

BÖLÜM 9

Teranostik Nanotaşıyıcılar

Burcu ÜNER¹

| Giriş

Tanısal ve tedavi edici özelliklere sahip nanomateryallerin üretimi ve yaygınlaştırılmasındaki son gelişmeler, tıbbın geleceğini hızla şekillendirmektedir. Çeşitli hastalıkların tedavisine yönelik yenilikçi terapötik nanomateryallerin tasarıımı ve üretiminde önemli ilerleme kaydedilmiştir, ancak bunların potansiyelleri şu anda düşük biyoyararlanım, biyouyumluluk veya istenmeyen farmakokinetik nedeniyle sınırlı olup, yaygın klinik kullanımlarını engellemektedir.

En sık kullanılan intravenöz (IV) uygulamaya ek olarak inovatif nanomateryallerin çeşitli uygulama yolları, bu sistemlerin verilmesini kolaylaşırıbmak, biyolojik engelleri ekarte ederek görüntülemeyi artırmak, belirli kullanım durumlarında duyarlılık ve terapötik etkinlik potansiyelinin faydalarını keşfetmek için derinlemesine açıklanmıştır. Nanopartikül ilaç taşıma sistemlerinin karşılaştığı en büyük zorluklardan bazıları bölgeye özgü hedefleme, nanopartiküllerin birikimi ve metabolizmadan güvenli şekilde atılım işlemidir. Bu bölümde teranostik nanopartiküller için en son teknolojiler özetlenmiş ve farklı hastalıkların teşhis, tanı ve tedavisinde kullanılan çeşitli uygulama yolları tartışılmıştır.

¹ Dr. St. Louis Sağlık Bilimleri Üniversitesi, Eczacılık Fakültesi, Missouri, ABD., burcu.uner@uhsp.edu, 0000-0003-4691-0432

4.3 Uzun Süreli Tedavi için İmplantasyon

Nanopartiküllerin IV yolla sistemik olarak verilmesi, ilaçların vücutta taşınabilmesine olanak sağlamaktadır. Ancak, hedefleme ligandlarına sahip nanopartiküler sistemlerde, spesifik olmayan dağılımdan kaçınılmaz. Sonuç olarak böbrekler dalak, ve karaciğer gibi hayatı organlarda hasara ve sistemik toksiteye neden olur (75, 76). Ek olarak, bu ilaçlar, nispeten vaskülarize olmayan veya kemik ve eklem hastalıkları veya kan-beyin bariyeri tarafından izole edilen bölgeleri hedefleme yetenekleri açısından da sınırlı olabilir (77, 78). Bu hastalıklar için nanopartiküler sistemleri taşıyan cihazların implantasyonu hedef bölgede lokal olarak ilaç iletimi sağlarken, istenilen bölgede ilacın etkili olduğu konsantrasyonu sağlayarak umut verici bir yaklaşım sunmaktadır (Şekil 3c) (12).

Sonuç

Nanoteranostik özelliklerinin ve uygulama yolunun dikkatli seçimi, hastalıkları teşhis edebilen ve terapötik etkiler sağlayan bir şekilde terapötik problemler geliştirmek için kritik öneme sahiptir. Bu sistemler klinik olarak uygun şekilde tasarlandığında, nanoteranostiklerin hedef hastalık bölgesindeki birikimi arttırılabilir ve daha sonra küçük boyutları nedeniyle vücuttan atılırlar. Bunun yanı sıra, hastalık tespitini hızlandıran daha kestirme bir yol sağlayarak tedavinin etkinliğini artırırlar. Ancak, büyük ilerlemelere rağmen teranostik problemler, sağlıklı dokulardaki hedef dışı etkilerden kaynaklı potansiyel toksite riskleri nedeniyle klinik kullanımları engellenmektedir. Bu teranostik nanomalzemelerin potansiyelini tam olarak gerçekleştirmek için ek iyileştirmeler gereklidir.

Kaynaklar

- Wei G, Wang Y, Yang G, Wang Y, Ju R. Recent progress in nanomedicine for enhanced cancer chemotherapy. *Theranostics*. 2021;11(13):6370-92.
- Rong L, Lei Q, Zhang X-Z. Recent advances on peptide-based theranostic nanomaterials. *VIEW*. 2020;1(4):20200050.
- Lindner T, Loktev A, Altmann A, Giesel F, Kratochwil C, Debus J, et al. Development of Quinoline-Based Theranostic Ligands for the Targeting of Fibroblast Activation Protein. *Journal of Nuclear Medicine* 2018;59(9):1415.
- Ji T, Zhao Y, Ding Y, Wang J, Zhao R, Lang J, et al. Transformable peptide nanocarriers for expeditious drug release and effective cancer therapy via cancer-associated fibroblast activation. *Angewandte Chemie International Edition* 2016;55(3):1050-5.

5. Ji T, Kohane DS. Nanoscale systems for local drug delivery. *Nano Today*. 2019;28:100765.
6. Zhang P, Li Y, Tang W, Zhao J, Jing L, McHugh KJ. Theranostic nanoparticles with disease-specific administration strategies. *Nano Today* 2022;42:101335.
7. Han X, Li H, Zhou D, Chen Z, Gu Z. Local and targeted delivery of immune checkpoint blockade therapeutics. *Accounts of chemical research* 2020;53(11):2521-33.
8. Abdou P, Wang Z, Chen Q, Chan A, Zhou DR, Gunadhi V, et al. Advances in engineering local drug delivery systems for cancer immunotherapy. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* 2020;12(5):e1632.
9. Jin J-f, Zhu L-l, Chen M, Xu H-m, Wang H-f, Feng X-q, et al. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient preference and adherence* 2015;923-42.
10. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology 2010, the American Society of Hematology Education Program Book*. 2010;2010(1):338-47.
11. Jain A, Jain S. Advances in tumor targeted liposomes. *Current molecular medicine* 2018;18(1):44-57.
12. Fadeel B, Farcal L, Hardy B, Vázquez-Campos S, Hristozov D, Marcomini A, et al. Advanced tools for the safety assessment of nanomaterials. *Nature nanotechnology* 2018;13(7):537-43.
13. Peng F, Setyawati MI, Tee JK, Ding X, Wang J, Nga ME, et al. Nanoparticles promote in vivo breast cancer cell intravasation and extravasation by inducing endothelial leakiness. *Nature nanotechnology* 2019;14(3):279-86.
14. Wang H, Su W, Tan M. Endogenous fluorescence carbon dots derived from food items. *The innovation* 2020;1(1).
15. Sonavane G, Tomoda K, Makino K. Biodistribution of colloidal gold nanoparticles after intravenous administration: effect of particle size. *Colloids and Surfaces B: Biointerfaces* 2008;66(2):274-80.
16. De Jong WH, Hagens WI, Krystek P, Burger MC, Sips AJ, Geertsma RE. Particle size-dependent organ distribution of gold nanoparticles after intravenous administration. *Biomatериалs* 2008;29(12):1912-9.
17. Cai R, Chen C. The crown and the scepter: roles of the protein corona in nanomedicine. *Advanced Materials* 2019;31(45):1805740.
18. Liu S, Han Y, Qiao R, Zeng J, Jia Q, Wang Y, et al. Investigations on the interactions between plasma proteins and magnetic iron oxide nanoparticles with different surface modifications. *The Journal of Physical Chemistry C* 2010;114(49):21270-6.
19. Maeda H. Macromolecular therapeutics in cancer treatment: the EPR effect and beyond. *Journal of Controlled Release* 2012;164(2):138-44.
20. Hill LJ, Pinna N, Char K, Pyun J. Colloidal polymers from inorganic nanoparticle monomers. *Progress in Polymer Science* 2015;40:85-120.
21. Ma T, Zhang P, Hou Y, Ning H, Wang Z, Huang J, et al. "Smart" nanoprobes for visualization of tumor microenvironments. *Advanced Healthcare Materials* 2018;7(20):1800391.
22. Lu Y, Aimetti AA, Langer R, Gu Z. Bioresponsive materials. *Nature Reviews Materials* 2016;2(1):1-17.
23. Hou Y, Zhou J, Gao Z, Sun X, Liu C, Shangguan D, et al. Protease-activated ratiometric fluorescent probe for pH mapping of malignant tumors. *ACS Nano* 2015;9(3):3199-205.
24. Ma T, Hou Y, Zeng J, Liu C, Zhang P, Jing L, et al. Dual-ratiometric target-triggered fluorescent probe for simultaneous quantitative visualization of tumor microenvironment protease activity and pH in vivo. *Journal of the American Chemical Society* 2018;140(1):211-8.
25. Fan Z, Zhao J, Chai X, Li L. A Cooperatively Activatable, DNA-based Fluorescent Reporter for Imaging of Correlated Enzymatic Activities. *Angewandte Chemie International Edition* 2021;60(27):14887-91.

26. Geng Z, Wang L, Liu K, Liu J, Tan W. Enhancing anti-PD-1 Immunotherapy by Nanomicelles Self-Assembled from Multivalent Aptamer Drug Conjugates. *Angewandte Chemie* 2021;133(28):15587-93.
27. Crich SG, Terreno E, Aime S. Nano-sized and other improved reporters for magnetic resonance imaging of angiogenesis. *Advanced Drug Delivery Reviews* 2017;119:61-72.
28. Kelley WJ, Safari H, Lopez-Cazares G, Eniola-Adefeso O. Vascular-targeted nanocarriers: design considerations and strategies for successful treatment of atherosclerosis and other vascular diseases. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* 2016;8(6):909-26.
29. Zhang H, Prince MR. Renal MR angiography. *Magnetic Resonance Imaging Clinics*. 2004;12(3):487-503.
30. Chan KW-Y, Wong W-T. Small molecular gadolinium (III) complexes as MRI contrast agents for diagnostic imaging. *Coordination Chemistry Reviews* 2007;251(17-20):2428-51.
31. Bogdanov Jr A, Weissleder R, Frank H, Boganova A, Nossif N, Schaffer B, et al. A new macromolecule as a contrast agent for MR angiography: preparation, properties, and animal studies. *Radiology* 1993;187(3):701-6.
32. Lin Y-H, Hwang R-M, Chen B-B, Hsu C-Y, Yu C-W, Kao J-H, et al. Vascular and hepatic enhancements at MR imaging: comparison of Gd-EOB-DTPA and Gd-DTPA in the same subjects. *Clinical Imaging* 2014;38(3):287-91.
33. Peldschus K, Hamdorf M, Robert P, Port M, Adam G, Herborn CU. Comparison of the high relaxivity Gd chelates P1152 and Gd-BOPTA for contrast-enhanced MR angiography in rabbits at 1.5 Tesla and 3.0 Tesla. *Journal of Magnetic Resonance Imaging* 2010;32(2):459-65.
34. Naccache R, Chevallier P, Lagueux J, Gossuin Y, Laurent S, Vander Elst L, et al. High relaxivities and strong vascular signal enhancement for NaGdF4 nanoparticles designed for dual MR/optical imaging. *Advanced Healthcare Materials* 2013;2(11):1478-88.
35. Gupta S, Knowlton AA. HSP60, Bax, Apoptosis and the Heart. *Journal of Cellular and Molecular Medicine* 2005;9(1):51-8.
36. Sugimoto T, Yamazaki N, Hayashi T, Yuba E, Harada A, Kotaka A, et al. Preparation of dual-stimuli-responsive liposomes using methacrylate-based copolymers with pH and temperature sensitivities for precisely controlled release. *Colloids Surface B Biointerfaces* 2017;155:449-58.
37. Jiao M, Jing L, Wei X, Liu C, Luo X, Gao M. The Yin and Yang of coordinating co-solvents in the size-tuning of Fe₃O₄ nanocrystals through flow synthesis. *Nanoscale* 2017;9(47):18609-12.
38. Tajiri N, De La Peña I, Acosta SA, Kaneko Y, Tamir S, Landesman Y, et al. A Nuclear Attack on Traumatic Brain Injury: Sequestration of Cell Death in the Nucleus. *CNS Neuroscience Therapy*. 2016;22(4):306-15.
39. Wang T, Hou Y, Bu B, Wang W, Ma T, Liu C, et al. Timely Visualization of the Collaterals Formed during Acute Ischemic Stroke with Fe₃O₄ Nanoparticle-based MR Imaging Probe. *Small* 2018;14(23):1800573.
40. Kudo S, Nagasaki Y. Facile and Quantitative Synthesis of a Poly(ethylene glycol)-b-Poly(l-arginine) Block Copolymer and Its Use for the Preparation of Polyion Complex Micelles with Polyanions for Biomedical Applications. *Macromolecular Rapid Communications*. 2015;36(21):1916-22.
41. Kim BH, Lee N, Kim H, An K, Park YI, Choi Y, et al. Large-scale synthesis of uniform and extremely small-sized iron oxide nanoparticles for high-resolution T 1 magnetic resonance imaging contrast agents. *Journal of the American Chemical Society* 2011;133(32):12624-31.
42. Qiao H, Wang Y, Zhang R, Gao Q, Liang X, Gao L, et al. MRI/optical dual-modality imaging of vulnerable atherosclerotic plaque with an osteopontin-targeted probe based on Fe₃O₄ nanoparticles. *Biomaterials* 2017;112:336-45.

43. Qiao R, Qiao H, Zhang Y, Wang Y, Chi C, Tian J, et al. Molecular Imaging of Vulnerable Atherosclerotic Plaques in Vivo with Osteopontin-Specific Upconversion Nanoprobes. *ACS Nano* 2017;11(2):1816-25.
44. Wang Y, Zhang Y, Wang Z, Zhang J, Qiao RR, Xu M, et al. Optical/MRI dual-modality imaging of M1 macrophage polarization in atherosclerotic plaque with MARCO-targeted upconversion luminescence probe. *Biomaterials* 2019;219:119378.
45. Choi JY, Ryu J, Kim HJ, Song JW, Jeon JH, Lee D-H, et al. Therapeutic effects of targeted PPAR activation on inflamed high-risk plaques assessed by serial optical imaging in vivo. *Theranostics* 2018;8(1):45.
46. Hou W, Li J, Cao Z, Lin S, Pan C, Pang Y, et al. Decorating bacteria with a therapeutic nanocoating for synergistically enhanced biotherapy. *Small* 2021;17(37):2101810.
47. Zhang Y, Li M, Du G, Chen X, Sun X. Advanced oral vaccine delivery strategies for improving the immunity. *Advanced Drug Delivery Reviews* 2021;177:113928.
48. Wang R, Zhou L, Wang W, Li X, Zhang F. In vivo gastrointestinal drug-release monitoring through second near-infrared window fluorescent bioimaging with orally delivered microcarriers. *Nature Communications* 2017;8(1):14702.
49. Abramson A, Frederiksen MR, Vegge A, Jensen B, Poulsen M, Mouridsen B, et al. Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors. *Nature biotechnology* 2022;40(1):103-9.
50. Yang X, Ma C, Chen Z, Liu J, Liu F, Xie R, et al. Single small molecule-assembled nanoparticles mediate efficient oral drug delivery. *Nano research* 2019;12:2468-76.
51. Bernkop-Schnürch A, Schmitz T. Presystemic metabolism of orally administered peptide drugs and strategies to overcome it. *Current Drug Metabolism* 2007;8(5):509-17.
52. Zhang Z, Gao F, Jiang S, Ma L, Li Y. Nano-based drug delivery system enhances the oral absorption of lipophilic drugs with extensive presystemic metabolism. *Current Drug Metabolism* 2012;13(8):1110-8.
53. Abramson A, Caffarel-Salvador E, Khang M, Dellal D, Silverstein D, Gao Y, et al. An ingestible self-orienting system for oral delivery of macromolecules. *Science* 2019;363(6427):611-5.
54. Yeom DW, Chae BR, Son HY, Kim JH, Chae JS, Song SH, et al. Enhanced oral bioavailability of valsartan using a polymer-based supersaturable self-microemulsifying drug delivery system. *International Journal of Nanomedicine* 2017;Volume 12:3533-45.
55. Naeem M, Bae J, Oshi MA, Kim M-S, Moon HR, Lee BL, et al. Colon-targeted delivery of cyclosporine A using dual-functional Eudragit® FS30D/PLGA nanoparticles ameliorates murine experimental colitis. *International journal of nanomedicine* 2018;1225-40.
56. Kang J-H, Hwang J-Y, Seo J-W, Kim H-S, Shin US. Small intestine-and colon-specific smart oral drug delivery system with controlled release characteristic. *Materials Science and Engineering: C* 2018;91:247-54.
57. Toffoli G, Corona G, Bassi B, Boiocchi M. Pharmacokinetic optimisation of treatment with oral etoposide. *Clinical pharmacokinetics* 2004;43:441-66.
58. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, et al. Analysis of nanoparticle delivery to tumours. *Nature reviews materials* 2016;1(5):1-12.
59. Weldon C, Ji T, Nguyen MT, Rwei A, Wang W, Hao Y, et al. Nanoscale Bupivacaine Formulations to Enhance the Duration and Safety of Intravenous Regional Anesthesia. *ACS Nano*. 2019;13(1):18-25.
60. Llovet JM, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nature Reviews Gastroenterology and Hepatology* 2021;18(5):293-313.
61. Zheng D, Giljohann DA, Chen DL, Massich MD, Wang XQ, Iordanov H, et al. Topical delivery of siRNA-based spherical nucleic acid nanoparticle conjugates for gene regu-

- lation. *Proceedings of the National Academy of Sciences of the United States of America*. 2012;109(30):11975-80.
- 62. Carvajal-Vidal P, Fábrega M-J, Espina M, Calpena AC, García ML. Development of H-lobetasol-loaded nanostructured lipid carrier for dermal administration: Optimization, physicochemical and biopharmaceutical behavior, and therapeutic efficacy. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2019;20:102026.
 - 63. Xiang J, Xu L, Gong H, Zhu W, Wang C, Xu J, et al. Antigen-Loaded Upconversion Nanoparticles for Dendritic Cell Stimulation, Tracking, and Vaccination in Dendritic Cell-Based Immunotherapy. *ACS Nano*. 2015;9(6):6401-11.
 - 64. Milling L, Zhang Y, Irvine DJ. Delivering safer immunotherapies for cancer. *Advanced Drug Delivery Reviews* 2017;114:79-101.
 - 65. Gardner A, Ruffell B. Dendritic Cells and Cancer Immunity. *Trends in Immunology* 2016;37(12):855-65.
 - 66. Sadaka A, Giuliani GP. Proliferative vitreoretinopathy: current and emerging treatments. *Clinical Ophthalmology* 2012;6:1325-33.
 - 67. Wang L, Wang X, Yang F, Liu Y, Meng L, Pang Y, et al. Systemic antiviral immunization by virus-mimicking nanoparticles-decorated erythrocytes. *Nano Today* 2021;40.
 - 68. Üner B, Özdemir S, Taş Ç, Özsoy Y, Üner M. Development of lipid nanoparticles for transdermal loteprednol etabonate delivery. *Journal of Microencapsulation* 2022;39(4):327-40.
 - 69. Ramadon D, McCrudden MTC, Courtenay AJ, Donnelly RF. Enhancement strategies for transdermal drug delivery systems: current trends and applications. *Drug Delivery and Translational Research* 2022;12(4):758-91.
 - 70. Tas C, Joyce JC, Nguyen HX, Eangoor P, Knaack JS, Banga AK, et al. Dihydroergotamine mesylate-loaded dissolving microneedle patch made of polyvinylpyrrolidone for management of acute migraine therapy. *Journal of Controlled Release* 2017;268:159-65.
 - 71. Bagde A, Dev S, Madhavi K, Sriram L, Spencer SD, Kalvala A, Nathani A, et al. Biphasic burst and sustained transdermal delivery in vivo using an AI-optimized 3D-printed MN patch. *International Journal of Pharmaceutics* 2023;636:122647.
 - 72. Li W, Tang J, Terry RN, Li S, Brunie A, Callahan RL, et al. Long-acting reversible contraception by effervescent microneedle patch. *Science Advances* 2019;5(11):eaaw8145.
 - 73. Sheng T, Luo B, Zhang W, Ge X, Yu J, Zhang Y, et al. Microneedle-Mediated Vaccination: Innovation and Translation. *Advanced Drug Delivery Reviews* 2021;179.
 - 74. Prausnitz MR, Langer R. Transdermal drug delivery. *Nature Biotechnology* 2008;26(11):1261-8.
 - 75. Hashizume R, Fujimoto KL, Hong Y, Guan J, Toma C, Tobita K, et al. Biodegradable elastic patch plasty ameliorates left ventricular adverse remodeling after ischemia-reperfusion injury: A preclinical study of a porous polyurethane material in a porcine model. *The Journal of Thoracic and Cardiovascular Surgery* 2013;146(2):391-9.e1.
 - 76. Fong R, Cavet ME, DeCory HH, Wittitow JL. Loteprednol etabonate (submicron) ophthalmic gel 0.38% dosed three times daily following cataract surgery: integrated analysis of two Phase III clinical studies. *Clinical Ophthalmology*. 2019;13:1427-38.
 - 77. Peters SA, Hultin L. Early identification of drug-induced impairment of gastric emptying through physiologically based pharmacokinetic (PBPK) simulation of plasma concentration-time profiles in rat. *Journal of Pharmacokinetic and Pharmacodynamic* 2008;35(1):1-30.
 - 78. Nomoto H, Shiraga F, Kuno N, Kimura E, Fujii S, Shinomiya K, et al. Pharmacokinetics of Bevacizumab after Topical, Subconjunctival, and Intravitreal Administration in Rabbits. *Investigative Ophthalmology & Visual Science* 2009;50(10):4807-13.