

- SUPPORTING INFORMATION -

Polymeric materials for ultrasound imaging and therapy

Roman A. Barmin,¹ Mirjavad Moosavifar,¹ Anshuman Dasgupta,¹ Andreas Herrmann,^{2,3}
Fabian Kiessling,¹ Roger M. Pallares,^{1,*} and Twan Lammers^{1,*}

¹ Institute for Experimental Molecular Imaging, RWTH Aachen University Hospital, Aachen 52074, Germany

² DWI – Leibniz Institute for Interactive Materials, Aachen 52074, Germany

³ Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Aachen 52074, Germany

* Corresponding authors: rmoltopallar@ukaachen.de; tlammers@ukaachen.de

Table of Contents

Table S1. Polymeric material designs, their applications, and the current stage of translation.....	S2
References.....	S3

Table S1. Polymeric material designs, applications, and the current stage of translation.

Formulation design	Main polymer	FDA status of the polymer	Applications	Translation stage of the design	Ref.
Microbubbles	PBCA	Approved as a surgical glue for wound closure	US imaging, molecular imaging, US-mediated drug and gas delivery, sonopermeation	Pre-clinical, marketed by SonoMAC GmbH	1-6
	PVA	Approved for food packaging	US imaging, molecular imaging, US-mediated drug and gas delivery, adhesive removal from cellulose-based materials, structural coloration for optical materials	Pre-clinical, marketed by Surflay Nanotec GmbH	7-11
	PLGA	Approved for depot formulations	US imaging, molecular imaging, US-mediated drug delivery	Pre-clinical	12-15
Nanocups	PMMA, PS	—	US-mediated drug delivery, US-mediated transdermal drug and vaccine delivery	Pre-clinical	16-19
Microcapsules	PVP	Approved as tablet binder, and solubilizer	US imaging, US-mediated drug delivery	Pre-clinical	20
	PMAA	—	US imaging (<i>in vivo</i> pH monitoring)	Pre-clinical	21
Gas-releasing nanoparticles	PVAX	—	US-based detection and anti-inflammatory therapy, passive drug delivery	Pre-clinical	22, 23
	PLGA	Approved for depot formulations	US imaging, molecular imaging, cancer treatment	Pre-clinical	24

References

1. S. Fokong, B. Theek, Z. Wu, P. Koczera, L. Appold, S. Jorge, U. Resch-Genger, M. van Zandvoort, G. Storm, F. Kiessling and T. Lammers, Image-guided, targeted and triggered drug delivery to tumors using polymer-based microbubbles, *Journal of controlled release : official journal of the Controlled Release Society*, 2012, **163**, 75-81.
2. P. Koczera, L. Appold, Y. Shi, M. Liu, A. Dasgupta, V. Pathak, T. Ojha, S. Fokong, Z. Wu, M. Van Zandvoort, O. Iranzo, A. J. C. Kuehne, A. Pich, F. Kiessling and T. Lammers, PBCA-based polymeric microbubbles for molecular imaging and drug delivery, *Journal of Controlled Release*, 2017, **259**, 128-135.
3. B. Theek, M. Baues, T. Ojha, D. Möckel, S. K. Veetil, J. Steitz, L. van Bloois, G. Storm, F. Kiessling and T. Lammers, Sonoporation enhances liposome accumulation and penetration in tumors with low EPR, *Journal of controlled release : official journal of the Controlled Release Society*, 2016, **231**, 77-85.
4. V. Pathak, K. Roemhild, S. Schipper, N. Groß-Weege, T. Nolte, S. Ruetten, E. M. Buhl, A. El Shafei, M. Weiler, L. Martin, G. Marx, V. Schulz, F. Kiessling, T. Lammers and P. Koczera, Theranostic Trigger-Responsive Carbon Monoxide-Generating Microbubbles, *Small*, 2022, **18**, 2200924.
5. J. N. May, S. K. Golombek, M. Baues, A. Dasgupta, N. Drude, A. Rix, D. Rommel, S. von Stillfried, L. Appold, R. Pola, M. Pechar, L. van Bloois, G. Storm, A. J. C. Kuehne, F. Gremse, B. Theek, F. Kiessling and T. Lammers, Multimodal and multiscale optical imaging of nanomedicine delivery across the blood-brain barrier upon sonopermeation, *Theranostics*, 2020, **10**, 1948-1959.
6. A. Dasgupta, T. Sun, R. Palomba, E. Rama, Y. Zhang, C. Power, D. Moeckel, M. Liu, A. Sarode, M. Weiler, A. Motta, C. Porte, Z. Magnuska, A. Said Elshafei, R. Barmin, A. Graham, A. McClelland, D. Rommel, E. Stickeler, F. Kiessling, R. M. Pallares, L. De Laporte, P. Decuzzi, N. McDannold, S. Mitragotri and T. Lammers, Nonspherical ultrasound microbubbles, *Proceedings of the National Academy of Sciences of the United States of America*, 2023, **120**, e2218847120.
7. R. Villa, B. Cerroni, L. Viganò, S. Margheritelli, G. Abolafio, L. Oddo, G. Paradossi and N. Zaffaroni, Targeted doxorubicin delivery by chitosan-galactosylated modified polymer microbubbles to hepatocarcinoma cells, *Colloids and surfaces. B, Biointerfaces*, 2013, **110**, 434-442.
8. M. Ahmed, B. Cerroni, A. Razuvaev, J. Härmark, G. Paradossi, K. Caidahl and B. Gustafsson, Cellular Uptake of Plain and SPION-Modified Microbubbles for Potential Use in Molecular Imaging, *Cellular and molecular bioengineering*, 2017, **10**, 537-548.
9. L. Duan, F. Yang, W. He, L. Song, F. Qiu, N. Xu, L. Xu, Y. Zhang, Z. Hua and N. Gu, A Multi-Gradient Targeting Drug Delivery System Based on RGD-I-TRAIL-Labeled Magnetic Microbubbles for Cancer Theranostics, *Advanced Functional Materials*, 2016, **26**, 8313-8324.
10. A. D'Andrea, L. Severini, F. Domenici, S. Dabagov, V. Guglielmotti, D. Hampai, L. Micheli, E. Placidi, M. Titubante, C. Mazzuca, G. Paradossi and A. Palleschi, Ultrasound-Stimulated PVA Microbubbles for Adhesive Removal from Cellulose-Based Materials: A Groundbreaking Low-Impact Methodology, *ACS Applied Materials & Interfaces*, 2021, **13**, 24207-24217.
11. H. Chen, H. Zhu, Y. Wang, J. Liu, Y. Wang, X. Hu, A. A. Solovev, G. Huang and Y. Mei, Structural Coloration by Internal Reflection and Interference in Hydrogel Microbubbles and Their Precursors, *Advanced Optical Materials*, 2021, **9**, 2100259.

12. Y. Chen, Y. Liang, P. Jiang, F. Li, B. Yu and F. Yan, Lipid/PLGA Hybrid Microbubbles as a Versatile Platform for Noninvasive Image-Guided Targeted Drug Delivery, *ACS Applied Materials & Interfaces*, 2019, **11**, 41842-41852.
13. S. Tsirkin, R. Goldbart, T. Traitel and J. Kost, Tailor-Made Single-Core PLGA Microbubbles as Acoustic Cavitation Enhancers for Therapeutic Applications, *ACS Applied Materials & Interfaces*, 2021, **13**, 25748-25758.
14. L. Xu, Y. Chen, Q. Jin, Y. Wu, C. Deng, Y. Zhong, L. Lin, L. Chen, W. Fu, L. Yi, Z. Sun, X. Qin, Y. Li, Y. Yang and M. Xie, Biomimetic PLGA Microbubbles Coated with Platelet Membranes for Early Detection of Myocardial Ischaemia-Reperfusion Injury, *Molecular Pharmaceutics*, 2021, **18**, 2974-2985.
15. Z. Li, M. Lai, S. Zhao, Y. Zhou, J. Luo, Y. Hao, L. Xie, Y. Wang and F. Yan, Ultrasound Molecular Imaging for Multiple Biomarkers by Serial Collapse of Targeting Microbubbles with Distinct Acoustic Pressures, *Small*, 2022, **18**, 2108040.
16. H. Lv, Q. Lin, K. Zhang, K. Yu, T. Yao, X. Zhang, J. Zhang and B. Yang, Facile fabrication of monodisperse polymer hollow spheres, *Langmuir*, 2008, **24**, 13736-13741.
17. J. J. Kwan, R. Myers, C. M. Coviello, S. M. Graham, A. R. Shah, E. Stride, R. C. Carlisle and C. C. Coussios, Ultrasound-Propelled Nanocups for Drug Delivery, *Small*, 2015, **11**, 5305-5314.
18. S. Bhatnagar, J. J. Kwan, A. R. Shah, C. C. Coussios and R. C. Carlisle, Exploitation of sub-micron cavitation nuclei to enhance ultrasound-mediated transdermal transport and penetration of vaccines, *Journal of controlled release : official journal of the Controlled Release Society*, 2016, **238**, 22-30.
19. R. Myers, C. Coviello, P. Erbs, J. Foloppe, C. Rowe, J. Kwan, C. Crake, S. Finn, E. Jackson, J. M. Balloul, C. Story, C. Coussios and R. Carlisle, Polymeric Cups for Cavitation-mediated Delivery of Oncolytic Vaccinia Virus, *Molecular therapy : the journal of the American Society of Gene Therapy*, 2016, **24**, 1627-1633.
20. J. Chen, S. Ratnayaka, A. Alford, V. Kozlovskaya, F. Liu, B. Xue, K. Hoyt and E. Kharlampieva, Theranostic Multilayer Capsules for Ultrasound Imaging and Guided Drug Delivery, *ACS Nano*, 2017, **11**, 3135-3146.
21. J. A.-T. Walker, X. Wang, K. Peter, K. Kempe and S. R. Corrie, Dynamic Solid-State Ultrasound Contrast Agent for Monitoring pH Fluctuations In Vivo, *ACS Sensors*, 2020, **5**, 1190-1197.
22. G.-W. Kim, C. Kang, Y.-B. Oh, M.-H. Ko, J.-H. Seo and D. Lee, Ultrasonographic Imaging and Anti-inflammatory Therapy of Muscle and Tendon Injuries Using Polymer Nanoparticles, *Theranostics*, 2017, **7**, 2463-2476.
23. E. Jung, J. Noh, C. Kang, D. Yoo, C. Song and D. Lee, Ultrasound imaging and on-demand therapy of peripheral arterial diseases using H₂O₂-Activated bubble generating anti-inflammatory polymer particles, *Biomaterials*, 2018, **179**, 175-185.
24. J. Lee, H.-S. Min, D. G. You, K. Kim, I. C. Kwon, T. Rhim and K. Y. Lee, Theranostic gas-generating nanoparticles for targeted ultrasound imaging and treatment of neuroblastoma, *Journal of Controlled Release*, 2016, **223**, 197-206.