Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Chemical Biology

Materials from peptide assembly: towards the treatment of cancer and transmittable disease

Monica C Branco, Dina M Sigano and Joel P Schneider

As the prevalence of cancer and transmittable disease persists, the development of new and more advanced therapies remains a priority in medical research. An emerging platform for the treatment of these illnesses is the use of materials formed via peptide assembly where the bulk material itself acts as the therapeutic. Higher ordered peptide structures with defined chemistry are capable of cellular targeting, recognition, and internalization. Recent design efforts are being made to exploit the nanoscale definition of the materials formed by assembling peptides to target cancer and microbial cells and to function as vaccines. This review focuses on assembled peptide materials that actively participate in the biological processes important to cancer and transmittable diseases to exert an anticipated functional outcome.

Address
Chemical Biology Laboratory, National Cancer Institute, National Institutes of Health, Frederick, MD 21702, United States

Corresponding author: Schneider, Joel P (Joel.Schneider@nih.gov)

Current Opinion in Chemical Biology 2011, **15**:427–434

This review comes from a themed issue on
Molecular Diversity
Edited by Ashton Cropp and Dewey McCafferty

Available online 18 April 2011

1367-5931/$ – see front matter
Published by Elsevier Ltd.

DOI 10.1016/j.cbpa.2011.03.021

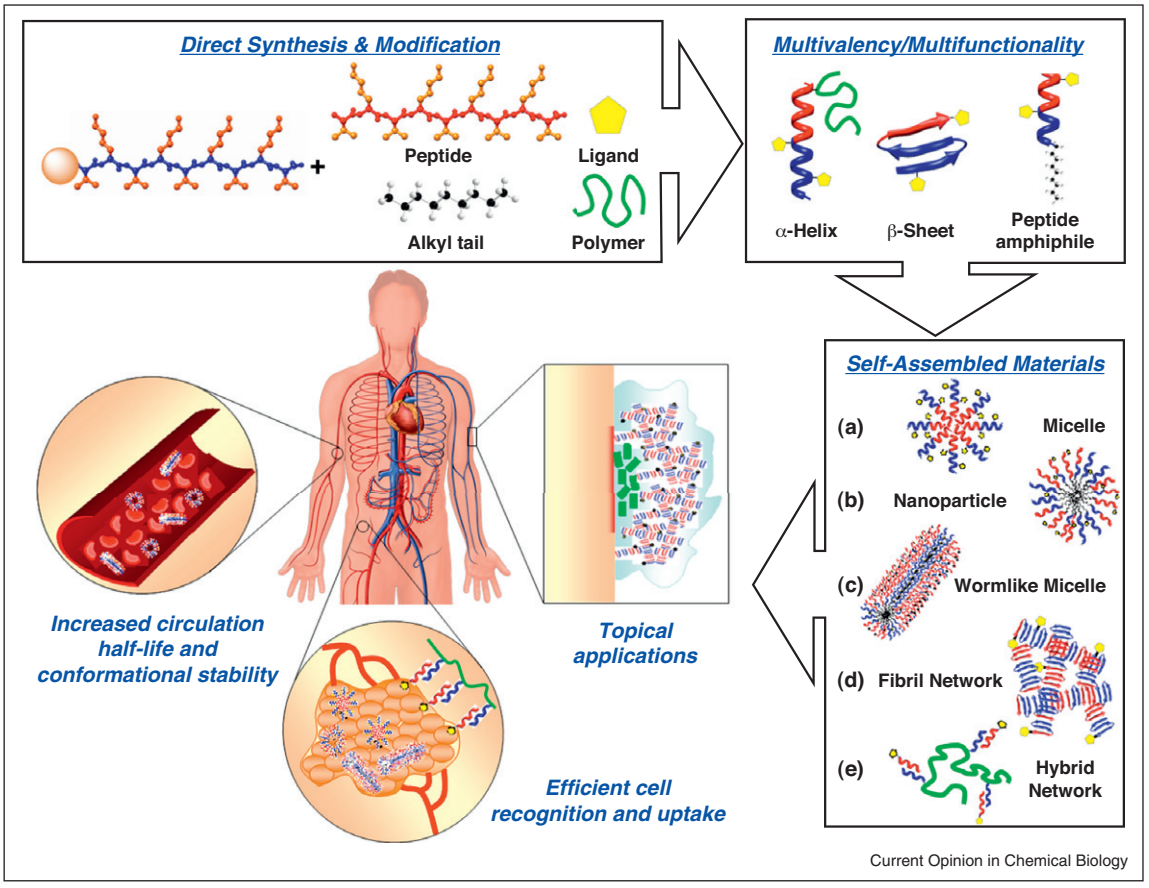
Introduction

The immune system is our primary defense towards microbial pathogens and foreign substances [1–3]. It is composed of a variety of cells that can recognize and destroy pathogens, and later gain immunity to them in the event of future encounters. To aid the immune system, antibiotics and vaccines have been developed to treat and prevent many illnesses [4,5]. Antibiotics assist the innate immune system in eliminating existing bacterial and fungal infections [4]. Alternatively, vaccines exploit the adaptive immune system to gain immunity towards disease, such as those transmitted by viruses [5]. For example, several vaccines have been developed to successfully prevent communicable illnesses including smallpox, diphtheria, measles, mumps, and polio. In addition, the vaccine, Gardasil®, has been approved for the prevention of anal, cervical, vulvar, and vaginal cancers. The first therapeutic cancer vaccine for metastatic prostate cancer, Provenge®, was recently FDA-approved, and at the time of this writing, Prostvac™ was in Phase III clinical trials for prostate cancer. Recently, the emergence of antibiotic resistant microbes and rapidly mutating viruses has greatly compromised current therapies [6]. In addition, there are illnesses, such as cancer and autoimmune diseases, in which the immune system fails [7]. These diseases necessitate the development of alternative and more advanced therapies.

An emerging platform for the treatment of cancer and transmittable disease is the use of materials formed via peptide assembly where the bulk material itself acts as the therapeutic [8,9]. Over the last several decades, peptide materials have been extensively developed as tissue engineering scaffolds or drug delivery vehicles, where the material serves in a passive role for the intended therapy [10–19]. Currently, design efforts are being made to exploit the nanoscale definition of the material formed by assembling peptides to target cancer and microbial cells and to function as vaccines. These materials are not passive bystanders that simply deliver drugs or serve as rebarb for cellular attachment and extracellular matrix elaboration, but actively engage intended biological targets to exert an anticipated functional outcome. This review will focus on assembled peptide materials that actively participate in the biological processes important to cancer and transmittable diseases. As will be highlighted, these higher ordered structures with defined chemistry are capable of cellular targeting, recognition, and internalization, and represent promising leads towards the treatment of these human ailments.

Why use self-assembling peptides as the building blocks for material construction rather than more traditional polymers? Peptides, in general, are biocompatible, biodegradable, provide exquisite selectivity in binding, and many are weakly immunogenic, contrary to common belief [11,20,21••]. A seemingly endless array of structural and functional diversity can be designed at the peptide monomer level that can be directly translated to the materials that are formed from their self-assembly (Figure 1). Peptides can be conveniently synthesized using solid phase methodology, taking advantage of a vast array of commercially available natural and non-natural amino acid residues. Peptides can be elaborated functionally by conjugating other peptides, biologically active ligands, lipids, and even polymers using synthetic bioconjugation strategies, such as native chemical ligation and oxime chemistry, to name a few [22]. Peptides can be designed to adopt desired structures such as helices and

Figure 1



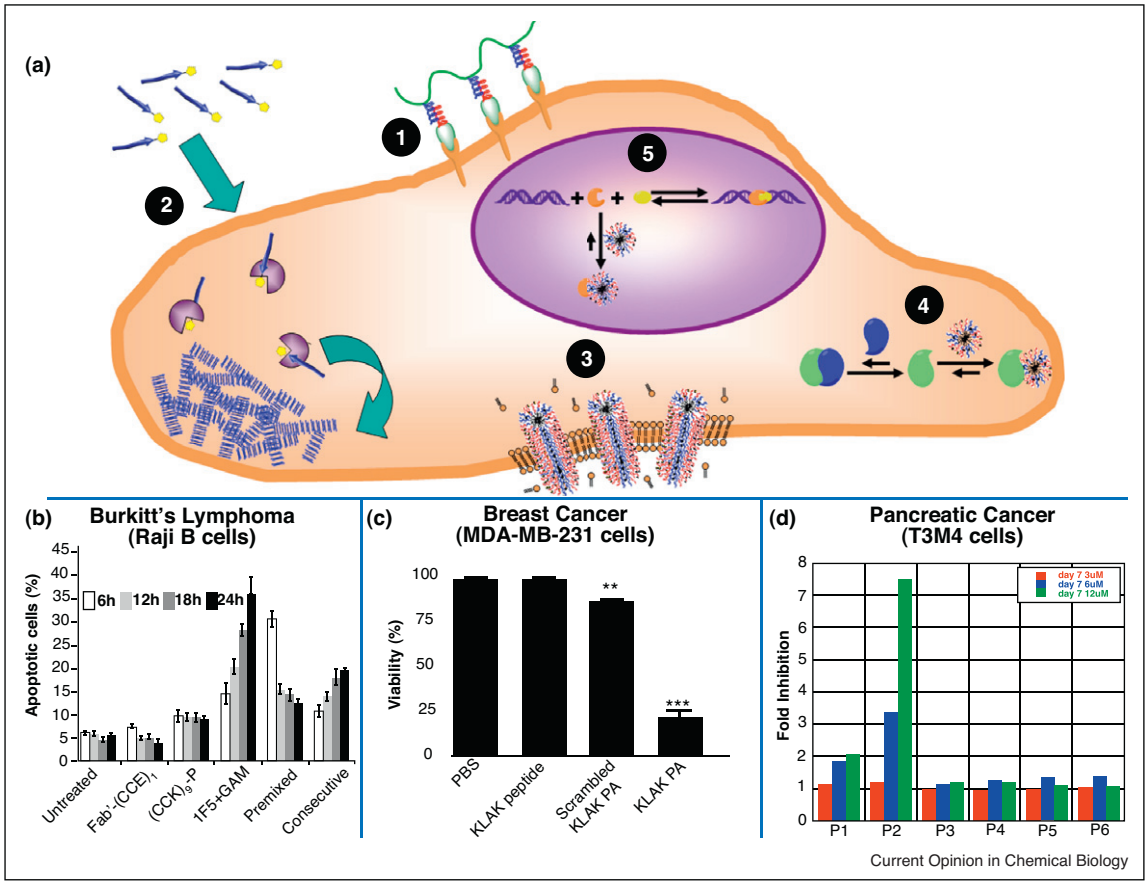
Peptides can be prepared chemically on solid support and functionalized via ligation chemistry with other peptides, ligands, lipids, and polymers to impart functionality and control folding and self assembly. Self-assembled materials can be engineered to controllably display biofunctionality that enables targeted applications. Assemblies are not drawn to scale.

sheets that can serve as the structural building blocks for higher-ordered structures. Facial and block amphiphilicity can be engineered into monomeric folded structures to drive self-assembly yielding targeted morphologies. Common material morphologies realized in peptide assembly include micelles, nanoparticles, wormlike micelles, fibrillar networks, and hybrid networks composed of mixtures of peptides and polymers. In these materials, the side chains of bioactive amino acid residues in the peptide sequence or appended ligands can be displayed with spatial fidelity and high copy number; if more than one bioactive moiety is displayed, multifunctionality can be realized from a single material. Each type of material shown in Figure 1 possesses distinct structural and mechanical properties that enable their use in targeted applications. For example, fibrillar networks that form hydrogels are easily administered topically for dermal applications. As will be discussed in this review, hybrid networks, micelles, nanoparticles, and wormlike micelles can be engineered to facilitate cell recognition and uptake. Although monomeric peptides introduced systemically can suffer from short circulation half-lives and conformational denaturation induced by components of the serum, such as albumin, peptides contained within assemblies can enjoy increased half-lives in serum and conformational stability [8,23–25,26•,27].

Self assembling peptides for anticancer therapy

An ideal treatment for cancer is the one that can discriminate between cancerous and healthy tissue [7]. The repertoire of proteins expressed on the surface of tumor cells are largely similar to those on cells comprising healthy tissue, thus allowing malignant cells to remain indistinguishable to the immune system [3]. However, some proteins, which are overexpressed or have mutations, can be exploited by cancer specific therapies [1,7]. A self assembling peptide system was recently designed to target and bind to cell membrane proteins present on cancerous cells by Kopecek *et al.*, Figure 2a(1) [28•]. Here, a strategy employing coiled coil peptides targets CD20 membrane proteins on the surface of Bur-

Figure 2



(a) Examples of peptide-based materials designed to interact with cancer cells extra-cellularly and intra-cellularly. Counter-clockwise: (1) CD20 cell membrane proteins (orange) bound to the Fab′ portion (white) of 1F5 antibody-CCE conjugate. CCE (red) forms a coiled coil with CCK peptide (blue) covalently attached to a HMPA polymer (green); (2) Pro-peptide (blue) with a leaving group (yellow) enters easily into cells, where it is hydrolyzed by an enzyme (purple), liberating a peptide that self assembles into nanofibers; (3) wormlike micelles or nanofibers (blue and red) formed from peptide amphiphiles disrupt lipids on the cellular membrane; (4) interaction between p53 protein (blue) and its oncoprotein counterparts, MDM2 or MDM4 (green), are inhibited by micelles formed from a peptide amphiphile containing the antagonistic peptide, $p53_{14–28}$; (5) interaction between HOX (orange) and its cofactor, PBX (yellow), to DNA is inhibited by micelles formed from a peptide amphiphile containing the antagonistic peptide, WYPWMKKHH. **(b)** Time-dependent apoptosis of Burkitt's lymphoma (Raji B) cells after exposure to no treatment, Fab′-$(CCE)_1$ alone, $(CCK)_9$-P alone, 1F5 anti-CD20 antibody and GAM secondary antibody, premixture of Fab′-$(CCE)_1$ and $(CCK)_9$-P, and consecutive addition of Fab′-$(CCE)_1$ followed by $(CCK)_9$-P. **(c)** Percentage of viable MDA-MB-231 breast cancer cells after exposure to PBS solution, and PBS solutions containing KLAK peptide, scrambled KLAK peptide amphiphile, and KLAK peptide amphiphile. **(d)** Fold inhibition of T3M4 pancreatic cancer cell proliferation by peptides P1-P6. P1: WYPWMKKHH-RQIKIWFQNRRMKWKK; P2: $CH_3(CH_2)_{14}$CONH-WYPWM KKHH-RQIKIWFQNRRMKWKK; P3: RQIKIWFQNRRMKWKK; P4: $CH_3(CH_2)_{14}$CONH-RQIKIWFQNRRMKWKK; P5: WYPWMKKHH; P6: $CH_3(CH_2)_{14}$CONH-WYPWMKKHH.

kitt's non-Hodgkin lymphoma Raji B-cells. One of the coiled coils, CCE, is attached to a Fab′ fragment of the 1F5 anti-CD20 antibody, whereas the other peptide, CCK, is bound to a HPMA (*N*-(2-hydroxypropyl)methacrylamide) polymer. When the antibody fragment binds to CD20, the bound CD20 protein remains on the cell surface, exposing the random coil CCE peptide. Recognition of the polymer-bound complementary peptide CCK results in coiled coil assembly of the two peptides and, according to the authors, concomitant cross-linking of CD20 receptors, which leads to apoptosis of Raji B-cells. The premixing of the antibody-conjugate with the polymer-conjugate induces high levels of apoptosis after six hour incubation as shown in Figure 2b, and the consecutive administration of the two components shows greater levels of apoptosis over 24 hours. The positive control, crosslinking of the 1F5 anti-CD20 antibody with a GAM secondary antibody, is shown for reference. Importantly, at higher concentrations, the activity of the assembled peptide system demonstrates comparable apoptotic activity as the positive control (data not shown).

The upregulation of enzymes, both extracellular and intracellular, is also common within tumors [29–34]. Outside of the cell, proteases are excreted to breakdown the extracellular matrix and allow migration of malignant cells

[29,30]. Inside the cell, enzymes control cell signaling pathways necessary for cell proliferation, migration, and survival [31–34]. Peptides designed to take advantage of enzymes are particularly advantageous because their activity is dependent on the occurrence and quantity of enzyme present, allowing for spatial and temporal resolution of the therapy at the cancer site. Xu *et al.* have developed a small peptide hydrogelator whose self-assembly is triggered by an endogenous esterase within HeLa cervical cancer cells [35•]. A pro-peptide was designed that remains soluble outside of cells and can diffuse easily into cells. Within the cellular cytoplasm, the pro-peptide is hydrolyzed, liberating a peptide that self assembles into nanofibers. Fibril formation within the cell results in cell death, Figure 2a(2). The proliferation of cells whose level of enzyme expression is low, is not affected by the presence of the pro-peptide, demonstrating the specificity in the peptide design.

Pre-assembled peptide nanostructures have also been designed as cancer therapies. For example, Stupp *et al.* have designed peptide amphiphiles composed of bioactive peptides conjugated to alkyl tails that promote micellar self-assembly in aqueous solution [15]. The ability of these assemblies to target tumors relies on the enhanced permeability and retention (EPR) effect found at developing tumors [36–38]. Leaky vasculature and poor lymphatic drainage allow nanostructures on the order of 10–500 nm to passively diffuse through vessel gaps and accumulate at the local tumor site. In one particular design, a peptide amphiphile ($CH_3(CH_2)_{14}CO$-$A_4G_3(KLAKLAK)_2$) was prepared containing a cytotoxic, cationic peptide sequence, $(KLAKLAK)_2$ appended to a palmitic alkyl tail. The peptidic portion is designed to form an amphiphilic α-helix that disrupts cellular and mitochondrial membranes (Figure 2a(3)) [39•]. This peptide amphiphile assembles into nanofibers that stabilize the helical conformation of the KLAK sequence and facilitate its interaction with the membranes of MDA-MB-231 and SKBR-3 breast cancer cells to ultimately disrupt membrane integrity and cause cell death. The data in Figure 2c clearly show that the self-assembled material, itself, is responsible for this activity. Here, the peptidic portion of the peptide alone, which is presumably monomeric in solution, is not active. The data also show that only the amphiphile containing the peptide of correct sequence is active, nicely demonstrating the power of peptides to facilitate selective activity from the materials in which they are contained.

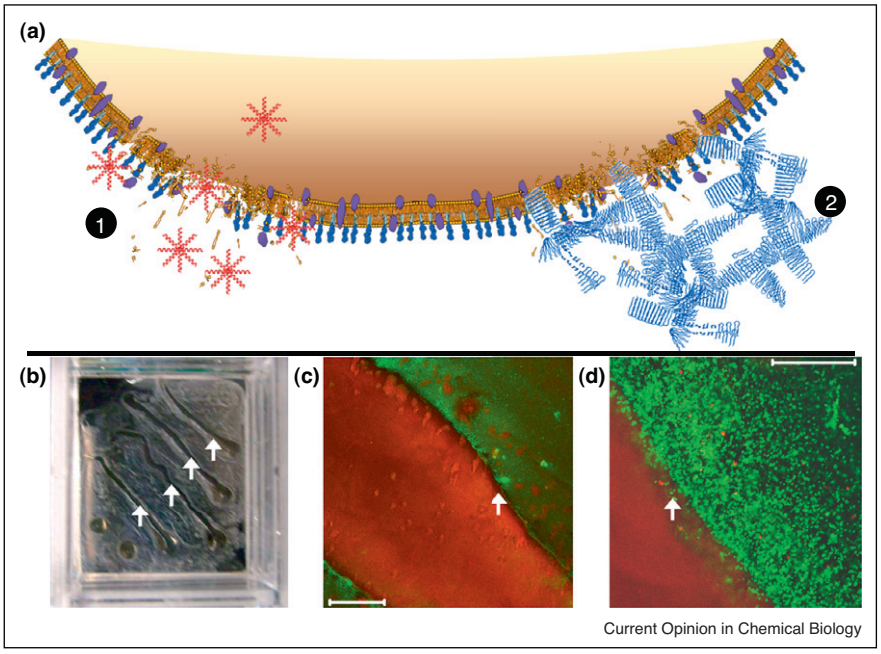
Peptide micelles can be used to actively engage cellular membranes and facilitate internalization to target intracellular proteins, such as upregulated oncoproteins and downregulated tumor suppressor proteins in cancer cells (Figure 2a(4, 5)) [15,40•]. For example, inhibition of the interaction between wild-type p53 protein and its oncoprotein counterparts, MDM2 or MDM4, is possible by a 16 residue sequence, $p53_{14–28}$, which is cell impermeable and thus, incapable of reaching its intended target [40•]. By tethering a double tailed lipid onto the peptide, Tirrell *et al.* have prepared a peptide amphiphile that assembles into micelles. These micelles are capable of entering SJSA-1 osteosarcoma, HeLa cervical cancer, and MDA-MB-435 breast cancer cells. Further studies are needed to demonstrate that MDM2 or MDM4 are targeted by the peptide amphiphile.

Transcription factors and other DNA binding proteins are also intracellular proteins that are often upregulated in cancer cells. One example is the deregulated HOX proteins in primary solid tumors and certain hematological malignancies that cause abnormal gene expression [41•]. Inhibition is possible by targeting the binding of HOX and its cofactor, PBX, to DNA using the antagonistic peptide, WYPWMKKHH. To facilitate its internalization into the cell, Hartgerink *et al.* have designed a peptide amphiphile P2 ($CH_3(CH_2)_{14}$CONH-WYPWMKKHH-RQIKIWFQNRRMKWKK) where the peptide antagonist domain is appended to a palmitic alkyl tail and capped with a cell penetrating sequence [41•]. This peptide amphiphile (P2) reduces the gene expression of several HOX genes in T3M4 pancreatic cancer cells after 24 hours. As shown in Figure 2d, P2 is capable of inhibiting growth of the T3M4 cells by 7.5-fold after 7 days, whereas P1, the peptide without the alkyl chain, inhibits cell growth only 2-fold. Control peptides comprised of the cell penetrating portion or the antagonistic portion alone and their palmityl chain derivatives (P3–P6) show no effect on cell growth. Therefore, by simply preparing self-assembling peptide amphiphiles from bioactive peptides, their intracellular activity can be strongly enhanced. In all of these examples, the self-assembled material, itself, exerts action, which precludes the necessity of adding drugs that are eventually delivered from the material to elicit activity.

Self-assembling peptides as antimicrobials

The emergence of multi-drug resistant microbes that challenge the immune response and current therapy has also drawn attention to peptide materials. Antimicrobial peptides are cationic, amphiphilic peptides that display non-specific, broad-spectrum activities towards several microorganisms and are typically monomeric in solution [42,43]. They are amphiphilic in a facial sense, which is quite different from the linear or block amphiphilicity that is typical of the peptide amphiphiles designed by Stupp, Tirrell, and Hartgerink. The folded structures of most antimicrobial peptides are typically helical or β-sheet and display a cation-rich face and a distinct, opposing hydrophobic face. Unlike small molecule antibiotics that have a particular cellular target, cationic peptides depend solely on their non-specific interaction with negatively charged bacterial cell surfaces. Here, the polycationic face of the peptide facilitates initial engagement of the cell wall. On binding to the cell

Figure 3



(a) Bacterial membrane disruption caused by (1) peptide nanoparticles formed by self assembling peptide amphilphiles (red) and (2) a fibrillar network of self assembled polycationic β-hairpins (blue). Only the outer leaflet of Gram-negative bacteria is shown; lipopolysaccharide is shown in blue; membrane proteins are shown in purple. **(b)** Strips of 2 wt% MARG1 hydrogel syringe-delivered to an agar bed of MRSA. Single arrows denote the location of hydrogel. **(c)** Confocal microscopy image of a live (green)/dead (red) viability assay of MRSA grown on agar. Image shows one of the strips of hydrogel from panel b. Arrow designates the hydrogel boundary on the MRSA-loaded agar. Scale bar = 200 μm. **(d)** Magnification of hydrogel–agar interface. Scale bar = 50 μm.

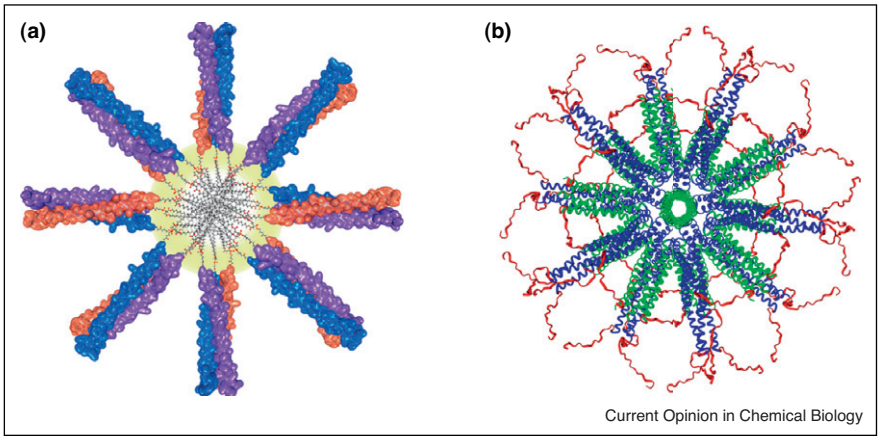
surface, peptide insertion into the membrane occurs, which is facilitated by the hydrophobic face of the peptide; the peptide then typically assembles, forming pores that disrupt the membrane and causes cell death [44].

Self-association of the peptides in solution prior to cell engagement can increase the potency of some cationic peptides. To take advantage of this self assembly effect, Yang *et al.* have developed nanoparticles comprised of an arginine-rich TAT peptide shell and a hydrophobic cholesterol core (Figure 3a(1)) [45•]. The nanoparticles showed strong antimicrobial activity against several bacteria, including drug-resistant strains, as well as yeast and fungi. Also, the minimal inhibitory concentration of the nanoparticle was six times lower than the peptide portion of the amphiphile from which it was made, suggesting that the high density of positive charge displayed from the particle leads to greater membrane disruption as compared to the peptide alone.

Similar to their design targeting cancer cells, Xu *et al.* have designed pro-peptides that are taken up by *Escherichia coli* and cleaved by an intracellular phosphatase. The cleaved peptide self assembles into nanofibers that inhibit bacterial growth [46].

Our group has designed a hydrogel scaffold from self-assembling peptides that exhibits inherent antibacterial activity [47•,48]. MAX1 is a twenty amino acid peptide that can undergo triggered intramolecular folding to adopt an amphiphilic β-hairpin that subsequently self-assembles into β-sheet rich fibrils, which constitute a mechanically rigid hydrogel. Solvent exposed cationic lysines on the surface of the fibrils interact with negatively charged bacterial cell surfaces ultimately compromising membrane integrity, Figure 3a(2). MAX1 gels show bactericidal activity towards Gram-negative *E. coli* and *K. pneumoniae*, and Gram-positive *S. epidermidis*, *S. pyrogenes*, and drug-susceptible *Staphylococcus aureus* [47•]. In this system, it is the material afforded by self-assembly that is active, namely fibrils that display a high density of positively charged amino acid side chains from their surface. In a subsequent design, the substitution of two lysines in the primary sequence of MAX1 with arginine residues, results in a peptide named MARG1. This peptide self-assembles to form a hydrogel that is active against Methicillin-resistant *S. aureus* (MRSA) [48]. Figure 3b shows an experiment wherein thin strips of MARG1 hydrogel are syringe delivered to a bed of MRSA grown on an agar surface. Live-dead assays employing confocal microscopy show that bacteria beneath the delivered hydrogel are dead, and bacterial growth only occurs on the outlying

Figure 4



(a) Model of a synthetic virus-like particle formed from lipopeptide helical bundles. **(b)** Model of self-assembled polypeptide nanoparticle composed of two coiled coil peptide domains displaying a B cell epitope on its surface.

agar that was not exposed to the gel, Figure 3(c) and 3(d). Taken together, these peptide material examples demonstrate how higher ordered structures with defined chemistry resulting from self assembly can offer excellent bacterial cell targeting and activity.

Self-assembling peptides as vaccines

Preventative measures such as vaccines for cancer and transmittable disease are also being explored to prime the immune response prior to exposure to such formidable illnesses. In addition, vaccines can be administered therapeutically to treat existing conditions, as is the case with the previously mentioned Provenge®. Often, the effectiveness of immunotherapies is complicated by non-optimal epitope display and use of heterogeneous adjuvants which fail to induce a robust antibody response [26•]. The use of self-assembling peptides as antigens holds promise since synthetic peptides can be prepared with precise chemical definition for optimized epitope display [49,50]. In addition, their self-assembled structures can present epitopes in a spatially defined, multivalent fashion, resulting in enhanced biorecognition by immune cells. Collier *et al.* prepared nanofibers from self-assembling peptides that display a T and B cell epitope from chicken egg ovalbumin [26•]. The nanofibers are able to elicit high antibody titers without the need of an additional adjuvant. The immune response to epitope is also dependent on its covalent attachment to the self-assembled fibril, and is comparable to the response observed for the epitope with complete Freund's adjuvant. This observation suggests that the fibril, itself, is an active participant in generating a response and not an innocent bystander that simply presents the epitope to the immune cells.

High antigen surface presentation can also be obtained using coiled coil peptide motifs [51–53]. Synthetic virus-like particles were derived by Robinson *et al.* from lipopeptides that first self assemble into α-helix bundles and then further assemble into spherical micelles through the clustering of lipid chains, Figure 4a. [54,55•] From the surface of the coiled bundles, multiple copies of a desired antigen can be displayed for adjuvant-free stimulation of the immune system. Burkhard *et al.* have also developed nanoparticles from self-assembling coiled coil peptides (Figure 4b) [56,57•]. Epitopes for malaria and severe acute respiratory syndrome (SARS) were displayed on the surface of separate nanoparticles. For both systems, the immune response is high and long-lived, and the resultant antibodies display high avidity to the epitope. Overall, self-assembling peptides are a novel strategy to construct simple, chemically defined particles as potential vaccines capable of productive presentation of desired antigens.

Conclusion

As the prevalence of cancer and infectious disease persists, the development of new and more advanced therapies remains a priority in the health research community. Novel therapies that show high specificity and enhanced potency are needed for diseases that confound the immune system and are unresponsive to current available treatments. The design of materials via peptide assembly has the potential to impact this need. Peptides, in general, are a growing class of therapeutics with over 50 products now in the market, and more in clinical trials [21••]. Materials made from these exquisite molecules represent a novel frontier in therapeutic design. With that said, the examples provided in this review are mainly academic in nature, and if warranted, a large amount of work must be done to translate them to the clinic. As with their small molecule cousins, many materials will fail somewhere along the costly, arduous path of development. However, the materials that do fail as therapies will surely find use as

tools to further our understanding of the biological processes that govern disease. Therefore, the design of novel materials that have the potential to significantly impact human ailments is important and is the first necessary step, namely discovery, in bringing any therapy into the clinic.

Acknowledgements

The cartoon of the human in Figure 1 was licensed by Medical Illustration Copyright© 2011 Nucleus Medical Media, All rights reserved (www.nucleusinc.com). We would also like to acknowledge Tyler Larsen for his help in preparing Figure 3 of this manuscript.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Borghaei H, Smith MR, Campbell KS: **Immunotherapy of cancer**. *Eur J Pharmacol* 2009, **625**:41-54.

2. Klippstein R, Pozo D: **Nanotechnology-based manipulation of dendritic cells for enhanced immunotherapy strategies**. *Nanomed: Nanotechnol Biol Med* 2010, **6**:523-529.

3. Pellegrini M, Mak TW, Ohashi PS: **Fighting cancers from within: augmenting tumor immunity with cytokine therapy**. *Trends Pharmacol Sci* 2010, **31**:356-363.

4. Anderson R, Tintinger G, Cockeran R, Potjo M, Feldman C: **Beneficial and harmful interactions of antibiotics with microbial pathogens and the host innate immune system**. *Pharmaceuticals* 2010, **3**:1694-1710.

5. Mills KHG: **Designer adjuvants for enhancing the efficacy of infectious disease and cancer vaccines based on suppression of regulatory T cell induction**. *Immunol Lett* 2009, **122**:108-111.

6. Donadio S, Maffioli S, Monciardini P, Sosio M, Jabes D: **Antibiotic discovery in the twenty-first century: current trends and future perspectives**. *J Antibiot* 2010, **63**:423-430.

7. Murphy JF: **Trends in cancer immunotherapy**. *Clin Med Insights: Oncol* 2010, **4**:67-80.

8. Rajagopal K, Schneider JP: **Self-assembling peptides and proteins for nanotechnological applications**. *Curr Opin Struct Biol* 2004, **14**:480-486.

9. Collier JH: **Modular self-assembling biomaterials for directing cellular responses**. *Soft Matter* 2008, **4**:2310-2315.

10. Branco MC, Schneider JP: **Self-assembling materials for therapeutic delivery**. *Acta Biomater* 2009, **5**:817-831.

11. Kopecek J, Yang JY: **Peptide-directed self-assembly of hydrogels**. *Acta Biomater* 2009, **5**:805-816.

12. Segers VFM, Lee RT: **Local delivery of proteins and the use of self-assembling peptides**. *Drug Discovery Today* 2007, **12**:561-568.

13. Woolfson DN: **Building fibrous biomaterials from alpha-helical and collagen-like coiled-coil peptides**. *Biopolymers* 2010, **94**:118-127.

14. Tamerler C, Khatayevich D, Gungormus M, Kacar T, Oren EE, Hnilova M, Sarikaya M: **Molecular biomimetics: GEPI-based biological routes to technology**. *Biopolymers* 2010, **94**:78-94.

15. Cui HG, Webber MJ, Stupp SI: **Self-assembly of peptide amphiphiles: from molecules to nanostructures to biomaterials**. *Biopolymers* 2010, **94**:1-18.

16. Galler KM, Aulisa L, Regan KR, D'Souza RN, Hartgerink JD: **Self-assembling multidomain peptide hydrogels: designed susceptibility to enzymatic cleavage allows enhanced cell migration and spreading**. *J Am Chem Soc* 2010, **132**:3217-3223.

17. Krishna OD, Kiick KL: **Protein- and peptide-modified synthetic polymeric biomaterials**. *Biopolymers* 2010, **94**:32-48.

18. MacEwan SR, Chilkoti A: **Elastin-like polypeptides: biomedical applications of tunable biopolymers**. *Biopolymers* 2010, **94**:60-77.

19. Chow D, Nunalee ML, Lim DW, Simnick AJ, Chilkoti A: **Peptide-based biopolymers in biomedicine and biotechnology**. *Mater Sci Eng: R: Reports* 2008, **62**:125-155.

20. McGregor DP: **Discovering and improving novel peptide therapeutics**. *Curr Opin Pharmacol* 2008, **8**:616-619.

21. •• Reichert J: *Development Trends for Peptide Therapeutics*. San Diego, CA: Peptide Therapeutics Foundation (PTF); 2010.
This report is a comprehensive assessment of the current status of peptide therapeutics in clinic or under development.

22. Tiefenbrunn TK, Dawson PE: **Chemoselective ligation techniques: modern applications of time-honored chemistry**. *Biopolymers* 2010, **94**:95-106.

23. Rughani RV, Schneider JP: **Molecular design of beta-hairpin peptides for material construction**. *MRS Bull* 2008, **33**:530-535.

24. Zhang SG, Marini DM, Hwang W, Santoso S: **Design of nanostructured biological materials through self-assembly of peptides and proteins**. *Curr Opin Chem Biol* 2002, **6**:865-871.

25. Jung JP, Gasiorowski JZ, Collier JH: **Fibrillar peptide gels in biotechnology and biomedicine**. *Biopolymers* 2010, **94**:49-59.

26. • Rudra JS, Tian YF, Jung JP, Collier JH: **A self-assembling peptide acting as an immune adjuvant**. *Proc Natl Acad Sci USA* 2010, **107**:622-627.
This paper demonstrates the first immune adjuvant developed from an epitope-bearing self-assembling peptide that forms β-sheet-rich fibrils.

27. Lee J-h, Choi YJ, Lim Y-b: **Self-assembled filamentous nanostructures for drug/gene delivery applications**. *Exp Opin Drug Deliv* 2010, **7**:341-351.

28. • Wu K, Liu J, Johnson RN, Yang J, Kopeček J: **Drug-free macromolecular therapeutics: induction of apoptosis by coiled-coil-mediated cross-linking of antigens on the cell surface**. *Angew Chem Int Ed* 2010, **49**:1451-1455.
This contribution reports a new approach to the induction of apoptosis in cancer cells through the biorecognition of a peptide-polymer hybrid network.

29. Bugge TH, Antalis TM, Affara NI, Andreu P, Coussens LM: **Delineating protease functions during cancer development**. In *Proteases and Cancer. Methods in Molecular Biology*, vol 539. Edited by Walker JM. Humana Press; 2009:1-32.

30. van Kempen LCL, de Visser KE, Coussens LM: **Inflammation, proteases and cancer**. *Eur J Cancer* 2006, **42**:728-734.

31. Iiizumi M, Liu W, Pai SK, Furuta E, Watabe K: **Drug development against metastasis-related genes and their pathways: A rationale for cancer therapy**. *Biochim Biophys Acta (BBA) — Rev Cancer* 2008, **1786**:87-104.

32. Liu C, He X: **Destruction of a destructor: a new avenue for cancer therapeutics targeting the Wnt pathway**. *J Mol Cell Biol* 2010, **2**:70-73.

33. Young A, Lyons J, Miller AL, Phan VT, Alarcón IR, McCormick F: **Ras signaling and therapies**. In: *Advances in Cancer Research*, Vande Woude GF, Klein, G. (Eds.) Academic Press; 2009, **102**:1–17.

34. Chen LS, Balakrishnan K, Gandhi V: **Inflammation and survival pathways: Chronic lymphocytic leukemia as a model system**. *Biochem Pharmacol* 2010, **80**:1936-1945.

35. • Yang ZM, Xu KM, Guo ZF, Guo ZH, Xu B: **Intracellular enzymatic formation of nanofibers results in hydrogelation and regulated cell death**. *Adv Mater* 2007, **19**:3152-3156.
This paper shows the smart design of a peptide that forms nanostructures only within a cell that ultimately affects cellular behavior.

36. Torchilin V.: **Tumor delivery of macromolecular drugs based on the EPR effect**. *Adv Drug Deliv Rev*, in press.

37. Maeda H: **Tumor-selective delivery of macromolecular drugs via the EPR effect: background and future prospects**. *Bioconjugate Chem* 2010, **21**:797-802.

38. Maeda H, Bharate GY, Daruwalla J: **Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect**. *Eur J Pharmaceut Biopharmaceut* 2009, **71**:409-419.

39. • Standley SM, Toft DJ, Cheng H, Soukasene S, Chen J, Raja SM, Band V, Band H, Cryns VL, Stupp SI: **Induction of cancer cell death by self-assembling nanostructures incorporating a cytotoxic peptide**. *Cancer Res* 2010, **70**:3020-3026.
This paper utilizes a peptide amphiphile platform to form wormlike micelles (nanofibers) that can disrupt breast cancer cell membranes and induce cell death.

40. • Missirlis D, Krogstad DV, Tirrell M: **Internalization of p53(14-29) peptide amphiphiles and subsequent endosomal disruption results in SJSA-1 cell death**. *Mol Pharmaceut* 2010, **7**:2173-2184.
This contribution shows preliminary work in the development of novel peptide amphiphile nanoparticles as potential inhibitors of cellular protein interactions.

41. • Aulisa L, Forraz N, McGuckin C, Hartgerink JD: **Inhibition of cancer cell proliferation by designed peptide amphiphiles**. *Acta Biomater* 2009, **5**:842-853.
This paper demonstrates novel peptide amphiphile micelles as inhibitors of nuclear protein interactions involved in DNA transcription.

42. Hancock REW: **Cationic peptides: effectors in innate immunity and novel antimicrobials**. *Lancet Infectious Dis* 2001, **1**:156-164.

43. Kindrachuk J, Napper S: **Structure–activity relationships of multifunctional host defence peptides**. *Mini Rev Med Chem* 2010, **10**:596-614.

44. Shai Y: **Mode of action of membrane active antimicrobial peptides**. *Biopolymers* 2002, **66**:236-248.

45. • Liu LH, Xu KJ, Wang HY, Tan PKJ, Fan WM, Venkatraman SS, Li LJ, Yang YY: **Self-assembled cationic peptide nanoparticles as an efficient antimicrobial agent**. *Nature Nanotechnol* 2009, **4**:457-463.
This contribution shows the design of robust self-assembled cationic peptide nanoparticles that show a high therapeutic index against several bacteria, fungi, and yeasts.

46. Yang Z, Liang G, Guo Z, Guo Z, Xu B: **Intracellular hydrogelation of small molecules inhibits bacterial growth**. *Angew Chem Int Ed* 2007, **46**:8216-8219.

47. • Salick DA, Kretsinger JK, Pochan DJ, Schneider JP: **Inherent antibacterial activity of a peptide-based beta-hairpin hydrogel**. *J Am Chem Soc* 2007, **129**:14793-14799.
This paper describes the design of a self assembling β-sheet rich hydrogel with inherent broad spectrum antibacterial activity towards Gram-negative and positive bacteria.

48. Salick DA, Pochan DJ, Schneider JP: **Design of an injectable beta-hairpin peptide hydrogel that kills methicillin-resistant *Staphylococcus aureus***. *Adv Mater* 2009, **21**:4120.

49. Perez SA, von Hofe E, Kallinteris NL, Gritzapis AD, Peoples GE, Papamichail M, Baxevanis CN: **A new era in anticancer peptide vaccines**. *Cancer* 2010, **116**:2071-2080.

50. Mocellin S, Pilati P, Nitti D: **Peptide-based anticancer vaccines: recent advances and future perspectives**. *Curr Med Chem* 2009, **16**:4779-4796.

51. Rudra JS, Tripathi PK, Hildeman DA, Jung JP, Collier JH: **Immune responses to coiled coil supramolecular biomaterials**. *Biomaterials* 2010, **31**:8475-8483.

52. Tang A, Kopecek J: **Presentation of epitopes on genetically engineered peptides and selection of lymphoma-targeting moieties based on epitope biorecognition**. *Biomacromolecules* 2002, **3**:421-431.

53. Tang AJ, Wang C, Stewart R, Kopecek J: **Self-assembled peptides exposing epitopes recognizable by human lymphoma cells**. *Bioconjugate Chem* 2000, **11**:363-371.

54. Perriman AW, Williams DS, Jackson AJ, Grillo I, Koomullil JM, Ghasparian A, Robinson JA, Mann S: **Synthetic virus-like particles and hybrid constructs based on lipopeptide self-assembly**. *Small* 2010, **6**:1191-1196.

55. • Boato F, Thomas RM, Ghasparian A, Freund-Renard A, Moehle K, Robinson JA: **Synthetic virus-like particles from self-assembling coiled-coil lipopeptides and their use in antigen display to the immune system**. *Angew Chem Int Ed* 2007, **46**:9015-9018.
This manuscript describes the design of a synthetic virus-like particle vaccine formed from a self-assembling coiled-coil lipopeptide.

56. Kaba SA, Brando C, Guo Q, Mittelholzer C, Raman S, Tropel D, Aebi U, Burkhard P, Lanar DE: **A nonadjuvanted polypeptide nanoparticle vaccine confers long-lasting protection against rodent malaria**. *J Immunol* 2009, **183**:7268-7277.

57. • Pimentel T, Yan Z, Jeffers SA, Holmes KV, Hodges RS, Burkhard P: **Peptide nanoparticles as novel immunogens: design and analysis of a prototypic severe acute respiratory syndrome vaccine**. *Chem Biol Drug Des* 2009, **73**:53-61.
This contribution describes a promising nanoparticle platform for vaccine design developed from self assembling coiled-coil peptides displaying antigenic epitopes.