Synthesis of Magnetic Lattices for Intravenous Chemotherapy Capture

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Background

Chemotherapeutics are administered into the bloodstream to effectively treat a range of malignancies. However, off-target tissue damage from these drugs can cause serious side effects. Many chemotherapeutics must be dose-limited due to severe cardio-or nephrotoxicity, but decreased dosages can be less effective at treating cancer.[1,2] It is essential to find ways to localize chemotherapeutics to a specific malignancy in order to overcome this tradeoff.

One approach to overcome this tradeoff involves targeting the release of a drug via catherization of the artery that feeds the tumor; this is known as transarterial chemoembolization (TACE). This is a well-known procedure to treat inoperable hepatocellular carcinoma, the third most common cause of cancer death globally.[3–6] This procedure often utilizes the anthracycline chemotherapeutic doxorubicin (DOX), a potent cardiotoxin. Despite the targeted administration of DOX through this method, 50% of the drug will exit into systematic circulation with much of it quickly passing to the heart.[7] Prior solutions center around intravenous devices to capture DOX exiting the liver, known as "ChemoFilters"— (see Fig. 1).[4,8,9] These devices may operate by ion exchange or selective capture mechanisms; notably, DOX intercalates between DNA strands as its mechanism of action.[9] These devices may take on membrane or lattice structures; both geometries require high surface areas for effective DOX capture, yet large structures can result in blood flow obstruction, stasis, and ultimately thrombosis. More concerningly, the introduction of heterogeneous DNA may result in an immune response.[10] As an alternative, magnetic iron nanoparticles coated in DNA could perform capture; recent work has demonstrate its ability to capture up to 98% of DOX in 10 minutes in vitro.[11] These nanoparticles may provide higher surface area for rapid DOX capture, yet a method for retrieval of the nanoparticles is lacking. Such a method, deployed intravenously, must avoid the difficulties surrounding flow obstruction discussed above.

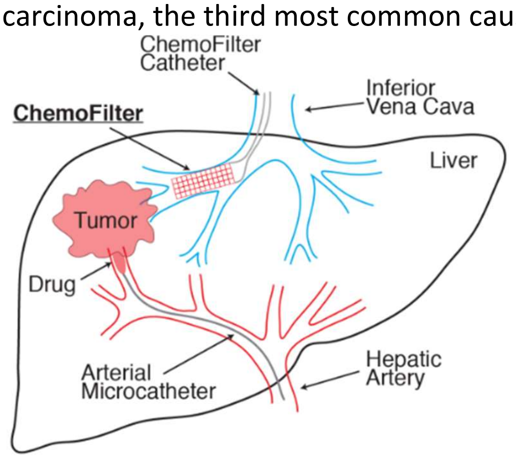

Figure 1: TACE setup to administer chemotherapy with a ChemoFilter that captures excess chemotherapeutic agent (from 7).

The goal of my SURF project is to create 3D lattices out of magnetizable materials that can act as intravenous nanoparticles retrieval devices. To address concerns surrounding blood flow obstruction, these lattices will be microarchitectured to minimize obstruction. However, the current approaches to fabricate microarchitected magnetic lattices including powder bed fusion, direct energy deposition, binder jetting, sheet lamination, and fused deposition modeling in an organic binder do not provide small enough structures.[12,13] Stereolithography and digital light processing (DLP) approaches are more promising, but recent approaches are focused around producing materials by creating new resins for new phases. Some recent work demonstrating this approach is incompatible with resins containing iron, a key magnetic metal, due to metal ion reactivity.[14] This approach would also require the generation and optimization of new resin compositions for each final product. More generally, printing with aqueous metal ion solutions can be difficult due to interactions with UV light and reactions with intermediate radical species.[15] To address these limitations, ongoing work in the Greer group involves the use of DLP to synthesize "blank" organic lattices that can be transformed into structures of varying metal composition through an aqueous "swell-in" procedure.[14,16,17]

During my project, I will implore a similar "swell-in" procedure to produce high-resolution Fe containing magnetic alloys with final feature size in the tens to hundreds of microns. Blank lattices will be swollen with aqueous metal nitrate solutions, calcined to remove the organic polymer, and reduced in forming gas (95% N_2, 5% H_2) to produce the final metal lattices. During fabrication, different compositions, swelling parameters, and heating profiles will be explored, the process of calcination will be assessed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), and the properties and compositions of the lattices will be assessed through scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDS), and powder X-ray diffraction (pXRD).

This project supports efforts to reduce off-target chemotherapy effects as well as explores ways of constructing magnetic metallic lattices. Architected, metallic lattices continue to be an area of active additive manufacturing research, and this project will elucidate protocols for creating intricate magnetic lattices with high resolution.[12,13]

Objectives

This SURF project aims to construct magnetic metal lattices via digital light processing (DLP).

(1) Adapt the swell-in additive manufacturing protocol used in constructing copper or lithium cobalt oxide lattices[14,16] to produce magnetic metal alloys.
   a. Identify candidate metal salt solutions that produce magnetic compositions.
   b. Optimize the wet chemistry steps during the metal salt swelling to increase the density of the final metallic lattice, especially around the nodes of the structure.
   c. Assess thermal behavior through TGA and DSC.

(2) Evaluate the structure of the lattices through SEM imaging and the chemical composition of the lattices through EDS. Selected structures will be sent for pXRD analysis.

Approach

In this project, an Autodesk Ember DLP 3D printer will be used to print organogel lattices using a resin consisting of PEGda as a polymer binder, Sudan I as a photoblocker, Irgacure 379 as a photoinitiator, and Michler's ketone as a sensitizer.[17] Solvent exchanging organogel lattices with water will result in "blank" hydrogel lattices. Blanks will then be soaked in aqueous metal nitrate solutions to "swell-in" the metal ions at various temperatures and for different lengths of time. Swollen blanks will be calcined in a tube furnace to remove organic components and counterions and then reduced in forming gas (95% N_2, 5% H_2) to form metals. The DLP printer will follow sliced .stl files for twisted honeycomb lattices, a geometry found to have favorable flow characteristics, as seen in Fig. 2.[18] For the "swell-in" step, aqueous metal nitrate solutions corresponding to ferromagnetic metal alloys such as alnico and permalloy will be used.[19,20] The concentration (1-5 M), temperature, and time of the "swell-in" step will be assessed.

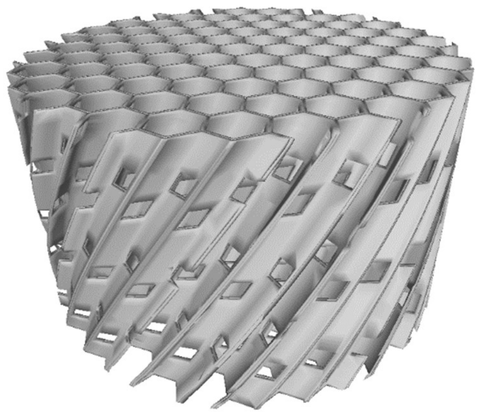

Figure 2: Twisted honeycomb structure to be manufactured out of a magnetic material and placed in the vein (STL courtesy of D. Yee).

Following fabrication, the metallic lattices will be imaged using a SEM. This will allow for microstructural and surface examination which will elucidate which procedures are best for the production of dense, uncracked lattices with minimal shrinkage. The micro-compositions of the final structures will be measured using EDS, and the bulk composition of said structures will be sent for analysis using pXRD. The optimal lattices will be purely composed of magnetic alloys without large quantities of impurities.

Work Plan

Week	Pre	1	2	3	4	5	6	7	8	9	10
Buy metal salts	x										
Instrument training	x	x									
Create resin, optimize organogels prints	x	x	x								
Fabrication, calcination, TGA, and DSC			x	x	x	x	x	x	x	x	x
Characterization (SEM, EDS)			x	x	x	x	x	x	x	x	x

References

(1) Pugazhendhi, A.; Edison, T. N. J. I.; Velmurugan, B. K.; Jacob, J. A.; Karuppusamy, I. Toxicity of Doxorubicin (Dox) to Different Experimental Organ Systems. *Life Sci.* **2018**, *200*, 26–30. https://doi.org/10.1016/j.lfs.2018.03.023.

(2) Qi, L.; Luo, Q.; Zhang, Y.; Jia, F.; Zhao, Y.; Wang, F. Advances in Toxicological Research of the Anticancer Drug Cisplatin. *Chem. Res. Toxicol.* **2019**, *32* (8), 1469–1486. https://doi.org/10.1021/acs.chemrestox.9b00204.

(3) Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R. L.; Torre, L. A.; Jemal, A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA. Cancer J. Clin.* **2018**, *68* (6), 394–424. https://doi.org/10.3322/caac.21492.

(4) Yee, C.; McCoy, D.; Yu, J.; Losey, A.; Jordan, C.; Moore, T.; Stillson, C.; Oh, H. J.; Kilbride, B.; Roy, S.; Patel, A.; Wilson, M. W.; Hetts, S. W. Endovascular Ion Exchange Chemofiltration Device Reduces Off-Target Doxorubicin Exposure in a Hepatic Intra-Arterial Chemotherapy Model. *Radiol. Imaging Cancer* **2019**, *1* (1), e190009. https://doi.org/10.1148/rycan.2019190009.

(5) Brown, D. B.; Geschwind, J.-F. H.; Soulen, M. C.; Millward, S. F.; Sacks, D. Society of Interventional Radiology Position Statement on Chemoembolization of Hepatic Malignancies. *J. Vasc. Interv. Radiol.* **2009**, *20* (7), S317–S323. https://doi.org/10.1016/j.jvir.2009.04.015.

(6) WHO. Cancer; 2022. https://www.who.int/news-room/fact-sheets/detail/cancer

(7) Hwu, W.; Salem, R.; Pollak, J.; Rosenblatt, M.; D'Andrea, E.; Leffert, J.; Faraone, S.; Marsh, J.; Pizzorno, G. A Clinical-Pharmacological Evaluation of Percutaneous Isolated Hepatic Infusion of Doxorubicin in Patients with Unresectable Liver Tumors. *Oncol Res* **1999**, *11* (11–12), 529–537.

(8) Patel, A. S.; Saeed, M.; Yee, E. J.; Yang, J.; Lam, G. J.; Losey, A. D.; Lillaney, P. V.; Thorne, B.; Chin, A. K.; Malik, S.; Wilson, M. W.; Chen, X. C.; Balsara, N. P.; Hetts, S. W. Development and Validation of Endovascular Chemotherapy Filter Device for Removing High-Dose Doxorubicin: Preclinical Study. *J. Med. Devices* **2014**, *8* (4). https://doi.org/10.1115/1.4027444.

(9) Yee, D. W.; Hetts, S. W.; Greer, J. R. 3D-Printed Drug Capture Materials Based on Genomic DNA Coatings. *ACS Appl. Mater. Interfaces* **2021**, *13* (35), 41424–41434. https://doi.org/10.1021/acsami.1c05209.

(10) Bai, Y.; Tong, Y.; Liu, Y.; Hu, H. Self-DsDNA in the Pathogenesis of Systemic Lupus Erythematosus. *Clin. Exp. Immunol.* **2018**, *191* (1), 1–10. https://doi.org/10.1111/cei.13041.

(11) Blumenfeld, C. M.; Schulz, M. D.; Aboian, M. S.; Wilson, M. W.; Moore, T.; Hetts, S. W.; Grubbs, R. H. Drug Capture Materials Based on Genomic DNA-Functionalized Magnetic Nanoparticles. *Nat. Commun.* **2018**, *9* (1), 2870. https://doi.org/10.1038/s41467-018-05305-2.

(12) Chaudhary, V.; Mantri, S. A.; Ramanujan, R. V.; Banerjee, R. Additive Manufacturing of Magnetic Materials. *Prog. Mater. Sci.* **2020**, *114*, 100688. https://doi.org/10.1016/j.pmatsci.2020.100688.

(13) Périgo, E. A.; Jacimovic, J.; García Ferré, F.; Scherf, L. M. Additive Manufacturing of Magnetic Materials. *Addit. Manuf.* **2019**, *30*, 100870. https://doi.org/10.1016/j.addma.2019.100870.

(14) Yee, D. W.; Citrin, M. A.; Taylor, Z. W.; Saccone, M. A.; Tovmasyan, V. L.; Greer, J. R. Hydrogel-Based Additive Manufacturing of Lithium Cobalt Oxide. *Adv. Mater. Technol.* **2021**, *6* (2), 2000791. https://doi.org/10.1002/admt.202000791.

(15) Abramov, L. I.; Zilberman, Ye. N.; Ivanova, V. I. Effect of Copper and Iron Salts on the Radical Polymerization of Acrylamide in Water. *Polym. Sci. USSR* **1989**, *31* (7), 1573–1578. https://doi.org/10.1016/0032-3950(89)90501-7.

(16) Yee, D. W. Additive Manufacturing of 3D Functional Materials: From Surface Chemistry to Combustion-Derived Materials, California Institute of Technology, 2020.

(17) Saccone, M. A.; Yee, D. W.; Gallivan, R. L.; Narita, K.; Greer, J. R. Microscale Metal Additive Manufacturing via Hydrogel Infusion. *Submitted*, **2022**.

(18) Maani, N.; Diorio, T. C.; Hetts, S. W.; Rayz, V. L. Computational Modeling of Drug Transport and Mixing in the Chemofilter Device: Enhancing the Removal of Chemotherapeutics from Circulation. *Biomech. Model. Mechanobiol.* **2020**, *19* (5), 1865–1877. https://doi.org/10.1007/s10237-020-01313-8.

(19) Zhou, L.; Miller, M. K.; Lu, P.; Ke, L.; Skomski, R.; Dillon, H.; Xing, Q.; Palasyuk, A.; McCartney, M. R.; Smith, D. J.; Constantinides, S.; McCallum, R. W.; Anderson, I. E.; Antropov, V.; Kramer, M. J. Architecture and Magnetism of Alnico. *Acta Mater.* **2014**, *74*, 224–233. https://doi.org/10.1016/j.actamat.2014.04.044.

(20) Arnold, H. D.; Elmen, G. W. Permalloy, A New Magnetic Material of Very High Permeability. *Bell Syst. Tech. J.* **1923**, *2* (3), 101–111. https://doi.org/10.1002/j.1538-7305.1923.tb03595.x.