ("serum sickness"), and the advent of the antibiotic era, passive immunization with serum largely fell out of favor clinically, especially for bacterial infections; however convalescent plasma continues to be used for pathogens such as Junin virus[5] and has been evaluated during outbreaks of Ebola virus[6,7] and SARS-CoV-2.[8] Hyper immunoglobulin (HIG), which is high titer polyclonal Ab purified from convalescent or immunized donors, offers a superior safety profile compared to convalescent plasma and forms the basis of 20 FDA-approved products.[9]

In this Special Focus Issue, Gayatri Mukherjee and colleagues review the history of plasma therapy and its evolution to passive immunization with purified polyclonal preparations such as intravenous immunoglobulin (IVIG) prepared from human donors.[10]

Similarly, Laura Saward and colleagues review clinical use of polyclonal antibody products,[9] and discuss experiences with the use of HIG for emerging public health threats, drawing on Zika, Influenza, and SARS-CoV-2 as examples.

A relatively new, alternative source of HIG relies on the use of transgenic cows that can produce human polyclonal Abs;[11] Sean Whelan and colleagues describe the use of this technology for generating HIG with high SARS-CoV-2 titers.[12]

In contrast to the polyclonal Ab approaches to passive immunization in which a diverse set of Abs are used, with the invention of monoclonal antibody (mAb) technology by Kohler and Milstein,[13] it became possible to develop products with highly specific, single mAb components. The first mAb pharmaceutical product was approved by the FDA in 1985 (OKT3 to reduce acute rejection of transplanted organs,[14]) and the first anti-infectious disease mAb (palivizumab; for immunoprophylaxis of respiratory syncytial virus infection in high risk neonates) was licensed in 1998.[15] Since then, the 21st century has seen an explosion of licensed mAbs, primarily for the treatment of cancers and autoimmune disorders, but with an emerging market for mAbs for infectious diseases.

Global accessibility to affordable mAb drugs remains a large public health problem.[16] Kevin Whaley and myself review some of the challenges with meeting manufacturing scales in order to ensure global access to future potential anti-infective mAbs.[17]

While antibiotics led to clinicians moving away from antibody therapy in the 1930s, the growing threat of antibiotic resistance has spurred new efforts to develop anti-bacterial mAbs for clinical use. This topic is reviewed by Vu Truong and colleagues.[18]

In addition to the high specificity mAbs offer, recent work has highlighted the capability of customizing the mechanism of action(s) by a given mAb: whether it is pure steric hindrance of a binding or fusion event, or recruitment/interaction with other components of the immune system (*e.g.* complement, macrophages, NK cells, etc.). Bronwyn Gunn and Shuangyi Bai provide a review of the growing knowledge base for optimizing the functionality of mAbs for passive immunization.[19]

Finally, while the presence of antibodies systemically is critical once a pathogen has breached the skin or mucosa, passive immunization of mucosal surfaces is an often overlooked strategy for minimizing infectious pathogen burden and even, in some cases, excluding pathogens entirely. Richard Cone's section of this Special Focus issue covers these approaches, which he introduces below.

CONTACT Larry Zeitlin larry.zeitlin@mappbio.com Mapp Biopharmaceutical Inc and ZabBio, Inc

Section 2. Our frontline immune system: protection by antibodies secreted into, or directly applied to mucus surfaces

Richard Cone, Ph.D.

Mucosal, as distinct from systemic immune functions, have long been protecting young offspring by maternal IgY antibodies delivered in egg by yolk in the case of birds, and maternal Ig in milk in the case of mammals. Colostrum, the initial dose of mammalian milk, is essentially a paste of a combination of antibodies the mother has developed by living in the same environment into which she delivers her newborn. Not surprisingly, mucosal delivery of antibodies has proven to be robustly protective in numerous animal studies.[20] But to date virtually all monoclonal antibodies (mAbs) for disease prevention and infection therapy are delivered systemically. This is evident from the numerous monoclonal antibody drugs now on the market. Why are mAbs to be delivered to mucosal surfaces virtually absent from the market? And why have the protective actions of antibodies in mucus been so little studied compared to the protective actions of systemic antibodies?

As has long been known, *most* antibodies produced by our immune systems are secreted into mucus instead of into blood and lymph. Unlike the intensively studied actions of systemic antibodies, the actions of secreted antibodies in mucus coats have been less studied. Part of the reason is it is comparatively difficult to obtain fresh unmodified mucus secretions, and mucus is a sticky and difficult substance to study compared to blood. In contrast to the systemic immune system, that only infrequently encounters pathogens and toxins, the mucosal system must monitor and keep changing the array of antibodies it secretes to protect against the high influx, and changing arrays, of pathogens and toxins that contact mucosal surfaces. Perhaps this is why the mucosal system typically exhibits relatively short memory times, and has been more challenging to develop long lasting vaccines; the outstanding exception is the long-lasting and highly effective polio vaccine.

How do antibodies protect against infections in mucus coats that are constantly being secreted and shed? Unless an infection is present, there are few if any active immune cells present, thus secreted antibodies must function without the help of immune cells. It has long been thought secreted antibodies act by neutralizing pathogens, "excluding" pathogens, blocking attachment sites, or by aggregating pathogens into clusters that cannot penetrate the mucus coat. But there is a little recognized and more potent mechanism they perform in mucus; they trap (immobilize) individual pathogens in the mucus gel. Pathogens and toxins trapped in mucus in the GI tract are shed in feces, and others are shed in mucus from the urethra, vagina, lungs, nose and mouth. Pathogens and toxins trapped in tears, respiratory mucus, and nasopharyngeal mucus are transported to the GI tract, where they can be inactivated by gastric acidity and/or digested and shed in feces.

Over 50 years ago Kremer and Jager[21,22] discovered that anti-sperm antibodies in cervico-vaginal mucus of infertile women can trap sperm even with vigorously shaking flagella. They showed that the anti-sperm antibodies did not kill or inactivate sperm since the trapped sperm continue to shake in place for many hours until they die. They termed this trapping action the "shaking phenomenon." This potent trapping function may also occur in the *systemic* immune system in gel-like intercellular spaces but has been little studied.

As Jiri Mestecky discusses in this Special Focus Issue, the mucosal and systemic immune systems are largely independent, and most antibodies delivered systemically fail to be secreted into and adequately protect mucosal surfaces.[23] Mucosal antibodies are produced locally in mucosal epithelia and transported *locally* through epithelial cells to the mucus coat by pIgR receptors for sIgA and sIgM, and FcRn receptors for IgG. They are also delivered by shed epithelial cells.

Deborah Anderson discusses the development of vaginal delivery of mAbs for protecting against STDs and conception.[24] With her coworkers, she is developing a convenient "on demand" contraceptive in a vaginally inserted, "Postage Stamp" film. Along with human contraceptive antibody, HCA, the film can also deliver mAbs against HIV and HSV, a multi-protection product.

Samuel Lai and his colleagues have recently shown that by trapping highly motile bacteria, as well as viral particles, in mucus gel, antibodies can be more potent than by otherwise neutralizing them.[25] In this Special Focus Issue he reviews the ability of *non*-neutralizing anti-HSV mAbs to protect mice against vaginal transmission of genital herpes infection, and of anti-LPS mAbs to trap otherwise vigorously motile bacteria, *Salmonella typhimurium*, in mouse intestinal mucus coat *in situ*.[26]

The trapping mechanism is both potent and elegant, but has been little studied in part because it requires working with intact mucus gels: Antibodies diffuse rapidly, almost unhindered through intact mucus gels,[27] and thus can rapidly reach and attach to the surfaces of the pathogens to which they bind specifically and tightly by means of Fab moieties. The effector function is performed by the Fc moiety to make transient, low-affinity bonds to the mucus fibers. In this way an array of outward facing Fc tails can make sufficient low-affinity bonds to form high-avidity adhesion to the gel. The critical feature of this trapping mechanism is that the mucus coat must be an intact visco-elastic gel. If the gel is diluted it becomes runny, less elastic, and sperm, bacteria, and even viruses can regain translational motility. Normal mucus is visco-elastic with optimal trapping ability while retaining good lubrication characteristics. In the respiratory tract if mucus becomes too runny, less elastic, it cannot be expelled by the ciliary "escalator" and pools in the lungs. Similarly, if mucus loses its elasticity it can run from the nose, and the vagina (a symptom of bacterial vaginosis) abrogating protection by trapping.

Anthony Hickey reviews recent advances with vibrating screen nebulizers for effective delivery of mAbs deep into the lungs for rapid immune therapy and protection against respiratory infections.[28] The initial trials are aimed at therapy for Respiratory Syncytial Virus, RSV. This method may become especially important for helping speed the end of the Covid-19 pandemic.

Nicholas Mantis discusses the use of transgenic mice to test passive immune protection against GI tract pathogens, and methods for efficient delivery of sIgA to the gut.[29] As has long been known to mucosal immunologists, most bacteria in the gut are restricted to the luminal surface of the mucus coat by the apparent viscidity (stickiness) of mucus and now as

revealed by the trapping actions of secreted antibodies. The predominant antibody in GI tract secretions, sIgA, is especially well designed for trapping in mucus gel since the pair of Fc moieties as well as the SC moiety increase the dwell-time of the antibody with the mucus gel.[30]

An overall aim of this section of the Special Focus Issue is to highlight the great potential for rapid advances in mucosal therapy and prophylaxis now that monoclonal antibodies have become significantly less costly to manufacture.[17]

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

1. Gonzalez-Quintela A, Alende R, Gude F, Campos J, Rey J, Meijide LM, Fernandez-Merino C, Vidal C. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. Clin Exp Immunol. 2008;151(1):42–50. doi:10.1111/j.1365-2249.2007.03545.x.
2. Feige MJ, Grawert MA, Marcinowski M, Hennig J, Behnke J, Auslander D, Herold EM, Peschek J, Castro CD, Flajnik M, et al. The structural analysis of shark IgNAR antibodies reveals evolutionary principles of immunoglobulins. Proc Natl Acad Sci U S A. 2014;111(22):8155–60. doi:10.1073/pnas.1321502111.
3. von Behring E, Kitasato S. The mechanism of diphtheria immunity and tetanus immunity in animals. 1890. Mol Immunol. 1991;28:1317, 1319–1320.
4. Casadevall A, Dadachova E, Pirofski LA. Passive antibody therapy for infectious diseases. Nat Rev Microbiol. 2004;2(9):695–703. doi:10.1038/nrmicro974.
5. Enria DA, Briggiler AM, Fernandez NJ, Levis SC, Maiztegui JI. Importance of dose of neutralising antibodies in treatment of Argentine haemorrhagic fever with immune plasma. Lancet. 1984;2(8397):255–56. doi:10.1016/S0140-6736(84)90299-X.
6. Lee JS, Adhikari NKJ, Kwon HY, Teo K, Siemieniuk R, Lamontagne F, Chan A, Mishra S, Murthy S, Kiiza P, et al. Anti-Ebola therapy for patients with Ebola virus disease: a systematic review. BMC Infect Dis. 2019;19(1):376. doi:10.1186/s12879-019-3980-9.
7. Zeitlin L, Whaley KJ, Olinger GG, Jacobs M, Gopal R, Qiu X, Kobinger GP. Antibody therapeutics for Ebola virus disease. Curr Opin Virol. 2016;17:45–49. doi:10.1016/j.coviro.2016.01.006.
8. Snow TAC, Saleem N, Ambler G, Nastouli E, McCoy LE, Singer M, Arulkumaran N. Convalescent plasma for COVID-19: a meta-analysis, trial sequential analysis, and meta-regression. Br J Anaesth. 2021;127:834–44. doi:10.1016/j.bja.2021.07.033.
9. Tharmalingam T, Han X, Wozniak A, Saward L. Polyclonal hyper immunoglobulin: a proven treatment and prophylaxis platform for passive immunization to address existing and emerging diseases. Hum Vaccin Immunother. 2021:1–20. doi:10.1080/21645515.2021.1886560.
10. Hansda A, Biswas D, Bhatta A, Chakravorty N, Mukherjee G. Plasma therapy: a passive resistance against the deadliest. Hum Vaccin Immunother. 2021:1–10. doi:10.1080/21645515.2021.2006026.
11. Sano A, Matsushita H, Wu H, Jiao JA, Kasinathan P, Sullivan EJ, Wang Z, Kuroiwa Y. Physiological level production of antigen-specific human immunoglobulin in cloned transchromosomic cattle. PloS One. 2013;8(10):e78119. doi:10.1371/journal.pone.0078119.
12. Liu Z, Wu H, Egland KA, Gilliland TC, Dunn MD, Luke TC, Sullivan EJ, Klimstra WB, Bausch CL, Whelan SP. Human immunoglobulin from transchromosomic bovines hyperimmunized with SARS-CoV-2 spike antigen efficiently neutralizes viral variants. Hum Vaccin Immunother. 2021:1–10. doi:10.1080/21645515.2021.1940652.
13. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495–97. doi:10.1038/256495a0.
14. Smith SL. Ten years of Orthoclone OKT3 (muromonab-CD3): a review. J Transplant Coord. 1996;6(3):109–119; quiz 120–101. doi:10.7182/prtr.1.6.3.8145l3u185493182.
15. Wu H, Pfarr DS, Losonsky GA, Kiener PA. Immunoprophylaxis of RSV infection: advancing from RSV-IGIV to palivizumab and motavizumab. Curr Top Microbiol Immunol. 2008;317:103–23. doi:10.1007/978-3-540-72146-8_4.
16. Wellcome Trust & IAVI. Expanding access to monoclonal antibody-based products: a global call to action; 2020 [accessed 2021 Nov 19]. https://wellcome.org/sites/default/files/expanding-access-to-monoclonal-antibody-based-products.pdf.
17. Whaley KJ, Zeitlin L. Emerging antibody-based products for infectious diseases: planning for metric ton manufacturing. Hum Vaccin Immunother. 2021.
18. Truong VL, Jafri H, Francois B. Clinical experience with human monoclonal antibodies for bacterial pathogens. Hum Vaccin Immunother. 2021.
19. Gunn BM, Bai S. Building a better antibody through the Fc: advances and challenges in harnessing antibody Fc effector functions for antiviral protection. Hum Vaccin Immunother. 2021;17(11):4328–44. doi:10.1080/21645515.2021.1976580.
20. Zeitlin L, Cone RA, Moench TR, Whaley KJ. Preventing infectious disease with passive immunization. Microbes Infect. 2000 May;2(6):701–08. doi:10.1016/s1286-4579(00)00355-5. PMID: 10884621.
21. Kremer J, Jager S. The significance of antisperm antibodies for sperm-cervical mucus interaction. Hum Reprod. 1992 Jul;7(6):781–84. doi:10.1093/oxfordjournals.humrep.a137737. PMID: 1500475.
22. Kremer J, Jager S. The sperm-cervical mucus contact test: a preliminary report. Fertil Steril. 1976 Mar;27(3):335–40. doi:10.1016/s0015-0282(16)41726-7. PMID: 1254029.
23. Mestecky J. Antibody-dependent passive protection of mucosal surfaces. Hum Vaccin Immunother. 2021:1–4. doi:10.1080/21645515.2021.1899549.
24. Anderson DJ. Passive immunization of the human vagina. Hum Vaccin Immunother. 2021:1–6. doi:10.1080/21645515.2021.1965423.
25. Wang YY, Kannan A, Nunn KL, Murphy MA, Subramani DB, Moench T, Cone R, Lai SK. IgG in cervicovaginal mucus traps HSV and prevents vaginal herpes infections. Mucosal Immunol. 2014 Sep;7(5):1036–44. doi:10.1038/mi.2013.120. Epub 2014 Feb 5.2014 Sep;7(5):1036-44.
26. Schaefer A, Lai SK. The biophysical principles underpinning muco-trapping functions of antibodies. Hum Vaccin Immunother. 2021:1–10. doi:10.1080/21645515.2021.1939605.
27. Olmsted SS, Padgett JL, Yudin AI, Whaley KJ, Moench TR, Cone RA. Diffusion of macromolecules and virus-like particles in human cervical mucus. Biophys J. 2001 Oct;81(4):1930–37. doi:10.1016/S0006-3495(01)75844-4. PMID: 11566767; PMCID: PMC1301668.
28. Hickey AJ, Stewart IE. Inhaled antibodies: quality and performance considerations 2021. Hum Vaccin Immunother. 2021:1–10. doi:10.1080/21645515.2021.1940650.
29. Richards A, Baranova D, Mantis NJ. The prospect of orally administered monoclonal secretory IgA (SIgA) antibodies to prevent enteric bacterial infections. Hum Vaccin Immunother. 2021:1–8. doi:10.1080/21645515.2021.1964317.
30. Phalipon A, Cardona A, Kraehenbuhl JP, Edelman L, Sansonetti PJ, Corthésy B. Secretory component: a new role in secretory IgA-mediated immune exclusion in vivo. Immunity. 2002 Jul;17(1):107–15. doi:10.1016/s1074-7613(02)00341-2. PMID:12150896.