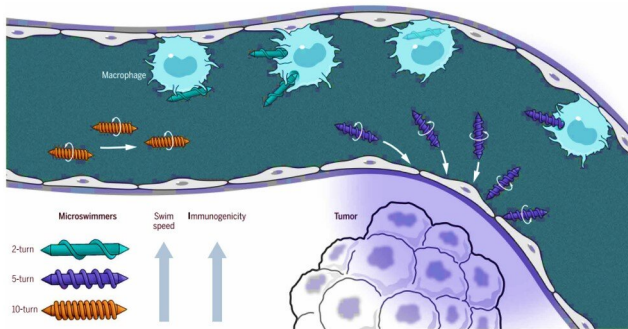


Interaction dynamics between designer microrobots and the immune system

21 July 2020, by Thamarasee Jeewandara



Optimization of microswimmer shape for targeted drug delivery. Illustration of a future use case for the medical microrobots emphasizing an important design tradeoff. Double-helical magnetic microswimmers with filled internal cores are 3D-printed as concentrated drug-carrying bodies. Three morphological derivatives of the same design are tested with the same body length, outer diameter, and body volume, only varying the number of helical turns along the major axis (2-turn, 5-turn, and 10-turn). Two-turn microswimmers exhibit the best locomotion performance, yet they were preferentially targeted by the macrophages. Increasing turn number deteriorates swimming performance while reducing immunogenicity, presenting a compromise between speed and physical interactions with the immune system. Credit: Science Robotics, doi: 10.1126/scirobotics.abc7620

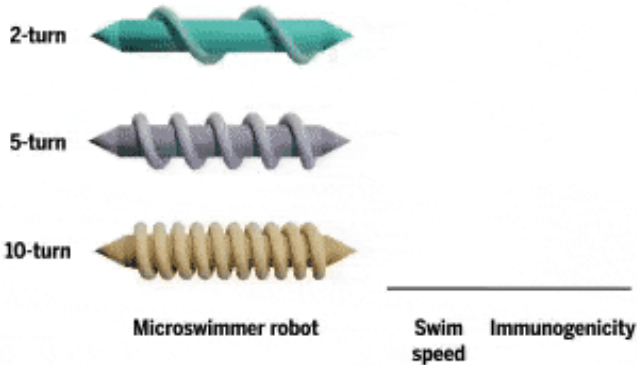
Mobile medical microrobots can now be engineered in the lab for broad ranging applications from personalized disease treatment to targeted drug delivery. During their structural design, bioengineers aim to minimize physical interactions with cells of the immune system by optimizing the morphology (shape) of the device and its surface chemistry. It is therefore important to understand the interplay between the contributions of such parameters toward effective, target-oriented locomotion and low immunogenicity. In a new report now published on *Science Robotics*, Immihan Ceren Yasa and a research

team in physical intelligence, medicine and engineering at the Max Planck Institute for Intelligent Systems and the Koç University in Germany and Turkey, investigated the interactions of magnetically steerable double-helical microswimmers.

A [biohybrid microrobot](#) integrates a living microorganism within a non-living body to explore the inherent machinery of the microorganism coupled to its properties of actuation, sensing and locomotion. The combined architecture can harness biological fuels in the microenvironment to perform specific tasks such as cargo delivery, targeted therapy and manipulation. The microrobots in this work had a changing helical shape integrated with [mouse macrophage](#) cell lines (a type of [phagocyte](#)/white blood cell). Macrophages and [splenocytes](#) (two types of [white blood cells](#)) in the living microenvironment recognized the biohybrid microrobots and elicited an [immune response](#) based on the helix turn numbers of the microswimmers. The work showed the significance of simultaneously considering structural optimization for locomotion performance and immune cell interactions during medical microrobot development. The macrophage-microswimmer hybrids present a unique engineering opportunity to develop biohybrid microrobots that combine the mobility of synthetic microswimmers and immunoregulatory capacity of macrophages for targeted immunotherapeutic applications.

Structural design and parameters of immunobots

Optimizing microswimmer robots for future use in drug delivery



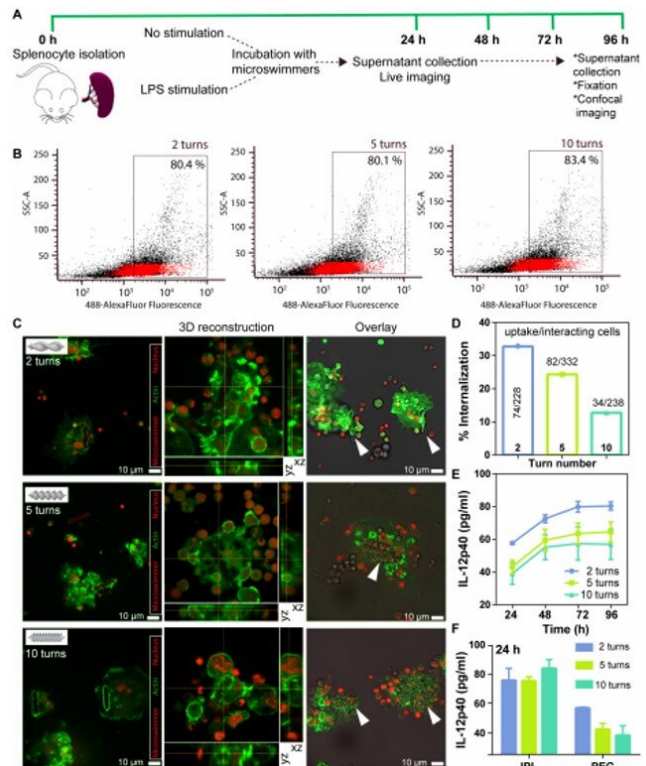
Designing microrobots that are fast, but safe -- functioning in harmony with the immune system. Animation Credit: Alice Kitterman, Credit: Science Robotics, doi: 10.1126/scirobotics.aaz3867

During their journey toward the target tissue, the microswimmers had to overcome a number of barriers including the [blood-brain barrier](#), mucus membrane and [the endothelium](#) that can alert their presence as 'threats' to the immune system. Yasa et al. investigated the interactions of magnetic microswimmers with the [cells](#) of the immune system and designed a benchmark method to routinely test future robotic designs in biomedicine. The team introduced the biohybrid microrobot as an "immunobot"—a magnetically driven and biologically activated macrophage with an engulfed synthetic magnetic, helical microswimmer. During the experiments they chose microswimmers with two- and 10-turn helices and microprinted them in three dimensions (3-D) using [two-photon polymerization](#).

During 3-D printing, they used a pre-polymer solution of [poly\(ethylene glycol\) diacrylate](#) (PEGDA) and a photoinitiator as constituents and magnetized the printed structures by sputter-coating them with 100-nm-thick Nickel and 50-nm thick gold films, followed by thiol-modified PEG

surface modifications. The surface modification minimized unintended chemical interactions with the immune system, allowing the scientists to dissect the impact of [structural effects alone on the immune response](#). Yasa et al. applied rotational magnetic fields to control and propel the microswimmers by exerting [torque around the helical axis](#), where torque-based magnetic propulsion steered microswimmers along an assigned trajectory. After testing the swimming performances of immunobots in buffer solutions, they observed the microswimmers inside whole fresh blood obtained from a mouse for further studies. Based on swimming speeds and rolling properties, the performance of microswimmers with helices for two turns were greater than five turns and subsequently greater than 10-turn helical microrobots in buffer and whole blood.

Interactions of microswimmers and macrophages



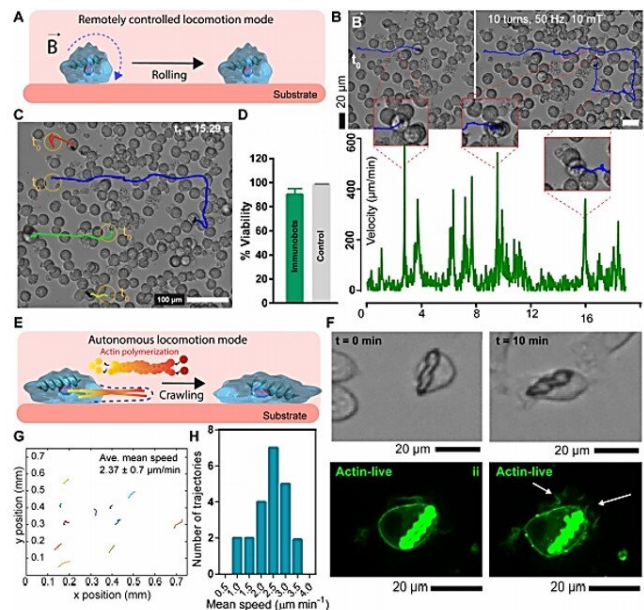
Primary immune cell response to the synthetic microswimmers. (A) Experimental workflow for coincubation of splenocytes freshly isolated from mouse spleen. SSC-A, side scatter. (B) Fluorescence-activated

cell sorting analysis showing the proliferation rates of the splenocytes at 72 hours. (C) Confocal images of the LPS-stimulated splenocytes at 96 hours. Lymphocytes around the spread macrophages are also evident. (D) The percentage of internalization rates of the microswimmers by LPS-stimulated splenocytes at 96 hours. Data represented as total uptake over total interacting cells. (E) IL-12 p40 in the culture supernatant, secreted from the splenocytes in response to microswimmers, detected by enzyme-linked immunosorbent assay. (F) IL-12p40 release in response to microswimmers made from commercial photoresist, IPL, and PEG at 24 hours. Credit: Science Robotics, doi: 10.1126/scirobotics.aaz3867

In [nanomedicine](#), scientists can tailor the physical properties of particles to either avoid recognition by the host or control the immune response for applications. A primary mechanism of the innate immune defence response is [phagocytosis by macrophages](#), which depends on the size and geometry of the target particle. When macrophages internalized the microswimmers [they did not degrade the helices](#), thereby providing long-term robotic task execution. The research team methodically varied the helical turn number along the major axis of the microswimmers while maintaining its body volume to examine interactions of the mouse macrophage cell lines and their internalized cargo using electron, optical and confocal microscopy. Based on time-lapse movies of macrophage-encapsulated, surface-bound microswimmers, they revealed the impact of the robot microarchitecture. During [phagocytosis](#), the microswimmer entered the macrophage cell for stable orientation in a process that took 20 minutes on average for two-turn microswimmers. This process took up to four hours, for five-turn and 10-turn microswimmers. After successful phagocytosis, the macrophages continued to crawl with their internal cargo. The findings highlighted how the optimized shape enhanced locomotion performance, while affecting the immunogenicity of the microswimmer, suited for a variety of applications in medicine.

Immunogenic responses of the helical swimmers

Yasa and coworkers then investigated the immunogenicity of the microswimmers by presenting them to primary mouse [spleen cells](#) containing a variety of white blood cell populations such as macrophages and lymphocytes. Typically, the microswimmers will encounter activated immune cells such as [lipopolysaccharides \(LPS\)](#) that stimulate surface receptors of macrophages to secrete [pro-inflammatory cytokines](#) for an inflammatory response. In this work, microswimmers with superior mobility induced higher production of [interleukin-12](#) an important cytokine to regulate the innate and adaptive immunity of cells. The team further noted the accumulation of [T and B cells](#) around macrophages when they internalized the microswimmers; to suggest a specific immune response. While the two-turn microswimmers had the highest speed of motion, they were the most immunogenic compared to the five-turn and 10-turn microswimmers, the team therefore recommended the use of two-turn microswimmers with higher speed in immune-privileged sites such as the central nervous system and the eye. They suggest using structures with lower speed to gain relative invisibility to the immune system on biological sites elsewhere.



Biohybrid immunobot design bringing together a

macrophage with a synthetic microswimmer to enable bimodal locomotion capability in a biological environment. (A) Illustration of the surface roller immunobot achieved by the magnetic torque-based actuation and (B) steering of an immunobot around and on top of the semi-adherent nonmagnetic macrophages. Increases in the instantaneous velocities were observed as the immunobot propelled on top of the adherent nonmagnetic macrophages (insets corresponding to peaks). (C) Tracking of multiple immunobots in roller mode actuated simultaneously. Orange circles denoting the initial positions of the immunobots at t_0 . (D) Viability of the immunobots compared with control cells at 72 hours. (E) Illustration of an immunobot in the autonomous (crawling) locomotion mode by the intrinsic dynamic reorganization of the actin cytoskeleton. (F) Snapshots of the time-lapse recordings during motion. Fluorescence images showing live actin protrusions during the crawling. (G) 2D displacement trajectories of the immunobots displaying crawling locomotion with an average speed of $2.4 \pm 0.5 \mu\text{m min}^{-1}$. (H) Mean speed distribution of the crawling immunobots. Credit: Science Robotics, doi: 10.1126/scirobotics.aaz3867

Entanglement of microrobot design parameter on swimming and immunogenicity and proof-of-principle immunobots

The team then considered [mechanobiology](#) or physical forces and their impact on cell mechanics as another significant parameter during [microrobot design](#). They assessed the microrobot surface chemistry to understand its locomotion, performance and immunogenicity. While a single macrophage could accommodate small microswimmers to form biohybrids, giant cells were thought to internalize larger microswimmers. While the immunobot showed uninterrupted locomotion, individual microswimmers were not as efficient by themselves. Yasa et al. demonstrated additional variations to the prototype of their primary work, although in both design types, the externally applied magnetic field drove the locomotion of the immunobots.

Supplementary Movie S3

Magnetic actuation of the immunobots

Magnetic actuation of the immunobots. Credit: Science Robotics, doi: 10.1126/scirobotics.aaz3867

The work will have significant impact on [cancer immunotherapy](#), which has revolutionized the field of [oncology](#) to meet the growing demands for targeted delivery of immunomodulated compounds to [eradicate cancer cells](#). In this instance, Yasa and colleagues aim to deviate from the original stealth approach to be invisible to the immune system and instead focus on joining forces with the immune system against tumors. The work will therefore represent new challenges to design and develop a multifunctional and versatile biohybrid system, which the team envision on developing with the same basic design principles. The work will also pave the way to design advanced personalized medicine approaches using biohybrid microrobots functionalized using the patient's own macrophages.

More information: Immihan Ceren Yasa et al. Elucidating the interaction dynamics between microswimmer body and immune system for medical microrobots, *Science Robotics* (2020). DOI: [10.1126/scirobotics.aaz3867](https://doi.org/10.1126/scirobotics.aaz3867)

Samir Mitragotri et al. Physical approaches to biomaterial design, *Nature Materials* (2008). DOI: [10.1038/nmat2344](https://doi.org/10.1038/nmat2344)

Ouajdi Felfoul et al. Magneto-aerotactic bacteria deliver drug-containing nanoliposomes to tumour hypoxic regions, *Nature Nanotechnology* (2016).

[DOI: 10.1038/nnano.2016.137](https://doi.org/10.1038/nnano.2016.137)

© 2020 Science X Network

APA citation: Interaction dynamics between designer microrobots and the immune system (2020, July 21) retrieved 20 September 2020 from <https://medicalxpress.com/news/2020-07-interaction-dynamics-microrobots-immune.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.