Retro-engineering of liposomal vaccine adjuvants: Role of a microarray-based screen

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Letter to the Editor

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To the Editor,

This is in response to several papers relating to the immunobiology of liposomes. The studies, while progressive in their own right, have produced disseminated data which needs to be bridged so that future liposomes may be used as engineered adjuvants for various diseases.

A study by Badiee et al. suggests that a Th1 type immune response (high IgG2a/IgG1 ratio, high IFN-γ and low IL-4) was more effectively obtained by neutral liposomes than positively charged liposomes, while negatively charged liposomes had the opposite effect of inducing a Th2 response [1]. Another study using soluble Leshmania antigen suggests that the positively charged liposomes, induced the most potent Th1 response [2]. In contrast, a study of the liposomes used for Th1 cell therapy showed that the phosphatidylserine content of negatively charged liposomes induced IFN-γ (Th1 cytokine) [3]. Further, a study by Yamamoto et al. [4], studying IL-6, IL-10, IL-1β, TNF-α and IFN-γ, suggested that it is the size of liposomes that is the most crucial parameter in determining cytokine output and that the lipid composition does not affect cytokine release.

While not being exhaustive, these examples clearly suggest that there is a lack of common inferences, which probably result form the lack of a common experimental paradigm. The immune system being so complex, with the presence of interacting molecular pathways, may be affected significantly by a small change in the physico-chemical properties of liposomes. Thus, differences in (i) the composition and size of liposomes, (ii) experimental models for assessment of immunological response, and (iii) antigens used, lead to ambiguous results and prevent the development of a common model for the immunological profile of liposomes.

Despite its shortcomings, until recently alum was the only approved adjuvant, for human use [5], thus making the need for a new generation of adjuvants acute. While liposomes have reached the market as carriers of drugs [6], and with several papers showing positive results using liposomal vaccine adjuvants for diseases such as HIV [7–9], tuberculosis [10,11], malaria [12–14] and leshmaniasis [1,15], liposomal systems have a real chance of becoming the vaccine adjuvants of the future.

With an increased understanding of the immune system we may now rationally design adjuvants with the aim to mimic and recapitulate pro-inflammatory signals to initiate the innate and adaptive immune response [16]. Moreover, preferences about the type of immune response required to combat various diseases is beginning to emerge [5,17,18–21], thus providing a chassis for the 'retro-engineering' of adjuvants to a particular disease.

Small changes in liposomal properties may produce large changes in their immune response. Thus, if we had a immunological profile of how a liposome with a particular charge, size and lipid composition behaves, we could use that liposome or a mixture of different liposomes to provide the correct immunochemical blend for a particular vaccine, enabling rational retro-design of liposomes as vaccine adjuvants. This approach would require generation of consolidated data, produced using a common and a very broad screen. Use of microarrays may provide the best tool for such an exercise. Yan et al. [22], have studied microarray-based gene expression for DOTAP (1,2-dioleoyl-3-trimethylammonium-propane) liposome treatment, setting the basis for the profiling of liposomes. Development of a common database for the immunoprofile of liposomes would provide scientists with an essential tool for the retro-engineering of liposomal adjuvants.

An important spin-off of such a profiling exercise would be the ability to assess in preliminary manner the toxicity profile of the liposomes during the microarray screen, since the general scan would cover a wide range of cellular markers.

We believe that a microarray screen would only be the starting point for such a retro- engineering approach, and that confirmation from other related experiments will need to be performed to select the best adjuvant specific for the disease.

References

[1] Badiee A, Jaafari MR, Khamesipour A, Samiei A, Soroush D, Kheiri MTF, et al. The role of liposome charge on immune response generated in BALB/c mice immunized with recombinant major surface glycoprotein of Leishmania (rgp63). Exp Parasitol 2009;121:362–9.
[2] Bhowmick S, Ravindran R, Ali N. Leishmanial antigens in liposomes promote protective immunity and provide immunotherapy against visceral leishmaniasis via polarized Th1 response. Vaccine 2007;25:6544–56.
[3] Yotsumoto S, Kakiuchi T, Aramaki Y. Enhancement of IFN-γ production for Th1-cell therapy using negatively charged liposomes containing phosphatidylserine. Vaccine 2007;25:5256–62.
[4] Yamamoto S, Ishida T, Inoue A, Mikami J, Muraguchi M, Ohmoto Y, et al. HEPC-based liposomes trigger cytokine release from peripheral blood cells: effects of liposomal size, dose and lipid composition. Int J Pharm 2002;236:125–33.
[5] Schmidt CS, Morrow WJW, Sheikh NA. Smart adjuvants. Expert Rev Vaccines 2007;6:391–400.
[6] Lian T, Ho RJY. Trends and developments in liposome drug delivery systems. J Pharm Sci 2001;90:667–80.
[7] Sakaue G, Hiroi T, Nakagawa Y, Someya K, Iwatani K, Sawa Y, et al. HIV mucosal vaccine: nasal immunization with gp160-encapsulated hemagglutinating virus of Japan-liposome induces antigen-specific CTLs and neutralizing antibody responses. J Immunol 2003;170:495–502.
[8] Ahmad N, Khan MA, Owais M. Liposome mediated antigen delivery leads to induction of CD8+ T lymphocyte and antibody responses against the V3 loop region of HIV gp120. Cell Immunol 2001;210:49–55.
[9] Akagi T, Ueno M, Hiraishi K, Baba M, Akashi M. AIDS vaccine: intranasal immunization using inactivated HIV-1-capturing core-corona type polymeric nanospheres. J Control Release 2005;109:49–61.
[10] Chambers MA, Wright DC, Brisker J, Williams A, Hatch G, Gavier-Widén D, et al. A single dose of killed *Mycobacterium bovis* BCG in a novel class of adjuvant (Novasome™) protects guinea pigs from lethal tuberculosis. Vaccine 2004;22:1063–71.
[11] Yoshida S, Tanaka T, Kita Y, Kuwayama S, Kanamaru N, Muraki YS, et al. DNA vaccine using hemagglutinating virus of Japan-liposome encapsulating combination encoding mycobacterial heat shock protein 65 and interleukin-12

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doi:10.1016/j.vaccine.2009.11.070

confers protection against Mycobacterium tuberculosis by T cell activation. Vaccine 2006;24:1191–204.
[12] Peek LJ, Middaugh CR, Berkland C. Nanotechnology in vaccine delivery. Adv Drug Deliv Rev 2008;60:915–28.
[13] Sharma SK, Farah D, Misra-Bhattacharya S, Bajpai P, Agarwal A, Mohammad O. Escheriosome entrapped soluble blood stage antigens impart protective immunity against a multi-drug resistant isolate of *Plasmodium yoelii nigeriensis* in BALB/c mice. Vaccine 2006;24:948–56.
[14] White K, Krzych U, Gordon DM, Porter TG, Richards RL, Alving CR, et al. Induction of cytolytic and antibody responses using *Plasmodium falciparum* repeatless circumsporozoite protein encapsulated in liposomes. Vaccine 1993;11:1341–6.
[15] Bhowmick S, Ravindran R, Ali N. Gp63 in stable cationic liposomes confers sustained vaccine immunity to susceptible BALB. Infect Immun 2008;76:1003–15.
[16] Moingeon P, Haensler J, Lindberg A. Towards the rational design of Th1 adjuvants. Vaccine 2001;19:4363–72.
[17] Bergmeier LA, Lehner T. Innate and adaptive mucosal immunity in protection against HIV infection. Adv Dent Res 2006;19:21–8.
[18] Cooper AM, Khader SA. The role of cytokines in the initiation, expansion, and control of cellular immunity to tuberculosis. Immunol Rev 2008;226:191–204.
[19] Wang LX. Bioorganic approaches towards HIV vaccine design. Curr Pharm Des 2003;9:1771–87.
[20] Girard MP, Osmanov SK, Kieny MP. A review of vaccine research and development: the human immunodeficiency virus (HIV). Vaccine 2006;24:4062–81.
[21] Kwissa M, Kasturi SP, Pulendran B. The science of adjuvants. Expert Rev Vaccines 2007;6:673–84.
[22] Yan W, Chen W, Huang L. Mechanism of adjuvant activity of cationic liposome: phosphorylation of a MAP kinase ERK and induction of chemokines. Mol Immunol 2007;44:3672–81.

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