Abstract: Described herein are hydrogelators that include a nucleobase, an amino acid, and a glycoside. The hydrogelators have increased resistance to proteases and can self-assemble into supramolecular nanofibers or hydrogels. The supramolecular structures may be used to help grow cells or deliver a substance to a cell.
Supramolecular Nanofibers and Hydrogels Based on Amino Acid-Nucleobase-Glycoside Conjugates

RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional Patent Application serial number 61/491,544, filed May 31, 2011, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Hydrogels, which consist of crosslinked matrices and water, have emerged as an important class of biomaterials due to their morphological similarity to extracellular matrices (ECM) in tissues and organs. Although both natural polymers (e.g., collagen, gelatin, hyaluronic acid, and alginate) and synthetic polymers (e.g., poly(D-L-lactide-co-glycolide), poly(N-isopropyl acrylic amide), and poly(ethylene oxide)) can serve as hydrogels in biomedical applications (e.g., tissue engineering and drug delivery), the currently known members of each class have considerable drawbacks or limitations. For example, the separation and purification of natural polymers are non-trivial, and synthetic polymers are largely passive even if they are functionalized.

Nanofibers, comprised of self-assembled peptides, that form supramolecular hydrogels have shown considerable promise. These self-assembled peptides have served as scaffolds to guide the differentiation of neuron progenitor cells, media for cell culture, and carriers for drug release. Like modified peptides, derivatives of glycosides can also self-assemble into nanofibers to give supramolecular gels or hydrogels, which has led to the development of semi-wet peptide/protein arrays as biosensors and intelligent soft materials. Recently, nanofibers of deoxynucleic acid (DNA) were found to form supramolecular hydrogels.

SUMMARY OF THE INVENTION

In certain embodiments, the invention relates to a hydrogelator of Formula I

![Chemical Structure](image)

wherein, independently for each occurrence,
is cytosinyl, guaninyl, adeninyl, thyminyl, uracilyl, or an oligonucleic acid;

is fructosyl, galactosyl, glucosyl, mannosyl, or an oligosaccharide;

R is H or alkyl;

R¹ is H, alkyl, alkylthioalkyl, aralkyl, heteroaralkyl, hydroxyaralkyl, H0₂C-alkyl, or guanidinylalkyl; and

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

In certain embodiments, the invention relates to a supramolecular structure, comprising a plurality of any one of the aforementioned hydrogelators.

In certain embodiments, the invention relates to a hydrogel, wherein the hydrogel comprises a plurality of any one of the aforementioned hydrogelators; and water.

In certain embodiments, the invention relates to a hydrogel, wherein the hydrogel comprises a plurality of any one of the aforementioned supramolecular structures; and water.

**BRIEF DESCRIPTION OF THE FIGURES**

**Figure 1** depicts (a) structures of exemplary hydrogelators (except 1C) comprising nucleobase, amino acid, and glycoside; and (b) a cartoon representing the resulting supramolecular structure.

**Figure 2** depicts an exemplary synthetic route for the preparation of hydrogelators 1A and 2A.

**Figure 3** depicts the molecular structures and exemplary synthetic routes for the preparation of hydrogelators 1A, 2A, 2C, 1G, 2G, and compound 1C.

**Figure 4** depicts photographs of the hydrogels of 1T (3.0 wt%, pH=7.0), 2T (3.0 wt%, pH=8.5), 2C (3.0 wt%, pH=7.5), 1A (3.0 wt%, pH=5.0), 2A (3.0 wt%, pH=5.0), 1G (3.0 wt%, pH=4.0) and 2G (3.0 wt%, pH=4.0); and the solution of 1C (3.0 wt%, pH=7.0).

**Figure 5** depicts transmission electron micrographs of negative stained hydrogels of IT, 2T, 2C, 1A, 2A, 1G and 2G; and solution of 1C. Scale bar = 100 nm; the concentration and pH value for each of them are same as in Figure 4.

**Figure 6** depicts transmission electron micrographs of hydrogels of (a) IT and (b) 2T.

**Figure 7** depicts transmission electron micrographs of (a) the solution of 1C and (b) the hydrogel of 2C.
Figure 8 depicts transmission electron micrographs of hydrogels of (a) 1A and (b) 2A.

Figure 9 depicts transmission electron micrographs of hydrogels of (a) 1G and (b) 2G.

Figure 10 depicts the UV-vis absorption spectrum of: (A) 1T in aqueous solution (c = 6.0x10^-4 M); and (B) 2T in aqueous solution (c = 3.0x10^-4 M); the data indicate there is no chromophoric absorption around 296 nm in the solutions.

Figure 11 depicts (A) the critical strain, and (B) dynamic storage moduli (G') of hydrogels of 1T, 2T, 2C, 1A, 2A, 1G and 2G; (C) the CD spectra of hydrogels of 1T, 1A, 1G and solution of 1C; (D) the CD spectra of hydrogels of 2T, 2C, 2A, and 2G. The concentration and pH value for each of them are same as for Figure 4.

Figure 12 depicts the circular dichroism (CD) spectra of the hydrogel of 1T, the solution of poly(IOA), the mixture solution of thymine acetic acid with poly(IOA) in 1:1 molecular ratio, and the hydrogel of 1T mixed with poly(IOA) in 1:1 molecular ratio.

Figure 13 depicts (A) strain dependence of dynamic storage moduli (G') and loss moduli (G'') of hydrogels of 1T, 2T, 2C, 1A, 2A, 1G and 2G; (B) frequency dependence of dynamic storage moduli (G') and loss moduli (G'') of hydrogels of 1T, 2T, 2C, 1A, 2A, 1G and 2G, as shown in Figure 4.

Figure 14 depicts 72 hr cell viability test of (A) hydrogelators 1, and (B) hydrogelators 2; optical images of the scratch-wound assay to assess the effects of 2T in the media on wound closure; optical images of HeLa cells on the surface at 0 h (C); and at 20 h (D) after the creation of wound in the presence of 2T (by adding 500 µM of 2T in the media); and (E) the time-dependent course of digestions of hydrogelators of 2T, 2C, 2A and 2G by proteinase K.

Figure 15 depicts the CD spectra of the hydrogels of 1T, 1A, 1G, and the solution of 1C.

Figure 16 depicts optical images of (A) the highly viscous solution of 1T (2.1 wt%, pH=7.0); (B) 1T+deoxyadenosine (A_{10}) mixed hydrogel after the addition of deoxyadenosine (Aio) in 1:1 molecular ratio.

Figure 17 depicts (left) strain dependence of dynamic storage moduli (G') and loss moduli (G'') of the hydrogels of 1T, and 1T+deoxyadenosine (A_{10}) mixed gel; (right) frequency dependence of dynamic storage moduli (G') and loss moduli (G'') of the hydrogels of 1T, and 1T+deoxyadenosine (A_{10}) mixed gel shown in Figure 16.
**Figure 18** depicts (A) The molecular structures of NapFFCGLDD and thymine-FF, and (B) their time-dependent course of the digestions by proteinase K as control experiment, in which NapFFCGLDD is the heptapeptide derivative and thymine-FF is the nucleopeptide without D-glucosamine in conjugation.

**Figure 19** depicts fluorescence and bright field microscopy images illustrating nuclear localization of DNA released from the IT and nucleic acid complex. Nucleic acid was labeled with fluorescien dye (FITC) (green). Cell nuclei were stained with SYTO 85. (A) 500 µM IT and 0.1 µM nucleic acid labeled with FITC complex incubated with HeLa cells for 24 h. (B) 0.1 µM nucleic acid labeled with FITC incubated with HeLa cells for 24 h.

**Figure 20** depicts the molecular structures and exemplary synthetic routes for the preparation of hydrogelators of the invention.

**Figure 21** depicts the molecular structures of hydrogelators consisting of nucleobase, RGD peptides, and glycoside. (a) 1A + RGD; (b) 1C + RGD; (c) 1G + RGD; (d) IT + RGD.

**Figure 22** depicts the cell viability (by cell number counting) of the 20,000 HeLa cells in Minimum Essential Medium treated with protease-tolerant supramolecular hydrogels of the compounds depicted in Figure 21 (left bar = 1A + RGD; second left bar = IT + RGD; second right bar = 1C + RGD; right bar = 1G + RGD).

**Figure 23** depicts cell viability (by cell number counting) of 20,000 Embryonic Stem Cells inhibited by a protease-tolerant supramolecular hydrogel of the compound depicted in Figure 21(a) (1A + RGD) in Primary Mouse Embryo Fibroblasts (PMEF) (left bar = 100 µM; middle bar = 200 µM; right bar = 500 µM).

**DETAILED DESCRIPTION OF THE INVENTION**

**OVERVIEW**

In certain embodiments, the invention relates to a hydrogelator, wherein the hydrogelator comprises, consists essentially of, or consists of a nucleobase, an amino acid, and a glycoside. In certain embodiments, the invention relates to a multifunctional, biocompatible supramolecular nanofiber or hydrogel, comprising, consisting essentially of, or consisting of an aforementioned hydrogelator.

In certain embodiments, the invention relates to a hydrogelator, comprising a nucleobase (e.g., thymine), an amino acid (e.g., phenylalanine), and a glycoside (e.g., D-glucosamine), wherein they are covalently tethered. In certain embodiments, the hydrogelator forms molecular nanofibers that result in a supramolecular hydrogel at pH of about 7.0, and concentration of about 3.0 wt%. In certain embodiments, the invention relates
to a nanofiber, comprising a plurality of said hydrogelators. In certain embodiments, the invention relates to a supramolecular hydrogel, comprising a plurality of said nanofibers.

In certain embodiments, the invention relates to a hydrogelator, wherein the hydrogelator comprises thymine, cytosine, adenine, or guanine.

In certain embodiments, the invention relates to a hydrogelator, wherein the hydrogelator comprises alanine, isoleucine, leucine, methionine, phenylalanine, tryptophan, tyrosine, or valine. In certain embodiments, the hydrogelator comprises phenylalanine. In certain embodiments, the hydrogelator comprises diphenylalanine.

In certain embodiments, the invention relates to a hydrogelator, wherein the hydrogelator comprises a glycoside. In certain embodiments, the inclusion of glycoside in the hydrogelator significantly enhances its resistance to proteases. In certain embodiments, the glycoside is or is derived from a glucosamine or a galactosamine.

In certain embodiments, the invention relates to a hydrogelator, wherein the hydrogelator does not inhibit the growth of mammalian cells.

In certain embodiments, the invention relates to a nanofiber or a hydrogel comprising any one of the aforementioned hydrogelators.

HYDROGELATOR DESIGN, SYNTHESIS, AND DISCUSSION

Figure 1 shows the molecular design of two exemplary types of hydrogelators (1 and 2). Hydrogelator 1 consists of a nucleobase (e.g., thymine, cytosine, adenine, or guanine), a phenylalanine, and a D-glucosamine; hydrogelator 2 consists of a nucleobase, a bis(phenylalanine), and a D-glucosamine. In certain embodiments, the nucleobase and the D-glucosamine connect to the amino acid(s) at the N-terminus and C-terminus, respectively. Figure 2 outlines an exemplary synthetic route for making these hydrogelators. For example, thymine acetic acid (3) is activated by N-hydroxysuccinimide (NHS) before reacting with L-Phe to afford 4. After undergoing the same NHS activation, 4 couples with D-glucosamine to give the hydrogelator 1T. The addition of the second phenylalanine to 4 affords 5, which couples with D-glucosamine to yield the hydrogelator 2T.

The synthesis of other hydrogelators (i.e., 2C, 1A, 2A, 1G and 2G) and compound 1C starts from protected nucleobases (e.g., (A^5-fos-Boc-cytosine-1-yFi-acetic acid, (A^6-bis-Boc-adenine-9-yl)-acetic acid, and (N^2-£zs-Boc-guanine-9-yl)-acetic acid). First, bis(tert-butylloxycarbonyl) (bis-Boc) protected adenine, (A^b-bis-Boc-adenine-Q-yFi-acetic acid (6), was synthesized. After being activated by NHS, 6 reacts with L-Phe to afford 7, which undergoes the same NHS activation and D-glucosamine coupling to give the product 8.
Subsequent removal of the Boc-protecting groups by the addition of trifluoroacetic acid (TFA) gives the hydrogelator 1A in 42% total yield. The addition of the second phenylalanine to the compound 7 gives 9, which reacts with D-glucosamine to afford intermediate 10. After the Boc groups being removed, 10 turns into hydrogelator 2A. This five-step synthesis affords 2A in 37% total yield. Based on the same strategy, we obtain 1C, 2C, 1G, and 2G in 45%, 39%, 41%, and 43% total yields, respectively.

In certain embodiments, protonation and deprotonation of an amine group may be used to dissolve any one of the aforementioned hydrogelators at low pH. In certain embodiments, hydrogelation may be triggered by increasing the pH. In certain embodiments, the hydrogelators dissolve in water at about 3.0 wt% and pH of about 10.0. In certain embodiments, the hydrogelators dissolve in water at about 3.0 wt% and pH of about 10.0 with gentle heating. In fact, changing the pH values of the solutions of 1T and 2T from 10.0 to 7.0 and 8.5, respectively, results in transparent hydrogels. The mixture containing 1C, however, remains as a solution at the same conditions. The increase of the pH value of the solution of 1C up to pH 10.0 only results in a small amount of white precipitate. While 1A forms an opaque hydrogel at pH 5.0, 1G produces a semitransparent hydrogel at pH 4.0. Hydrogelators 2T, 2C, 2A and 2G all are able to self-assemble in water to form semitransparent hydrogels at a concentration of about 3.0 wt% and a pH of about 8.5, 7.5, 5.0 and 4.0, respectively. The different optical appearances of the hydrogels and the final pH for hydrogelation suggest subtle differences in solubility for these hydrogelators.

Transmission electron microscopy (TEM) was used to examine the microstructures of the matrices of the hydrogels formed by these hydrogelators. As revealed by TEM in Figure 5, each hydrogelator exhibits distinctive morphology of the nanostructures in the corresponding hydrogels. For example, while the nanofibers of 1T are thin and straight and with the diameter of about 12 nm, the nanofibers of 2T (about 15 nm in diameter) appear to bend easily and to crosslink relatively heavily. The solution of 1C only results in featureless aggregates, likely due to non-specific absorption of the 1C on the carbon film of TEM grid. The hydrogel of 2C consists of nanobelts (about 25 nm wide) that physically crosslink into networks. The nanofibers of 2C also form bundles that likely contribute to the high storage modulus (Figure 11B). While both short nanofibers (14 nm in width and 200 nm in length) and nanoparticles (average diameter of 18 nm) present as the solid phase in the hydrogel of 1A, the hydrogel of 2A exhibits only nanofibers, which tend to crosslink physically to afford the network. The hydrogel of 1G appears to comprise thin nanofibers (9 nm in width) and
aggregated nanoparticles whose diameters are about 27 nm. Hydrogelator 2G self-assembles in water to form long thin nanofibers with a width of about 13 nm, and the nanofibers in 2G entangle with each other to form a dense nanofiber network, which also contributes to its relatively high storage modulus (Figure 11B).

Because hydrogels are viscoelastic they resist external destruction. Rheometry was used to study the viscoelastic properties of the instant hydrogels and to evaluate their critical strains and storage moduli (G'). Based on the results from the strain sweep (Figure 10), the hydrogel of IT shows the highest tolerance to external shear force with critical strain value at 0.5 % (Figure 11A). The critical strain values of the hydrogels of 1A, 1G, 2T, 2C, 2A, and 2G are at 0.23, 0.28, 0.31, 0.27, 0.39, and 0.18 %, respectively, suggesting that the networks in these hydrogels lose their integrity relatively easily upon application of external force. The frequency sweep shows that the dynamic storage moduli (G') of the hydrogels (IT, 2T, 2C, 1A, 2A, 1G and 2G) dominate their dynamic loss moduli (G") (Figure 10), indicating that all samples behave as viscoelastic materials. Among these hydrogels, the hydrogel of 2C exhibits the highest storage modulus (220 KPa). The hydrogels of 1G, 2G, IT, 2T, and 1A possess relatively high storage moduli of 139, 101, 34, 32, and 6 KPa, respectively. The hydrogel of 2A exhibits the lowest storage modulus (0.37 KPa), likely due to the short constituent nanofibers and nanoparticles, which disfavour the formation of crosslinked network.

Circular dichroism (CD) spectroscopy provides helpful information about self-assembled superstructures in the gel phase or liquid crystal phases. Thus, we used circular dichroism (CD) to study the secondary structures of nanofibers self-assembled from different compounds in the gel phase. As shown in Figure 11, hydrogels of IT, 2T, 2C, 2A, 2G all exhibit a positive peak near 195 nm and a negative peak around 210 nm, suggesting that the backbones of the hydrogelators adopt β-sheet-like configurations in the self-assembled structures. The CD spectrum of the hydrogel of 2T shows a negative broad band around 296 nm, which likely originates from the formation of a mesophase of 2T because it locates far from the chromophoric absorption region (ca. 268 nm) of compound 2T (Figure 10). The CD spectra of hydrogels of 1A and 1G display a maximum around 201 nm and a minimum near 210 nm, slightly red-shifted from the maxima and minima found in typical β-sheets, indicating that the supramolecular structures share the common feature of a β-sheet structure, but in a less ordered conformation or in a mixture of β-sheet and random coil structures. The
solution of 1C exhibits the weakest CD absorptions, agreeing with the poor tendency for compound 1C to self-assemble in water to form ordered structures.

To verify the biocompatibility of the hydrogelators, hydrogelators 1 and 2 were added into a culture of mammalian cells, and the proliferation of the cells was measured. MTT assay results, shown in Figure 14A and Figure 14B, revealed cell viability remained at 90% after incubation with 500 μM hydrogelator (IT, 1G, 2T, 2C, 2A, 2G) for 72 hours. Although the cell viability decreased slightly when the cells were incubated with 500 μM of 1C or 1A for 72 hours, the value of IC₅₀ is still > 500 μM. These results suggest that hydrogelators 1 and 2 are biocompatible. In order to further examine the biocompatibility of the hydrogelators, we also conducted a simple wound-healing assay with hydrogelator IT. As shown in Figure 14D, the presence of the hydrogelator of IT in cell culture has little inhibitory effect on the migration of cells.

Besides biocompatibility, biostability is also an essential prerequisite for a biomaterial. Thus, we examined the stability of hydrogelators 2 by incubating them with proteinase K, a powerful protease that hydrolyzes a broad spectrum of peptides. As shown in Figure 14E, hydrogelators 2 exhibit excellent resistance to enzymatic digestion, indicated by more than 85% of 2T and 2G and 95% of 2C and 2A remaining intact after 24 hours of incubation. Due to their high resistance to proteases, the hydrogels formed by hydrogelators 2 promise to serve as new biomaterials for applications that require long-term biostability.

DEFINITIONS

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are
conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another
embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.
EXEMPLARY HYDROGELATORS OF THE INVENTION

In certain embodiments, the invention relates to a hydrogelator of Formula I

wherein, independently for each occurrence,

- A is cytosinyl, guaninyl, adeninyl, thyminyl, uracilyl, or an oligonucleic acid;
- B is fructosyl, galactosyl, glucosyl, mannosyl, or an oligosaccharide;
- R is H or alkyl;
- R¹ is H, alkyl, alkylthioalkyl, aralkyl, heteroaralkyl, hydroxyaralkyl, HO₂C-alkyl, or guanidinylalkyl; and

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein A is cytosinyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein A is guaninyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein A is adeninyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein A is thyminyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein A is uracilyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein A is an oligonucleic acid.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein B is glucosyl. In certain embodiments, the invention relates to
any one of the aforementioned hydrogelators, wherein \( \text{B} \) is an oligosaccharide. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( \text{B} \) is chondrosinyl.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R \) is H.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is H.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is alkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is methyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is ethyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is propyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is isopropyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is butyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is isobutyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is sec-butyl.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is alkylthioalkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is \( \text{CH}_3\text{-S-CH}_2\text{CH}_2\text{-} \).

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is aralkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is benzyl.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is heteroaralkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein \( R^1 \) is indolyl-\( \text{CH}_2\text{-} \). In certain
embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein

\[
\begin{array}{c}
\text{R}^1 \text{is} \\
\text{NH} \\
\end{array}
\]

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is hydroxyaralkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is hydroxybenzyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is 4-hydroxybenzyl.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is HO\(_2\)C-alkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is HO\(_2\)C-CH\(_2\)-.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is guanidinylalkyl. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein R\(^1\) is guanidinyl-CH\(_2\)CH\(_2\)CH\(_2\)-.

In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein n is 1. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein n is 2. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein n is 3. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein n is 4. In certain embodiments, the invention relates to any one of the aforementioned hydrogelators, wherein n is 5.

In certain embodiments, the invention relates to a compound selected from the group consisting of:
In certain embodiments, the invention relates to a supramolecular structure, comprising a plurality of any one of the aforementioned hydrogelators.

In certain embodiments, the invention relates to any one of the aforementioned supramolecular structures, wherein the supramolecular structure is in the form of nanofibers or nanobelts. In certain embodiments, the average diameter of the nanofibers or the average width of the nanobelts is about 8 nm, about 9 nm, about 10 nm, about 11 nm, about 12 nm, about 13 nm, about 14 nm, about 15 nm, about 16 nm, about 17 nm, about 18 nm, about 19 nm, about 20 nm, about 21 nm, about 22 nm, about 23 nm, about 24 nm, or about 25 nm.
certain embodiments, the nanofibers are crosslinked. In certain diameters, the nanofibers are substantially straight. In certain embodiments, the nanofibers are bent. In certain embodiments, the nanofibers form bundles of nanofibers. In certain embodiments, the nanofibers are about 100 nm, about 120 nm, about 140 nm, about 160 nm, about 180 nm, about 200 nm, about 220 nm, about 240 nm, about 260 nm, about 280 nm, or about 300 nm in length.

In certain embodiments, the invention relates to any one of the aforementioned supramolecular structures, wherein the supramolecular structure is in the form of aggregated nanoparticles. In certain embodiments, the average diameter of the aggregated nanoparticles is about 20 nm, about 21 nm, about 22 nm, about 23 nm, about 24 nm, about 25 nm, about 26 nm, about 27 nm, about 28 nm, about 29 nm, about 30 nm, about 31 nm, about 32 nm, about 33 nm, about 34 nm, or about 35 nm.

**EXEMPLARY HYDROGELS OF THE INVENTION**

In certain embodiments, the invention relates to a hydrogel, wherein the hydrogel comprises a plurality of any one of the aforementioned hydrogelators; and water.

In certain embodiments, the invention relates to a hydrogel, wherein the hydrogel comprises a plurality of any one of the aforementioned supramolecular structures; and water.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel is formed from a solution of the hydrogelators in water. In certain embodiments, the hydrogelator is present in an amount from about 1.5% to about 6% by weight. In certain embodiment, the hydrogelator is present in an amount of about 2.0%, about 2.5%, about 3.0%, about 3.5%, or about 4.0% by weight.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel is formed from a solution of the hydrogelators in water. In certain embodiments, the pH of the solution is about 10.0, about 9.5, about 9.0, or about 8.5.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel is formed from a solution of the hydrogelators in water. In certain embodiments, the temperature of the solution is about 20 °C, about 25 °C, about 30 °C, about 35 °C, or about 40 °C.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel is formed by decreasing the pH of the solution of hydrogelators in water. In certain embodiments, the pH at which...
structure is formed is about 9.0, about 8.5, about 8.0, about 7.5, about 7.0, about 6.5, about 6.0, about 5.5, about 5.0, about 4.5, about 4.0, or about 3.5.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel has a critical strain value of from about 0.15% to about 0.45%. In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel has a critical strain value of about 0.15%, about 0.16%, about 0.17%, about 0.18%, about 0.19%, about 0.20%, about 0.21%, about 0.22%, about 0.23%, about 0.24%, about 0.25%, about 0.26%, about 0.27%, about 0.28%, about 0.29%, about 0.30%, about 0.31%, about 0.32%, about 0.33%, about 0.34%, about 0.35%, about 0.36%, about 0.37%, about 0.38%, about 0.39%, about 0.40%, about 0.41%, about 0.42%, about 0.43%, about 0.44%, or about 0.45%.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel has a storage modulus of from about 0.2 KPa to about 150 KPa. In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel has a storage modulus of about 0.2 KPa, about 0.3 KPa, about 0.4 KPa, about 0.5 KPa, about 0.6 KPa, about 0.8 KPa, about 1 KPa, about 2 KPa, about 3 KPa, about 4 KPa, about 5 KPa, about 6 KPa, about 7 KPa, about 8 KPa, about 9 KPa, about 10 KPa, about 15 KPa, about 20 KPa, about 25 KPa, about 30 KPa, about 35 KPa, about 40 KPa, about 50 KPa, about 60 KPa, about 70 KPa, about 80 KPa, about 90 KPa, about 100 KPa, about 110 KPa, about 120 KPa, about 130 KPa, about 140 KPa, or about 150 KPa.

In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel is substantially biocompatible. In certain embodiments, the invention relates to any one of the aforementioned hydrogels, wherein the hydrogel is substantially biostable.

**EXEMPLARY METHODS OF THE INVENTION**

In certain embodiments, the invention relates to a method of growing cells, comprising contacting a plurality of cells with any one of the aforementioned supramolecular structures or any one of the aforementioned hydrogels. In certain embodiments, the cells are engineered tissue cells. In certain embodiments, the cells are stem cells. In certain embodiments, the cells are skin cells.
In certain embodiments, the invention relates to a method of delivering a substance to a cell, comprising contacting the substance with any one of the aforementioned supramolecular structures or any one of the aforementioned hydrogels, thereby forming a substance-hydrogel delivery vehicle; and contacting the substance-hydrogel delivery vehicle and a cell.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the substance is a drug. In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the substance is a protein. In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the substance is a gene. In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the substance is siRNA. In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the substance is microRNA. In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the substance is a second cell.

In certain embodiments, the invention relates to a method of binding a nucleic acid, comprising contacting a nucleic acid with any one of the aforementioned supramolecular structures or any one of the aforementioned hydrogels.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the nucleic acid binding is selective nucleic acid binding.

In certain embodiments, the invention relates a method of separating a protein from a substance, comprising contacting a mixture with any one of the aforementioned supramolecular structures or any one of the aforementioned hydrogels, wherein the mixture comprises a protein.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the mixture comprises at least two proteins.

In certain embodiments, the invention relates to a method of treating or preventing a viral infection, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned hydrogelators.
In certain embodiments, the invention relates to a method of treating or preventing cancer, comprising
administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned hydrogelators.

In certain embodiments, the invention relates to a method of preventing adhesion of an organism or a cell to a surface, comprising
contacting the surface with any one of the aforementioned supramolecular structures or any one of the aforementioned hydrogels.

**EXEMPLIFICATION**

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

**Example 1 - Materials, Techniques, and General Procedures**

The materials, techniques, and general procedures apply to the remainder of the Examples. Chemical reagents and solvents were used as received from commercial sources. $^1$H and $^13$C, spectra were obtained on Varian Unity Inova 400, CD on a JASCO J-810 spectrometer, LC-MS on Waters Acquity ultra Performance LC with Waters MICROMASS detector, TEM on Morgagni 268 transmission electron microscope.

**Example 2 - Synthetic Methods**

Figure 3 depicts six synthetic schemes for various compounds of the invention.

**Synthesis of Thymine-Phe (4).** Thymine acetic acid (184 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in 20 mL of DMF, and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction mixture was stirred at room temperature overnight, and the resulted solid was filtered off. The filtrate was evaporated under reduced pressure to dryness, and the crude product was used in the next reaction without purification.

L-Phenylalanine (166 mg, 1 mmol) and Na$_2$C$_3$O$_4$ (84.8 mg, 0.8 mmol) were dissolved in 20 mL of water with stirring, and the solution of crude product (dissolved in 20 mL DMF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. The reaction mixture was vacuum-dried, then 30 mL of water was added and acidified to pH=3. The resulted product was obtained by filtration, washed with water, and then dried in vacuum. The white solid was purified by using HPLC with water-acetonitrile as eluent (from
8:2 to 4:6) to afford the product (4) in 78% yield for next step reaction. $^1$H NMR (400 MHz, OMSO-d$_6$): $\delta$ 8.56-8.54 (m, 1H), 7.33-7.20 (m, 6H), 4.45-4.40 (m, 1H), 4.19 (dd, $J$=16.0, 28.0 Hz, 2H), 3.04 (dd, $J$=4.0, 12.0Hz, 1H), 2.89 (dd, $J$=8.0, 16.0Hz, 1H), 1.73 (s, 3H) ppm.

**Synthesis of Thymine-Phe-glucosamine (IT).** Compound 4 (331.3 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in DMF (30 mL), and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction mixture was stirred at room temperature for 12 h, the resulted solid was filtered off, and the filtrate was evaporated under reduced pressure to dryness. The crude product was used for the next reaction without purification.

D-glucosamine hydrochloride (215.64 mg, 1 mmol) and Na$_2$CO$_3$ (212 mg, 2 mmol) were dissolved in water (20 mL) with stirring, and the solution of crude product (dissolved in 30 mL of DMF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. The reaction mixture was vacuum-dried, followed by the addition of 30 mL of water. The resulted product was isolated by filtration, washed with water, and then dried in vacuum. The white solid was purified by using HPLC with water-acetonitrile as eluent (from 8:2 to 5:5) to afford the product (2T) in 42% yield (206 mg). $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.34 (d, $J$ = 12.0 Hz, 1H), 8.05 (d, $J$ = 8.0 Hz, 1H), 7.32-7.14 (m, 5H), 6.54 (d, $J$ =4.0 Hz, 1H), 4.96-4.91 (m, 2H), 4.7-4.61 (m, 1H), 4.48-4.43 (m, 1H), 4.33-4.15 (m, 2H), 3.65-3.43 (m, 4H), 3.18-3.00 (m, 3H), 2.79-2.69 (m, 2H), 1.74-1.69 (s, 3H) ppm.

**Synthesis of Thymine-Phe-Phe (5).** Compound 4 (331 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in 20 mL of DMF, and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction mixture was stirred at room temperature overnight, the resulted solid was filtered off, and the filtrate was evaporated under reduced pressure to dryness. The crude product was used in the next reaction without purification.

L-Phenylalanine (166 mg, 1 mmol) and Na$_2$CO$_3$ (84.8 mg, 0.8 mmol) were dissolved in 20 mL of water with stirring, and the solution of crude product (dissolved in 20 mL DMF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. The reaction mixture was vacuum-dried, then 30 mL of water was added and the mixture was acidified to pH=3. The resulted product was obtained by filtration, washed with water, and then dried in vacuum. Compound 5 (white powder) was collected with 76%> yield (364 mg). $^1$H NMR (400 MHz, DMSG-d$_4$): $\delta$ 8.41-8.37 (m, 1H), 7.29-7.18 (m, 10H), 4.57-4.52 (m,
Synthesis of Thymine-Phe-Phe-glucosamine (2T). Compound 5 (478.5 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in DMF (30 mL), and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction mixture was stirred at room temperature for 12 h, the resulted solid was filtered off, and the filtrate was evaporated under reduced pressure to dryness. The crude product was used for the next reaction without purification.

D-glucosamine hydrochloride (215.64 mg, 1 mmol) and Na₂C₀₃ (212 mg, 2 mmol) were dissolved in water (20 mL) with stirring, and the solution of crude product (dissolved in 30 mL of DMF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. The reaction mixture was vacuum-dried, then 30 mL of water was added. The resulted product was isolated by filtration, washed with water, and then dried in vacuum. The white solid was purified by using HPLC with water-acetonitrile as eluent (from 8:2 to 5:5) to afford the product (2T) in 48% yield (382 mg). \( ^{1}H \) NMR (400 MHz, DMSO-<¾): \( \delta \) 8.27 (d, \( J = 12.0 \) Hz, 1H), 8.13 (d, \( J = 8.0 \) Hz, 1H), 7.93 (d, \( J = 8.0 \) Hz, 1H), 7.33-7.13 (m, 10H), 6.56 (d, \( J = 4.0 \) Hz, 1H), 4.98-4.92 (m, 2H), 4.71-4.43 (m, 3H), 4.28-4.19 (m, 2H), 3.67-3.44 (m, 4H), 3.18-2.64 (m, 7H), 1.74-1.69 (s, 3H) ppm.

Synthesis of Bis-Boc-Adenine-Phe (7). Bis-Boc adenine acetic acid (393.4 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in 30 mL of THF, and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction, the mixture was stirred at room temperature overnight, and the resulting solid was filtered off. The filtrate was evaporated under reduced pressure to dryness to afford the crude product for the next reaction without purification.

L-Phenylalanine (166 mg, 1 mmol) and Na₂C₀₃ (84.8 mg, 0.8 mmol) were dissolved in 20 mL of water with stirring, and the solution of crude product (dissolved in 30 mL THF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. After evaporation of the organic solvent, the residue was redissovled in 30 mL of water and acidified with hydrochloric acid to pH 2-3. The white precipitate was filtered off and purified by column chromatography over silica gel using chloroform/methanol as the eluents to afford compound 7 (443 mg, 82%) for next step reaction. \( ^{1}H \) NMR (400 MHz, DMSO-<¾): \( \delta \) 8.80 (s, 1H), 8.66 (b, 1H), 8.50 (s, 1H), 7.27-7.17 (m, 5H), 5.03 (dd, \( J = 20.0 \) Hz, 24.0 Hz,
2H), 4.37 (m, 1H), 3.08 (dd, J =4.0, 12.0 Hz, 1H), 2.92 (dd, J =8.0, 12.0 Hz, 1H), 1.37 (s, 18H) ppm.

Synthesis of Adenine-Phe-glucosamine (1A). Compound 7 (584.66 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in THF (30 mL), and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction mixture was stirred at room temperature for 12 h, the resulting solid was filtered off. Then the filtrate was evaporated under reduced pressure to dryness. The crude product was used for the next step reaction without purification.

D-glucosamine hydrochloride (215.64 mg, 1 mmol) and Na₂CO₃ (84.8 mg, 0.8 mmol) were dissolved in water (20 mL) with stirring, and the solution of crude product (dissolved in 30 mL of THF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. After evaporation of the organic solvent, the residue treated with 90% trifluoroacetic acid in water for 2 h. Then the mixture was concentrated by vacuum and purified by using HPLC with water-acetonitrile as eluent (from 8:2 to 5:5) to afford the product (1A) in 42% yield. H NMR (400 MHz, DMSO-<¾): δ 8.57-8.49 (m, 1H), 8.13-8.09 (m, 2H), 7.91 (s, 1H), 7.30-7.15 (m, 5H), 6.55 (d, J =4.0 Hz, 1H), 4.95-4.47 (m, 5H), 3.71-3.48 (m, 4H), 3.16-2.71 (m, 5H) ppm.

Synthesis of Bis-Boc-Adenine-Phe-Phe (9). Compound 7 (540 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in THF (30 mL), and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction mixture was stirred at room temperature for 12 h, the resulting solid was filtered off. Then the filtrate was evaporated under reduced pressure to dryness. The crude product was used for the next step reaction without purification.

L-Phenylalanine (166 mg, 1 mmol) and Na₂CO₃ (84.8 mg, 0.8 mmol) were dissolved in water (20 mL) with stirring, and the solution of crude product (dissolved in 30 mL of THF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. After evaporation of the organic solvent, the residue was redissolved in 30 mL of water and acidified with hydrochloric acid to pH 2-3. The white precipitate was filtered off and purified by column chromatography over silica gel using chloroform/methanol as the eluents to afford compound 9 (488 mg, 80% ). H NMR (400 MHz, DMSO-<¾): δ 8.78 (s, 1H), 8.70 (d, J=8.0 Hz, 1H), 8.49 (d, J=8.0 Hz, 1H), 8.42 (s, 1H), 7.24-7.10 (m, 10H), 4.96 (dd, J =16.0, 28.0 Hz, 2H), 4.61-4.56 (m, 1H), 4.46-4.40 (m, 1H), 3.09-2.99 (m, 2H), 2.91 (dd, J =8.0, 12.0 Hz, 1H), 2.75 (dd, J =8.0, 12.0 Hz, 1H), 1.37 (s, 18H) ppm.
Synthesis of Adenine-Phe-Phe-glucosamine (2A). Compound 9 (687.7 mg, 1 mmol) and NHS (126.5 mg, 1.1 mmol) were dissolved in THF (30 mL), and DCC (226.6 mg, 1.1 mmol) was added to the above solution with stirring. After the reaction, the mixture was stirred at room temperature for 12 h, and the resulted solid was filtered off. The filtrate was evaporated under reduced pressure to dryness. The crude product was used for the next reaction without purification.

D-glucosamine hydrochloride (215.64 mg, 1 mmol) and Na₂CO₃ (212 mg, 2 mmol) were dissolved in water (20 mL) with stirring, and the solution of crude product (dissolved in 30 mL of THF) was added. The resulted reaction mixture was stirred at room temperature for 24 h. After evaporation of the organic solvent, the residue treated with 90% trifluoroacetic acid in water for 2 h. Then the mixture was concentrated by vacuum and purified by using HPLC with water-acetonitrile as eluent (from 8:2 to 5:5) to afford the product (2A) in 37% yield. H NMR (400 MHz, DMSO-d₆): δ 8.45 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.95-7.90 (m, 2H), 6.57 (d, J = 4.0 Hz, 1H), 4.96 (b, 1H), 4.82-4.50 (m, 5H), 3.67-3.45 (m, 4H), 3.18-2.69 (m, 7H) ppm.

Synthesis of Bis-Boc-Cytosine-Phe (11). Compound 11 was synthesized by following the procedures described in synthesis of compound 7 except replacing the bis-Boc adenine acetic acid with bis-Boc cytosine acetic acid. Compound 11 (white powder) was collected with 83% yield (429 mg). H NMR (400 MHz, DMSO-d₆): δ 8.29 (s, 1H), 8.01 (d, J = 4.0 Hz, 1H), 7.22-7.16 (m, 5H), 6.79 (d, J = 8.0 Hz, 1H), 4.58-4.41 (m, 2H), 4.27 (s, 1H), 1.49 (s, 18H) ppm.

Synthesis of Cytosine-Phe-Glucosamine (1C). Compound 1C was synthesized by following the procedures described in synthesis of compound 1A except replacing the bis-Boc adenine acetic acid with bis-Boc cytosine acetic acid. Compound 1C (white powder) was collected with 45% yield. H NMR (400 MHz, DMSO-d₆): δ 8.52-8.44 (m, 1H), 8.01-7.92 (m, 1H), 7.71-7.63 (m, 1H), 7.30-7.13 (m, 5H), 6.53 (d, J = 8.0 Hz, 1H), 5.93-5.84 (m, 1H), 5.03-4.90 (m, 2H), 4.69-4.28 (m, 4H), 3.72-3.34 (m, 4H), 3.18-2.69 (m, 5H) ppm.

Synthesis of Bis-Boc-Cytosine-Phe-Phe (12). Compound 12 was synthesized by following the procedures described in synthesis of compound 9 except replacing the bis-Boc adenine acetic acid with bis-Boc cytosine acetic acid. Compound 12 (white powder) was collected with 61% yield (283 mg). H NMR (400 MHz, DMSO-d₆): δ 8.51 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.29-7.16 (m, 10H), 6.77 (d, J = 8.0 Hz, 1H), 4.58-4.38 (m, 4H), 3.07-2.71 (m, 4H), 1.48 (s, 18H) ppm.
Synthesis of Cytosine-Phe-Phe-Glucosamine (2C). Compound 2C was synthesized by following the procedures described in synthesis of compound 2A except replacing the bis-Boc adenine acetic acid with bis-Boc cytosine acetic acid. Compound 2C (white powder) was collected with 39% yield (360 mg). H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.32 (d, J = 8.0 Hz, 1H), 8.17-8.10 (m, 1H), 7.95-7.87 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.32-7.13 (m, 10H), 6.56 (s, 1H), 5.80 (d, J = 8.0 Hz, 1H), 4.96 (m, 2H), 4.71-4.29 (m, 5H), 3.71-3.45 (m, 4H), 3.18-2.66 (m, 7H) ppm.

Synthesis of Bis-Boc-Guanine-Phe (13). Compound 13 was synthesized by following the procedures described in synthesis of compound 7 except replacing the bis-Boc adenine acetic acid with bis-Boc guanine acetic acid. Compound 13 (white powder) was collected with 81% yield (462 mg). H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.71 (d, J = 8.0 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 7.31-7.19 (m, 5H), 4.91-4.79 (m, 2H), 4.44 (m, 1H), 3.06-3.01 (m, 2H), 2.94-2.88 (m, 2H), 1.34 (s, 18H) ppm.

Synthesis of Guanine-Phe-glucosamine (1G). Compound 1G was synthesized by following the procedures described in synthesis of compound 1A except replacing the bis-Boc adenine acetic acid with bis-Boc guanine acetic acid. Compound 1G (white powder) was collected with 41% yield (462 mg). H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.43 (d, J = 8.0 Hz, 1H), 8.11-8.04 (m, 1H), 7.30-7.14 (m, 5H), 6.57 (d, J = 4.0 Hz, 1H), 4.92 (b, 2H), 4.71-4.46 (m, 4H), 3.70-3.44 (m, 4H), 3.16-2.67 (m, 5H) ppm.

Synthesis of Bis-Boc-Guanine-Phe-Phe (14). Compound 9 was synthesized by following the procedures described in synthesis of compound 4 except replacing the bis-Boc adenine acetic acid with bis-Boc guanine acetic acid. Compound 14 (white powder) was collected with 75% yield (528 mg). H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.52 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.23-7.17 (m, 10H), 4.83-4.70 (m, 2H), 4.56 (s, 1H), 4.40 (s, 1H), 3.08-2.99 (m, 2H), 2.92-2.71 (m, 2H), 1.33 (s, 18H) ppm.

Synthesis of Guanine-Phe-Phe-glucosamine (2G). Compound 2G was synthesized by following the procedures described in synthesis of compound 2A except replacing the bis-Boc adenine acetic acid with bis-Boc guanine acetic acid. Compound 2G (white powder) was collected with 43% yield (292 mg). H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.41 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.72 (b, 1H), 7.33-7.10 (m, 10H), 6.57 (s, 1H), 4.96 (s, 2H), 4.70-4.61 (m, 3H), 4.51 (m, 2H), 3.72-3.47 (m, 4H), 3.17-2.67 (m, 7H) ppm.
**Example 3 - Transmission Electron Microscopy (TEM)**

Micrographs are depicted in Figure 5, Figure 6, Figure 7, Figure 8, and Figure 9.

**Example 4 - UV-Vis and Circular Dichroism (CD) Spectroscopy**

CD spectra were recorded (185-350 nm) using a JASCO 810 spectrometer under a nitrogen atmosphere. The hydrogels (0.2 mL, 3.0 wt %) were placed evenly on the 1 mm thick quartz cuvet and scanned with 0.5 nm interval.

Figure 10, Figure 11, Figure 12, and Figure 15 depict various UV-Vis and CD spectra.

**Example 5 - Rheological Measurements**

Rheological tests were conducted on TA ARES G2 rheometer (with TA Orchestrator Software). 25 mm parallel plate was used during the experiment. 0.5 mL of hydrogel sample was placed on the parallel plate. Figure 11 and Figure 13 depict data from these experiments.

i) Dynamic Strain Sweep Test

Test range (0.1 to 10 % strain, frequency = 10 rad s⁻¹), 10 points per decade. Sweep mode is "log" and temperature was carried out at 25 °C.

ii) Critical strain determination

The critical strain (γ₀) value was determined from the storage-strain profiles of the hydrogel sample. The strain applied to the hydrogel sample increased from 0.1 to 100 % (10 rad/s and 25°C). Over a certain strain, a drop in the elastic modulus was observed, and the strain amplitude at which storage moduli just begins to decrease by 5 % from its maximum value was determined and taken as a measure of the critical strain of the hydrogels, which correspond to the breakdown of the cross-linked network in the hydrogel sample.

**Example 6 - Wound-Healing Assay**

HeLa cells were re-suspended in 10 cm tissue culture dish after washing cells once with PBS. 0.8 mL 0.25 % trypsin containing 0.1 % EDTA was then added, and the cells were re-suspended with 1.6mL complete medium. 5000 cells (in 100 μL medium) were plated into each vial on a 96 well plate to create a confluent monolayer. After adherent for 24 hr, a wound was created by scraping the cell monolayer with a p200 pipet tip. The cells were washed once with 100 μL of complete medium to remove flowing cells and replace with 100 μL of complete medium. 0 hr image was acquired as a reference point. The medium was replaced with 100 μL of medium containing 500 μM of hydrogelator IT and the plate was
incubate at 37 °C, 5 % CO₂ for 20 hr. 0 hr and 20 hr images were acquired at the match photographed region.

Example 7 - Biostability

1 mg of each compound was dissolved in 5 mL HEPES buffer at pH=7.5. Then proteinase K were added in concentration 3.2 units/mL and incubated at 37 °C for 24 hr, then 100 μL of sample were taken out each time and analyzed by HPLC.

For the control experiment, 1 mg of NapFFCGLDD (heptapeptide derivative) and 1 mg of thymine-FF (nucleopeptides without glucosamine in conjugation) were dissolved in 5 mL HEPES buffer at pH=7.5 respectively. Then proteinase K were added in concentration 3.2 units/mL and incubated at 37 °C for 24 hr, then 100 μL of sample were taken out each time and analyzed by HPLC. Figure 18.

Example 8 - Preparation of IT+deoxyadenosine (A10) mixed gel and test of the interaction between IT and A10

The typical procedure for hydrogelation: 5.9 mg of IT dissolves in 224 μL water in 2.1 wt% with gentle heating to make clear solution, and followed by the addition of 57 μL of deoxyadenosine (Aₒ) (20 mM) to afford stable mixed hydrogel. And this mixed hydrogel was subject to CD, TEM and rheological studies to test the interaction between IT and deoxyadenosine (Aₒ). Figure 16 and Figure 17.

Example 9 - Nucleic Acid Delivery to the cell nuclei with aid of IT

HeLa cells were seeded in 2 well chamber slide at a density of 10,000 cell/well. After allowing the attachment at 37°C for 4 h, we removed culture medium and applied ImL of culture medium containing 0.1 μM fluorescein (FITC) labeled poly(IOA) with or without 500 μM hydrogelator IT. After incubation at 37°C for 24 h, we removed the culture medium, washed the cells by ImL PBS for 3 times, then resin the cells in ImL PBS. Fluorescence images were taken by using confocal fluorescence microscope. Figure 19.

INCORPORATION BY REFERENCE

All of the U.S. patents and U.S. patent application publications cited herein are hereby incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.
I claim:

1. A hydrogelator of Formula I

   \[ \text{I} \]
   
   \begin{align*}
   &\text{A} \\
   &\text{R} \quad \text{R}^{1} \quad \text{R} \\
   &\text{N} \quad \text{N} \\
   &\text{B}
   \end{align*}

   wherein, independently for each occurrence,

   - A is cytosinyl, guaninyl, adeninyl, thyminyl, uracilyl, or an oligonucleic acid;
   - B is fructosyl, galactosyl, glucosyl, mannosyl, or an oligosaccharide;

   R is H or alkyl;
   R\(^1\) is H, alkyl, alkylthioalkyl, aralkyl, heteroaralkyl, hydroxyaralkyl, H\(_2\)C-alkyl, or guanidinylalkyl; and

   n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

2. The hydrogelator of claim 1, wherein A is cytosinyl.

3. The hydrogelator of claim 1, wherein A is guaninyl.

4. The hydrogelator of claim 1, wherein A is adeninyl.

5. The hydrogelator of claim 1, wherein A is thyminyl.

6. The hydrogelator of claim 1, wherein A is uracilyl.

7. The hydrogelator of claim 1, wherein A is an oligonucleic acid.

8. The hydrogelator of any one of claims 1-7, wherein B is glucosyl.

9. The hydrogelator of any one of claims 1-7, wherein B is an oligosaccharide.

10. The hydrogelator of any one of claims 1-7, wherein B is chondrosinyl.
11. The hydrogelator of any one of claims 1-10 where in R is H.
12. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is H.
13. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is alkyl.
14. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is methyl.
15. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is ethyl.
16. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is propyl.
17. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is isopropyl.
18. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is butyl.
19. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is isobutyl.
20. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is sec-butyl.
21. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is alkylthioalkyl.
22. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is CH\(_3\)S-CH\(_2\)CH\(_2\)\(^-\).
23. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is aralkyl.
24. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is benzyl.
25. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is heteroaralkyl.
26. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is indolyl-CH\(_2\)\(^-\).
27. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is indolyl-CH\(_2\)\(^-\).
28. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is hydroxyaralkyl.
29. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is hydroxybenzyl.
30. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is 4-hydroxybenzyl.
31. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is H0\(_2\)C-alkyl.
32. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is H0\(_2\)C-CH\(_2\)\(^-\).
33. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is guanidinylalkyl.
34. The hydrogelator of any one of claims 1-11, wherein R\(^1\) is guanidinyl-CH\(_2\)CH\(_2\)CH\(_2\)\(^-\).
35. The hydrogelator of any one of claims 1-34, wherein n is 1.
36. The hydrogelator of any one of claims 1-34, wherein n is 2.
37. The hydrogelator of any one of claims 1-34, wherein n is 3.
38. The hydrogelator of any one of claims 1-34, wherein n is 4.
39. The hydrogelator of any one of claims 1-34, wherein n is 5.
40. A compound selected from the group consisting of:

- ![Chemical Structure 1]
- ![Chemical Structure 2]
- ![Chemical Structure 3]
- ![Chemical Structure 4]
41. A supramolecular structure, comprising a plurality of hydrogelators of any one of claims 1-40.

42. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers or nanobelts.

43. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers or nanobelts; and the average diameter of the nanofibers or the average width of the nanobelts is about 8 nm, about 9 nm, about 10 nm, about 11 nm, about 12 nm, about 13 nm, about 14 nm, about 15 nm, about 16 nm, about 17 nm, about 18 nm,
about 19 nm, about 20 nm, about 21 nm, about 22 nm, about 23 nm, about 24 nm, or about 25 nm.

44. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers; and the nanofibers are crosslinked.

45. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers; and the nanofibers are substantially straight.

46. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers; and the nanofibers are bent.

47. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers; and the nanofibers form bundles of nanofibers.

48. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of nanofibers; and the nanofibers are about 100 nm, about 120 nm, about 140 nm, about 160 nm, about 180 nm, about 200 nm, about 220 nm, about 240 nm, about 260 nm, about 280 nm, or about 300 nm in length.

49. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of aggregated nanoparticles.

50. The supramolecular structure of claim 41, wherein the supramolecular structure is in the form of aggregated nanoparticles; and the average diameter of the aggregated nanoparticles is about 20 nm, about 21 nm, about 22 nm, about 23 nm, about 24 nm, about 25 nm, about 26 nm, about 27 nm, about 28 nm, about 29 nm, about 30 nm, about 31 nm, about 32 nm, about 33 nm, about 34 nm, or about 35 nm.

51. A hydrogel, wherein the hydrogel comprises a plurality of hydrogelators of any one of claims 1-40; and water.

52. A hydrogel, wherein the hydrogel comprises a plurality of supramolecular structures of any one of claims 41-50; and water.

53. The hydrogel of any one of claims 51-52, wherein the hydrogel is formed from a solution of the hydrogelators in water.

54. The hydrogel of any one of claims 51-53, wherein the hydrogelator is present in an amount from about 1.5% to about 6% by weight.

55. The hydrogel of any one of claims 51-53, wherein the hydrogelator is present in an amount of about 2.0%, about 2.5%, about 3.0%, about 3.5%, or about 4.0% by weight.

56. The hydrogel of any one of claims 51-53, wherein the hydrogel is formed from a solution of the hydrogelators in water.
57. The hydrogel of claim 56, wherein the pH of the solution is about 10.0, about 9.5, about 9.0, or about 8.5.
58. The hydrogel of claim 56, wherein the temperature of the solution is about 20 °C, about 25 °C, about 30 °C, about 35 °C, or about 40 °C.
59. The hydrogel of any one of claims 56-58, wherein the hydrogel is formed by decreasing the pH of the solution of hydrogelators in water.
60. The hydrogel of claim 59, wherein the pH at which the supramolecular structure is formed is about 9.0, about 8.5, about 8.0, about 7.5, about 7.0, about 6.5, about 6.0, about 5.5, about 5.0, about 4.5, about 4.0, or about 3.5.
61. The hydrogel of any one of claims 51-60, wherein the hydrogel has a critical strain value of from about 0.15% to about 0.45%.
62. The hydrogel of any one of claims 51-60, wherein the hydrogel has a critical strain value of about 0.15%, about 0.16%, about 0.17%, about 0.18%, about 0.19%, about 0.20%, about 0.21%, about 0.22%, about 0.23%, about 0.24%, about 0.25%, about 0.26%, about 0.27%, about 0.28%, about 0.29%, about 0.30%, about 0.31%, about 0.32%, about 0.33%, about 0.34%, about 0.35%, about 0.36%, about 0.37%, about 0.38%, about 0.39%, about 0.40%, about 0.41%, about 0.42%, about 0.43%, about 0.44%, or about 0.45%.
63. The hydrogel of any one of claims 51-62, wherein the hydrogel has a storage modulus of from about 0.2 KPa to about 150 KPa.
64. The hydrogel of any one of claims 51-62, wherein the hydrogel has a storage modulus of about 0.2 KPa, about 0.3 KPa, about 0.4 KPa, about 0.5 KPa, about 0.6 KPa, about 0.8 KPa, about 1 KPa, about 2 KPa, about 3 KPa, about 4 KPa, about 5 KPa, about 6 KPa, about 7 KPa, about 8 KPa, about 9 KPa, about 10 KPa, about 15 KPa, about 20 KPa, about 25 KPa, about 30 KPa, about 35 KPa, about 40 KPa, about 50 KPa, about 60 KPa, about 70 KPa, about 80 KPa, about 90 KPa, about 100 KPa, about 110 KPa, about 120 KPa, about 130 KPa, about 140 KPa, or about 150 KPa.
65. The hydrogel of any one of claims 51-64, wherein the hydrogel is substantially biocompatible.
66. The hydrogel of any one of claims 51-64, wherein the hydrogel is substantially biostable.
67. A method of growing cells comprising contacting a plurality of cells with a supramolecular structure of any one of claims 41-50 or a hydrogel of any one of claims 51-66.
68. The method of claim 67, wherein the cells are engineered tissue cells.

69. A method of delivering a substance to a cell, comprising

   contacting the substance with a supramolecular structure of any one of claims 41-50
or a hydrogel of any one of claims 51-66, thereby forming a substance-hydrogel delivery vehicle; and

   contacting the substance-hydrogel delivery vehicle and a cell.

70. The method of claim 69, wherein the substance is a drug.

71. The method of claim 69, wherein the substance is a protein.

72. The method of claim 69, wherein the substance is a gene.

73. The method of claim 69, wherein the substance is siRNA.

74. The method of claim 69, wherein the substance is microRNA.

75. The method of claim 69, wherein the substance is a second cell.

76. A method of binding a nucleic acid, comprising

   contacting a nucleic acid with a supramolecular structure of any one of claims 41-50
or a hydrogel of any one of claims 51-66.

77. The method of claim 76, wherein the nucleic acid binding is selective nucleic acid binding.

78. A method of separating a protein from a substance, comprising

   contacting a mixture with a supramolecular structure of any one of claims 41-50 or a
hydrogel of any one of claims 51-66, wherein the mixture comprises a protein.

79. The method of claim 78, wherein the mixture comprises at least two proteins.

80. A method of treating or preventing a viral infection, comprising

   administering to a mammal in need thereof a therapeutically effective amount of a
hydrogelator of any one of claims 1-40.

81. A method of treating or preventing cancer, comprising

   administering to a mammal in need thereof a therapeutically effective amount of a
hydrogelator of any one of claims 1-40.

82. A method of preventing adhesion of an organism or a cell to a surface, comprising

   contacting the surface with a supramolecular structure of any one of claims 41-50 or
a hydrogel of any one of claims 51-66.
Figure 1

(a)

(b)
Figure 2

(i) DIC, NHS; (ii) L-Phe; (iii) D-glucosamine; (iv) TFA. Boc = tert-butyloxycarbonyl
Figure 3

(i) DIC, NHS; (ii) L-Phe; (iii) D-glucosamine; (iv) 90% TFA
Figure 6

(a)

(b)
Figure 9

(a)

(b)
Figure 10

Graph A shows the absorption spectrum with a peak at 268.03394 nm. Graph B also shows an absorption spectrum with a peak at 268.03394 nm.
Figure 11
Figure 13
Figure 15

The diagram shows the CD (mdeg) as a function of Wavelength (nm) for different samples:
- 1T gel
- 1C sol
- 1A gel
- 1G gel

The CD values range from -10 to 10 mdeg, and the wavelength range is from 200 to 300 nm.
Figure 18
Figure 19

1T+nucleic acid  nucleic acid

A

FITC

SYTO 85

Bright field

Overlap
Figure 20

(i) DCC, NHS; (ii) L-Phe; (iii) D-glucosamine; (iv) 90% TFA; (v) L-Arg(pbf); (vi) L-Gly; (vii) L-Asp(OtBu)
Figure 23

The figure shows a bar graph representing cell viability over three days (1, 2, and 3) for different concentrations: 100 μM, 200 μM, and 500 μM. The y-axis represents cell viability in percent (%) and the x-axis represents days.