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PATENT NEWS

Recently Published Patents on Janus Base Nanomaterials for RNA Delivery

Wuxia Zhang[1] and Yupeng Chen[1,*]

[1]*Department of Biomedical Engineering, University of Connecticut, Storrs, CT 06269, USA*

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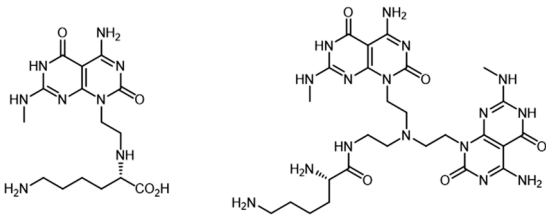
1. INTRODUCTION

Various nanoparticles, including liposomes [1], polymers [2], dendrimers [3], and inorganic nanoparticles [4], have been developed to transport molecules to cells and tissues in drug delivery systems. Currently, clinically approved lipid nanoparticles are mostly used as carriers [5]. However, lipid nanoparticles tend to accumulate in the liver and can cause proinflammation reactions; besides, low efficacy and toxicity also limit their applications (Fig. **1**).



1 **2**

Fig. (1). Structures of compound **1** and twin base compound **2**.

In 2001, Dr. Fenniri and co-workers [6] synthesized compound **1** consisting of Janus (guanine-cytosine fused) base core, ethylene linker, and lysine side chain. It could self-assemble into nanotubes in water by H-bonds and π-π stacking interactions, and could be further developed into delivery vehicles encapsulating RNAs [7]. In 2005, the same group [8] developed another twin base **2** with tunable stability and hierarchy. Janus base nanomaterial has been reported to show many advantages over conventional delivery vehicles, such as low cytotoxicity and immunogenicity, good stability, and biocompatibility. Moreover, its enhanced endosomal escape leads to high efficacy in delivering therapeutic RNAs [9].

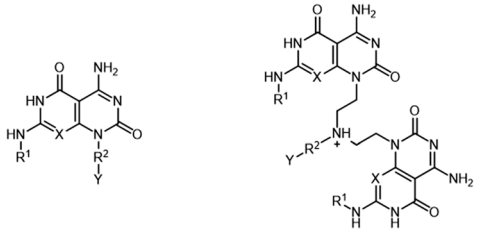
2. RECENT PATENTS ON JANUS BASE NANOMATERIALS

2.1. Nanotubes for Nucleic Acid Delivery

Webster *et al.* [10] claimed the formulas (Fig. **2**) based on compounds **1** and **2**. The invention mainly focused on delivering nucleic acids or polynucleotides into cells using Janus base nanotubes to modulate gene expression or cell function, regulate cell signaling and function, and influence tissue or organ activities.

The inventors successfully delivered siRNA, miRNA365, and GAPDH molecular beacons into cells.

*Address correspondence to this author at the Department of Biomedical Engineering, University of Connecticut, Storrs, CT 06269, USA;
E-mail: yupeng.chen@uconn.edu



2.1-I **2.1-II**

Fig. (2). Structures of formulas **2.1-I** and **2.1-II**, wherein X is CH or nitrogen; R^2 is H or a linker group; Y is absent when R^2 is hydrogen or amino acid or polypeptide; R^1 is H or an aliphatic moiety.

2.2. A Broader Range of Nanomaterial Formulations

Based on the first patent, Chens and Yu developed more Janus base structures [11]. They synthesized an adenine-thymine (in which the adenine side was modified with one more H-bond donor) fused Janus base nanomaterial. The invention included analogs of guanine-cytosine and adenine-thymine fused units and twin base units (Fig. **3**).

The inventors claimed that the formulas above could form nanostructures, including nanotubes, nanosheets, nanorods, nanopieces, nanostructured particles, nanostructured matrices, nanowires, nano-whiskers, and nanoribbons. It was suggested that these nanocarriers can be used to deliver therapeutic agents or diagnostic agents, such as peptides, proteins, small molecules, nucleic acids, molecular probes, molecular beacons, and fluorescence dyes.

The inventors showed molecular beacons and siRNA to be delivered into cells, cartilage, and chondrocytes. Functional knockdown of TNF-α was also achieved.

Furthermore, Chens and Yu applied the previously mentioned structures for various small RNA cargos to target cartilage tissue and cells [12]. They claimed the same formulas as **2.1-I** and **2.1-II**. This invention disclosed a system for selective drug (a diagnostic reagent or therapeutic compound) delivery to a cell or bodily tissue. Depending on the processing conditions, different sizes of rosette nanotubes could be created for different delivery purposes, such as entering a cellular or tissue matrix.

siRNA, GAPDH molecular beacon, MATN3 siRNA, miRNA365, ADAMTS-4&5 siRNA, and TNF-α siRNA were successfully delivered into cartilage tissue and inside chondrocytes.

2.3. New Compositions for Targeted Delivery

Chen *et al.* recently developed new chemical compositions [13]. They claimed the above formulas (Fig. **4**); unlike previous patents, this patent also covered the formulas chemically conjugated with therapeutic agents (small molecules, peptides, nucleic acids, gene

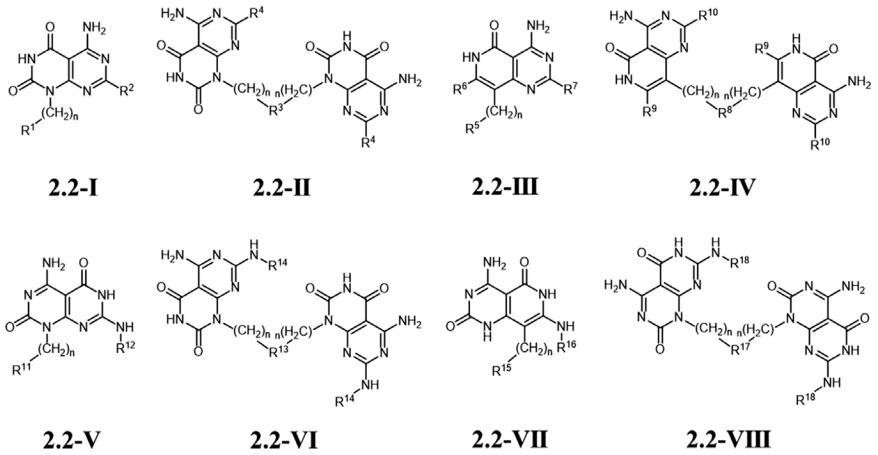


Fig. (3). Structures of formulas **2.2-I**, **II**, **III**, **IV**, **V**, **VI**, **VII**, **VIII**, wherein n is an integer between 0-6; R^1, R^3, R^5, R^8, R^{11}, R^{13}, R^{15}, R^{17} are independently selected from amino acids or polypeptides; R^2, R^4, R^6, R^7, R^9, R^{10} are independently selected from H, CH_3, or NHR^z; and R^z, R^{12}, R^{14}, R^{16}, R^{18} are independently selected from H or aliphatic molecules.

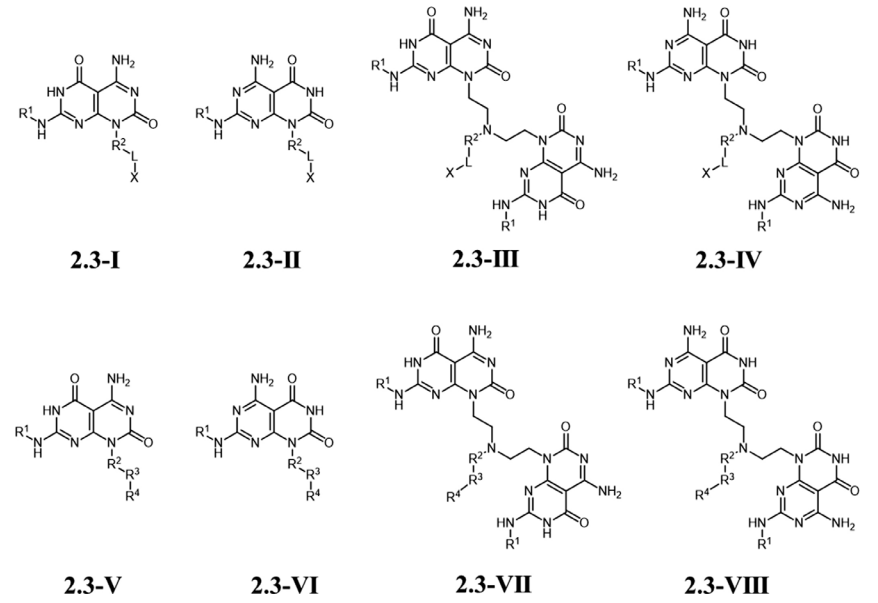


Fig. (4). Structures of formulas **2.3-I**, **II**, **III**, **IV**, **V**, **VI**, **VII**, and **VIII**, wherein R is H or CH_3; R^2 is $(CH_2)_j$, $(CH_2CH_2O)_k$, $(CH_2CH_2N)_m$; j, k and m are each independently 0-200; L is absent or a linker group; X is a therapeutic agent; R^3 is absent or amino acid or polypeptide; R^4 is absent or a coating material.

editing reagents, or targeting molecules, like folic acid and its analogs) or coating materials. This provided several advantages as follows: 1) cargoes can be encapsulated through covalent or non-covalent bonds; 2) chemically cleavable linkers can be used to control the release of cargoes; 3) surface modification with various targeting molecules can facilitate specific and selective uptake pathways by binding to specific receptors on cell surfaces; 4) coating materials can protect the delivery vehicle from specific/nonspecific clearance of cells and organs.

The inventors successfully delivered a wide range of cargoes besides nucleic acids (such as small RNAs, proteins, small molecules, *etc*.) into cells.

The applications were also beyond joint/cartilage tissues. For example, the inventors delivered small-molecule chemotherapy drugs for anticancer applications.

CONCLUSION

These recent patents provide new solutions for drug delivery and regenerative medicine, especially for delivering therapeutic RNA and cartilage tissue regeneration. In summary, the DNA-inspired Janus base nanopieces are an innovative family of safe, versatile, and effective nanomaterials for biomedicine applications. The Janus base nanomaterials show low toxicity and high efficacy in general. More importantly, the most recent patent published by Chen *et al*. [13] has developed novel Janus base nanomaterial structures for targeted delivery to specific types of cells, tissues, or organs.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

Dr. Yupeng Chen is a co-founder of Eascra Biotech, Inc.

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Declared none.

REFERENCES

[1] Tenchov, R.; Bird, R.; Curtze, A.E.; Zhou, Q. Lipid nanoparticles─from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano,* **2021**, *15*(11), 16982-17015. http://dx.doi.org/10.1021/acsnano.1c04996 PMID: 34181394

[2] Zielińska, A.; Carreiró, F.; Oliveira, A.M.; Neves, A.; Pires, B.; Venkatesh, D.N.; Durazzo, A.; Lucarini, M.; Eder, P.; Silva, A.M.; Santini, A.; Souto, E.B. Polymeric nanoparticles: Production, characterization, toxicology and ecotoxicology. *Molecules,* **2020**, *25*(16), 3731. http://dx.doi.org/10.3390/molecules25163731 PMID: 32824172

[3] Mittal, P.; Saharan, A.; Verma, R.; Altalbawy, F.M.A.; Alfaidi, M.A.; Batiha, G.E.S.; Akter, W.; Gautam, R.K.; Uddin, M.S.; Rahman, M.S. Dendrimers: A new race of pharmaceutical nanocarriers. *BioMed Res. Int.,* **2021**, *2021*, 1-11. http://dx.doi.org/10.1155/2021/8844030 PMID: 33644232

[4] Auffan, M.; Rose, J.; Bottero, J.Y.; Lowry, G.V.; Jolivet, J.P.; Wiesner, M.R. Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective. *Nat. Nanotechnol.,* **2009**, *4*(10), 634-641. http://dx.doi.org/10.1038/nnano.2009.242 PMID: 19809453

[5] Thi, T.T.H.; Suys, E.J.A.; Lee, J.S.; Nguyen, D.H.; Park, K.D.; Truong, N.P. Lipid-based nanoparticles in the clinic and clinical trials: From cancer nanomedicine to COVID-19 vaccines. *Vaccines,* **2021**, *9*(4), 359. http://dx.doi.org/10.3390/vaccines9040359 PMID: 33918072

[6] Fenniri, H.; Mathivanan, P.; Vidale, K.L.; Sherman, D.M.; Hallenga, K.; Wood, K.V.; Stowell, J.G. Helical rosette nanotubes: Design, self-assembly, and characterization. *J. Am. Chem. Soc.,* **2001**, *123*(16), 3854-3855. http://dx.doi.org/10.1021/ja005886l PMID: 11457132

[7] Sands, I.; Lee, J.; Zhang, W.; Chen, Y. RNA delivery *via* DNA-inspired janus base nanotubes for extracellular matrix penetration. *MRS Adv.,* **2020**, *5*(16), 815-823. http://dx.doi.org/10.1557/adv.2020.47 PMID: 32405433

[8] Moralez, J.G.; Raez, J.; Yamazaki, T.; Motkuri, R.K.; Kovalenko, A.; Fenniri, H. Helical rosette nanotubes with tunable stability and hierarchy. *J. Am. Chem. Soc.,* **2005**, *127*(23), 8307-8309. http://dx.doi.org/10.1021/ja051496t PMID: 15941263

[9] Lee, J.; Sands, I.; Zhang, W.; Zhou, L.; Chen, Y. DNA-inspired nanomaterials for enhanced endosomal escape. *Proc. Natl. Acad. Sci. USA,* **2021**, *118*(19), e2104511118. http://dx.doi.org/10.1073/pnas.2104511118 PMID: 33941681

[10] Webster, T.J.; Chen, Q.; Chen, Y.; Fenniri, H.; Hemraz, U.D. Nanotubes as carriers of nucleic acids into cells. US Patent 0171482, **2014**.

[11] Chen, Q.; Yu, H.; Chen, Y. Nanomaterial compositions, synthesis, and assembly. US Patent 0362238, **2017**.

[12] Chen, Q.; Chen, Y.; Yu, H. *In vitro* and *in vivo* intracellular delivery of siRNA *via* self-assembled nanopieces. US Patent 0023117, **2021**.

[13] Chen, Y.; Lee, J. Therapeutic nanomaterials. US Patent 0133893, **2022**.