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Supramolecular peptide vaccines: tuning adaptive immunity

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Abstract

Successful immunotherapies must be designed to elicit targeted immune responses having a specifiable phenotype across many dimensions, including the phenotypes of T cells, B cells, antigen-presenting cells, and others. For synthetic or subunit vaccines, stimulation of strong enough immune responses usually requires adjuvants, which can cause local inflammation and complicate the targeting of such phenotypes. Supramolecular materials provide routes for reducing or eliminating supplemental adjuvants. Owing to their compositional controllability, supramolecular assemblies show promise for fine-tuning immune responses by adjusting combinations of material attributes including epitope content, multivalency, size, dose, and small quantities of specific adjuvants. Here we focus on supramolecular vaccines incorporating multiple epitopes in precise ratios, with an emphasis on peptides that form high-aspect ratio (i.e. fibrillar) structures.

Graphical Abstract

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Supramolecular material attributes

Contributors to Immune Phenotype

Introduction: the need for tuned immunotherapies

A successfully engineered immunotherapy elicits a specific immune phenotype by orchestrating the activities of a broad range of different immune cells [1–4]. However, in some cases this ideal phenotype is not easily achieved or even ascertained, and there remain many infectious and non-infectious conditions that have yet to be treatable using vaccines and other immunotherapies. In this short review, we will discuss supramolecular assemblies, primarily those composed of peptides and peptide derivatives, that are currently being investigated as modular platforms for discovering and eliciting precisely tuned immune responses in such areas that lack effective immunotherapies, including infectious diseases, cancer, and various other therapeutic applications.

Control over immune phenotype can occur in many dimensions, because many different cell types combine and interact to generate an overall immune response (Figure 1). T helper cells can take on a range of phenotypes (e.g. Th1, Th2, Th17, Tfh, or Treg), each carrying out distinct functions [5]. Tfh cells in particular are important for the formation of germinal centers and in helping B cells to produce high-affinity antibodies of various subclasses [6,7]. These antibody subclasses can have varying functions, especially with respect to their ability to bind complement, FcγR, or antigens [7]. After activation, helper (CD4+) and cytotoxic (CD8+) T cells not only differentiate into effector cells but also memory T cells [8], and B cells likewise develop into plasma cells and memory cells [9]. For prophylactic vaccines, it is essential not only to induce the proper T cell and antibody responses following vaccination, but also to establish immunological memory, but for therapeutic vaccines long-term memory responses may be less important. In this way, the optimal immune response for each pathogen, disease, or condition can be unique with regard to T cell specificities and phenotypes, antibody subclasses, and T and B cell memory responses. In each case, failure of an immunotherapy can come about not only from insufficient stimulation of each cell type, but also with strong but incorrectly polarized responses. Therefore, an ideal vaccine

system should be able to target a precise phenotype and strength of an immune response across each of these dimensions.

Owing to shortcomings of vaccines based on killed or attenuated pathogens, including cost of production, reduced engineerability and manufacturability [10,11], and sensitivity to cold chain deviations [12], considerable effort has been placed recently on the development of subunit vaccines containing purified or recombinant antigens and epitopes [11]. Because subunit vaccines tend to be less immunogenic than those based on whole organisms, adjuvants are usually required to elicit strong enough immune responses [10]. However, with adjuvant incorporation comes some reduction in the ability to finely tune the immune phenotype. For example, many current and emerging adjuvants can cause some degree of local inflammation, which leads to a complex combination of downstream effects [13–15]. To address this, significant effort has recently been directed toward engineering platforms that contain highly defined combinations of epitopes and antigens, immunomodulatory compounds, minute quantities of adjuvanting molecules, or no supplemental adjuvants at all [1,3,16,17]. Supramolecular assemblies, in particular those based on peptides forming high aspect ratio fibers, are part of this effort and will be highlighted here. Although peptide assemblies have not reached clinical use, at this time they do offer a potentially powerful way to create experimental platforms capable of searching for and identifying desirable immune phenotypes and to engineer formulations that precisely elicit them. The research described here is part of a burgeoning field of immunoengineering, which holds potential for developing therapeutics for a wide range of yet-to-be-treated conditions including infectious diseases, cancer, autoimmune disorders, chronic inflammation, and others [1,3,4].

Examples of supramolecular peptide vaccines

Supramolecular peptide assemblies usually take the form of nanofibers, nanoparticles, or gels, and are stabilized by non-covalent forces (hydrophobic interactions, hydrogen bonding, and electrostatic interactions). Their immunological properties arise from their size and shape, their particulate nature, their multivalency, and their ability to mix multiple different functional components with stoichiometric precision [1,18–20] (Figure 1). By attaching different epitopes to a self-assembling domain, multiple epitopes can be co-displayed both with a high degree of multivalency and in precise ratios, particularly within peptide nanofibers [18,19], peptide amphiphiles [21–23], and polypeptide nanoparticles [24,25]. Owing to their nanoscale dimensions, especially in sub-gelation concentrations, they are capable of draining to lymph nodes and being acquired by antigen-presenting cells [26–29]. In combination, these properties can reduce or eliminate the necessity of adjuvants, which in turn promises to allow a more subtle variation of immune phenotypes. Recently, it is becoming apparent that such compositional control over the materials' formulation can have a significant influence over the immune phenotypes that are elicited [19] (Figure 1).

High-aspect ratio structures (nanofibers and cylindrical micelles)

Self-assembling β -sheet peptides have been employed in tissue engineering [30], drug delivery [31], and recently in vaccine development [32]. These peptide nanofibers are particularly modular because the conjugation of functional peptide epitopes or proteins does

not disrupt the self-assembling capacity in many [19,32–37] cases – though not all [38]. This robust assembly allows the display of multiple different peptides and proteins in predetermined ratios across several orders of magnitude [18,19]. When an epitope sequence is conjugated to the self-assembling peptide Q11 (QQKFQFQFEQQ), the obtained fusion peptides have been able to self-assemble into nanofibers and elicit strong antibody response without additional adjuvants [32]. The self-adjuvanting capacity is consistent for many antigens of different origins and sizes, including mixed B and T cell epitopes (from ovalbumin, OVA₃₂₃₋₃₃₉) [32], an ovalbumin cytotoxic T cell epitope (OVA₂₅₇₋₂₆₄) [33], a malaria epitope [35], a *Staphylococcus aureus* epitope [19], a cutinase-GFP fusion protein [37], and a tumor associated antigen MUC1 glycopeptide [34]. While Q11 lost its self-adjuvancy for a *Streptococcus* epitope J14 in a recent report, this may have been caused by inefficient formation of nanofibers as shown in TEM images [38]. Our own experiences also indicate that poorly formed nanofibers can have compromised immunogenicity, and one way to circumvent this issue is by adding extra Q11 into the formulation (data not shown). Unlike Alum and other adjuvants, these peptide nanofibers are minimally inflammatory [26].

By being able to eliminate adjuvant use, it is possible that these materials can be modulated to reveal more subtle phenotypic variations in the immune response, although such work is in its infancy [19]. For example, in one very recent study, peptide nanofibers were formed by co-assembly of a universal T helper cell epitope (PADRE-Q11) and a B cell epitope (E214-Q11) from *Staphylococcus aureus* in a range of different concentrations (Figure 2a). The concentration of PADRE displayed on the nanofibers was varied from micromolar to millimolar, and optimal T helper cell and antibody responses were selected. Co-assembly of PADRE-Q11 and E214-Q11 in the same nanofiber was required, as separate injections of PADRE-Q11 and E214-Q11 did not elicit antibody responses. Although all showed a bell-shaped dose-responses pattern, different subsets of T cells responded differently to varying PADRE ratios. For example, it was found that the epitope ratios for maximal T_{fh} and antibody responses were one magnitude higher than those for maximal Th1 or Th2 responses [19]. The down-regulation of Th1, Th2, and T_{fh} cells at high PADRE concentrations (0.5 mM) may be associated with antigen-specific deletion of T cells or by subtle morphological differences in the nanofibers as different epitopes are mixed, though this aspect has yet to be investigated. It is also not yet known how robust this phenomenon is or whether it will occur in other supramolecular systems.

Besides peptide epitopes, the Q11 system has also been deployed to display larger, folded protein antigens by fusing them to a “ β -tail” sequence and expressing them in bacterial systems. The β -tail sequence undergoes an α -helix to β -strand transition when other β -sheet fibrillizing peptides such as Q11 are present [18]. In this way, fusion proteins can be maintained in a soluble and monomeric form during expression and purification, but subsequently co-assembled along with fibrillizing peptides into nanofibers [18]. Using the β -tail system, multiple proteins could be combined in precise ratios, and like peptide epitopes the protein antigens could also elicit significant antibody responses [18].

Other systems that form immunogenic high-aspect ratio structures include peptide amphiphiles, formed by conjugating peptide antigens or epitopes to a lipid tail [39]. These

amphiphilic molecules self-assemble into cylindrical or spherical micelles. One advantage of such platforms is that it has been shown that the secondary structure of some epitopes can be stabilized, for example in an α -helical conformation [23]. Tirrell's group is investigating platforms constructed from peptides conjugated to a dialkyl lipid tail (diC₁₆), which form cylindrical micelles that are self-adjuncting (Figure 2b). When a model cytotoxic T cell epitope (EQLESIINFEKLTE) was delivered as part of a peptide amphiphile assembly, the material stimulated a SIINFEKL-specific cytotoxic (CD8+) T cell response that was capable of inhibiting the growth of E.G7-OVA tumors in mice [23]. More recently, a Group A *Streptococcus* B cell epitope (J8) was displayed on similar micelles, and strong IgG and IgM responses were obtained [40]. One interesting feature of this system is that additional T helper cell epitopes have not been required to elicit humoral or cellular responses, in contrast with peptide fibrils such as Q11, which depend on T helper epitopes being incorporated [19,36]. The source of this difference is not known but may constitute an interesting point of future study.

Low-aspect ratio structures (nanoparticles)

Supramolecular assembly is becoming a common strategy in vaccine design that goes well beyond the fibrillizing systems discussed above. Notably, these include systems forming more uniformly shaped particles. For example, lipoamino acids have been employed to develop nanoparticle vaccines, where peptide sequences are linked to the α - and side chain amines of N-terminal lysines [41]. Two C16 lipoamino acids are required for a strong immune response [38,42]. In such systems, the adjuvanting effects arise from activation of TLR-2 by the lipoamino acids [43]. Interestingly, this seems not to be a universal mechanism for lipidated peptides, since other peptide amphiphile systems appear not to depend on TLR-2 [23,40].

In other recent work utilizing lipid-conjugated peptides, the Robinson group has constructed synthetic virus-like particles using coiled-coil lipopeptides as building blocks. In these systems, the bundling of the helical peptides and the hydrophobic burial of the lipid tails both contribute to nanoparticle formation [44]. Epitope peptides are linked to the C-termini of lipopeptides and are thus co-displayed on the surface of the nanoparticles. When a B cell epitope and a T helper epitope from *P. falciparum* were delivered in this manner, strong antibody responses were obtained in mice and rabbits [22]. The nanoparticles were found to be endocytosized by dendritic cells, mainly via caveolin-independent and lipid raft-mediated micropinocytosis [45].

In a system that lacks lipid components altogether, peptides containing two coiled-coil oligomerization domains have been engineered for vaccine development (Figure 2c) [24,25,46]. A peptide sequence in the pentamerization domain serves as a T helper epitope; alternatively, a different T cell epitope can be inserted into the trimerization domain. Both ends of the self-assembling domain are capable of displaying antigen epitopes on the nanoparticle surface. In one study, a B cell epitope, a cytotoxic T cell epitope, and a T helper epitope (PADRE) were engineered into the N-terminus, C-terminus, and trimerization domain of the polypeptide sequence, respectively. These polypeptide nanoparticles were able to elicit long lasting antibodies and memory cytotoxic T cells and provide protection

against malaria parasites for up to one year [24]. The long-term immunity was found to be associated with slow and persistent antigen processing and presentation via recruited transporter associated with antigen processing (TAP) in early endosomes [47].

Besides the peptide-based assemblies discussed, non-peptide platforms also utilize supramolecular design principles. For instance, Irvine's group has developed PEGylated and lipase-sensitive interbilayer-crosslinked multilamellar vesicles (ICMV) as vaccine carriers (Figure 2d) [48]. Strong antigen-specific cytotoxic T cell responses were observed by delivering protein antigens in the aqueous core and a lipid adjuvant in the bilayer [48]. In another report, the ICMVs were designed to display malaria antigens on the surface, a formulation that expanded T_{fh} cells and elicited strong humoral responses [28]. The particles were also able to elicit cytotoxic and effector memory T cell responses at several mucosal surfaces, which resulted in protection against tumor and pulmonary viral infection [27]. In an approach based on synthetic polymers, the Hubbell group has engineered pyridyl disulfide functionalized pluronic stabilized poly(propylene sulfide) nanoparticles with precise size control, efficient lymph node draining, and convenient surface epitope and adjuvant loading. Owing to these properties, adjuvant dose can be greatly reduced. Delivery of antigen and/or CpG led to expansion of cytotoxic T cells via several administration routes in several models [29,49–51].

Current challenges and future development

While some supramolecular vaccines can stimulate particular immune responses without additional adjuvants, several aspects of their mechanism of adjuvancy remain unclear. First, because many different supramolecular platforms have been developed largely independently by different research groups, a systematic comparison of each platform's mechanism of action has yet to be conducted. Different platforms may engage different mechanisms, including TLR activation, inflammasome signaling, autophagy, T-independent B cell signaling, or combinations thereof, and overarching design rules have yet to crystallize out of the considerable work being undertaken in parallel. With respect to fibrillar peptides, our findings indicate that they act via T cell-dependent pathways, as antibody responses were abolished in T cell-knockout mice [36]. In addition, myeloid differentiation factor 88 (MyD88), a key adaptor in signaling of TLRs, was identified as a necessary component for antibody responses against these materials [35]. At the same time, antibody responses can still be raised in knockout mouse models lacking upstream components of MyD88 signaling, including various Toll-like receptors such as TLR-2 [35], TLR-4 [26], TLR-5 [35], TLR-7 (unpublished data), and TLR-9 (unpublished data). NALP3 knockout mice also were competent at raising responses [35]. It is possible that redundant signaling enables antibody production if only one TLR is knocked out. It will be interesting to continue to expand the knowledge of the signaling pathways responsible for the strong antibody responses yet minimal inflammation incurred by peptide nanofibers.

Another shortcoming of peptide nanofiber vaccines is that their length, while providing room for incorporating a range of different epitopes, tends to be somewhat heterogeneous and difficult to control. While several supramolecular platforms have defined numbers of monomer units per particle, and therefore consistent particle morphology and size, peptide

nanofibers and cylindrical micelles lack this controllability. It has been demonstrated that monomeric analogs of fibrillizing peptides are not able to elicit immune responses [36], but it is still unclear whether only a particular population or all nanofibers are responsible for immune stimulation, or whether different sub-populations may engage different immune mechanisms. Another remaining concern with fibrillized nanofibers relates to their amyloid-like nature. Although many functional and technologically useful amyloids have been identified [52–54], the critical parameters that influence or predict amyloid pathogenicity and toxicity are still being developed [55]. Finally, as proofs-of-concept, desirable antibody and T cell responses have been demonstrated in mouse models, but it remains to be seen how efficacious these platforms will be in humans [56].

Despite these challenges, supramolecular assemblies offer great advantages in immunoengineering owing to their exceptional modularity and ability to combine different epitopes, antigens, and potentially immunomodulating components with precision. Much work remains to engineer formulations that will achieve clinically meaningful protective effects for various diseases, but their engineerability makes supramolecular assemblies a powerful experimental tool to identify the optimal immune phenotypes in such contexts.

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Highlights

- Successful immunotherapies must target a precise phenotype and strength of an immune response.
- Supramolecular materials may offer strategies for identifying and eliciting such phenotypes.
- Comparative studies of how material properties influence immune phenotypes are in early stages.

Figure 1.

Modulating adaptive immunity by controlling material properties. The optimal immune responses for a given pathogen or disease consist of many contributing cells and processes. Each component is ideally adjusted to an optimal phenotype and strength (yellow circle, center). Supramolecular assemblies offer controllability over the size, morphology, multivalency, dose, epitope content, and adjuvant dose (left circle). All of these properties can be manipulated to experimentally optimize a particular immune phenotype and strength. For instance, titration of the concentration of a T cell epitope on peptide nanofibers results in different responses of T helper subsets (schematic at right) [19].

Figure 2.

Structures of representative supramolecular vaccines. (a) Peptide nanofibers are useful for displaying multiple epitopes with precise ratios. Functional epitopes are synthesized in tandem with a self-assembling domain, and these peptides co-assemble into nanofibers. (b) Peptide amphiphiles containing a peptide epitope and a dialkyl lipid tail form cylindrical micelles that can elicit strong immune responses. (c) Polypeptides with two coiled-coil self-assembling domains form nanoparticles with epitopes at both ends displayed on the surface. (d) In interbilayer-crosslinked multilamellar vesicles (ICMVs), protein antigens are loaded in the aqueous core and a lipid adjuvant is embedded in the lipid bilayers. 2a reproduced with permission from Pompano et al. [19]; Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. 2b reproduced with permission from Black et al. [23]; Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. 2c reproduced with permission from Kaba et al. [24]; copyright Kaba et al. 2d reproduced with permission from Moon et al. [48]; Copyright 2011 Nature Publishing Group.