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February 15, 2020

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

Happy Valentines Day to those who have already celebrated this special day and to those who are celebrating it this weekend.

The last topic I covered was "New Approaches to Alzheimer's Disease" If you missed this article, click here to read it. This month we will cover "Sick or Injured, Microrobots to the Rescue!"

Please read on for other current news in the Table of Content below. The next newsletter will be published on March 15th, 2020.

We encourage you to share this newsletter with your colleagues by using the social

Please email me, Regina Au, if you have any questions, comments, or suggestions.

Sincerely,
Regina Au
Principal, New Product Planning/
Strategic Planning Consultant
BioMarketing Insight

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Developing a Product? Commercializing a Product?

If you are developing a product and have not conducted the business due diligence to determine commercial viability or success, contact me for an appointment. For successful commercial adoption of your product or looking to grow your business, contact me for an appointment.

For more information on our services, click on the links below:

Product Development
Market Development
Marketing Strategies

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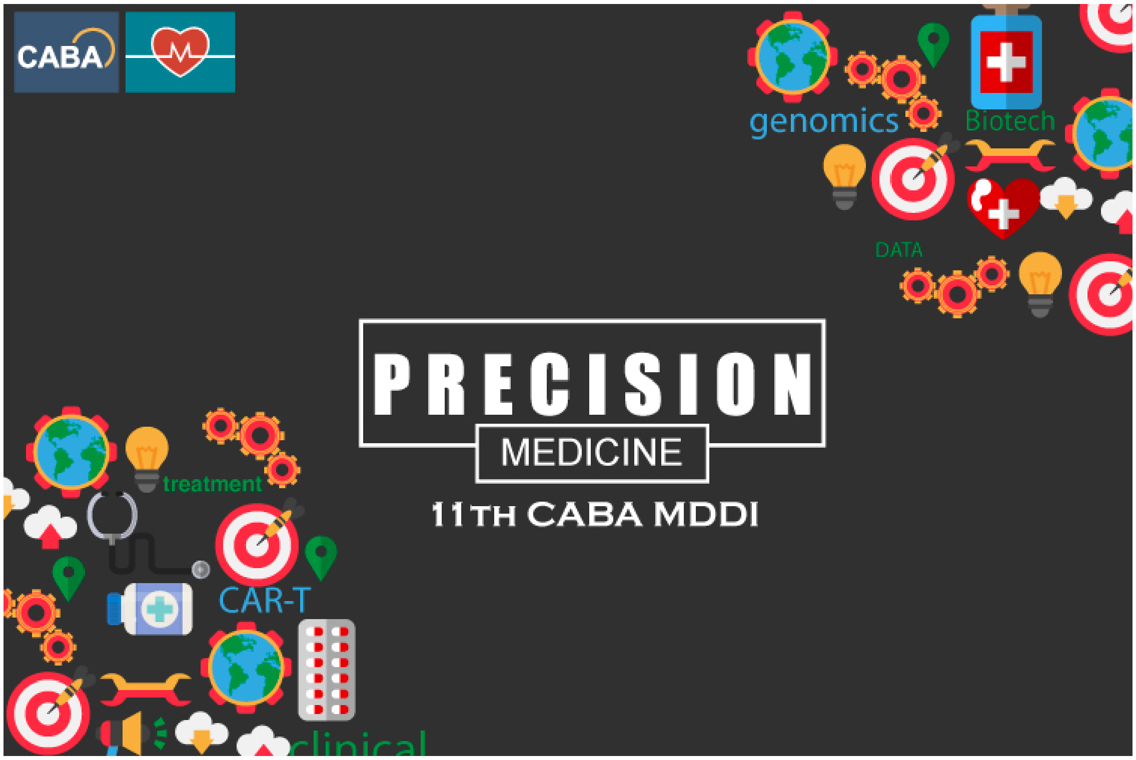
SCIENCE FROM SCIENTISTS

Science from Scientists

I'm pleased to announce that I will be a judge for the Spofford Pond School's 4th Annual Science Fair in Boxford, MA on Friday, March 6, 2020. This fair is hosted by Science from Scientists, their mission is to improve the attitudes & aptitudes of 4-8th graders in STEM. To find out more about this organization, click here.



11st CABA Medical Device and Diagnostics Innovation Symposium (MDDI)

I am pleased to announce that I was a panelist at the MDDI Symposium on Saturday, December 14, 2019 at the Conference Center at Waltham Woods, 860 Winter St, Waltham. The panel discussion is on "Precision Medicine in Medical Device." To find out more, click here.

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Asian American Women in Leadership Conference

I am pleased to announce that I conducted a workshop titled "Develop Your Leadership Skills While Maintaining Your Authenticity" at the Asian American Women in Leadership Conference on Saturday, November 16th, Simmons University. For more information on the conference, click here.

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BioProcess International

Why Conducting Marketing Due Diligence Early in Product Development Is Important

I am pleased to announce that my article entitled "Why Conducting Marketing Due Diligence Early in Product Development Is Important" was published in the BioProcess International Magazine. To read the article, click here.

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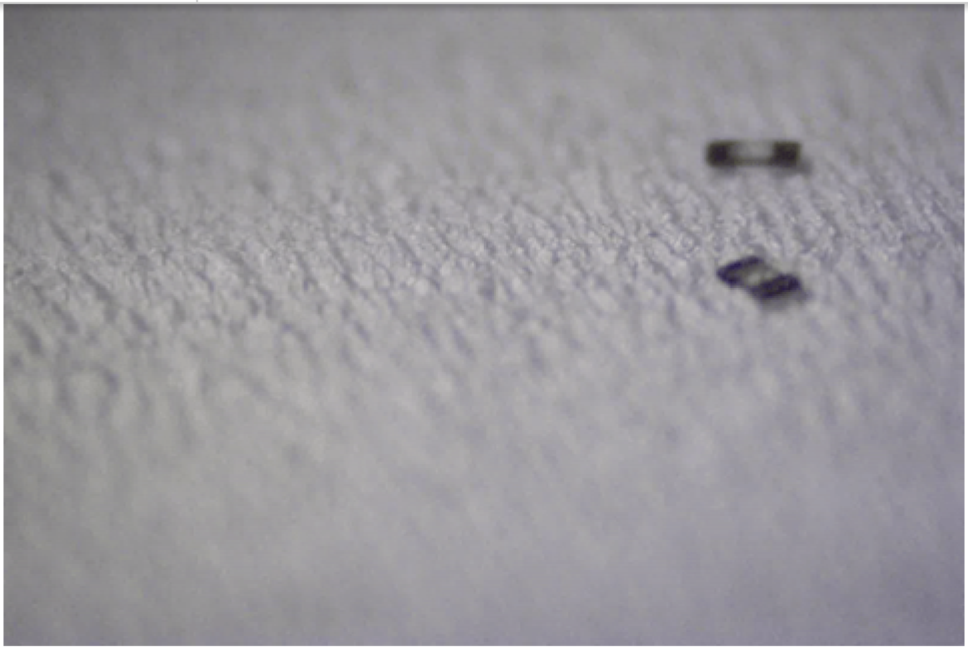


Sick or Injured, Microrobots to the Rescue!

What are Microrobots?

Scientists and engineers have been working on microrobots for the last three decades. Microrobots similar in size to a living cell (see Figure 1) are designed to move throughout the body. Microbiots are less likely to cause tissue damage compared to surgery or catheter insertions. They can also deliver a drug to their target and minimize side effects compared to drugs that are delivered systemically and are more widely dispersed. Some predict that in the future, microrobots will be able to repair or rebuild tissue in pursuit of tissue engineering and regenerative medicine.

Figure 1: A mobile microrobot compared to a penny. Credit: D. Cappelleri et el. American Scientist

A mobile microrobot is smaller than 1 millimeter and bigger than 1 micron in length—a size range that would allow unimpeded travel throughout the human body while remaining trackable and recoverable.

However, there are two main challenges with microrobots: 1) locomotion and 2) control.

1) **Locomotion**:
The microrobots must be able to move reliably through wet areas as well as traverse through pockets of air found in places such as the stomach, intestines, and lungs. The sheer microsize makes it hard to visualize or track their location in the body.

In the past, scientist have used various mobile or actuation methods:

a) *Acoustic actuation*, in which microrobots move toward sound-generated pressure points driven by oscillating sound waves that are applied to the fluid surrounding them.

b) *Chemical actuation* methods include propulsive chemical motors that expel microbubbles, such as hydrogen microbubbles used to treat gastric bacterial infections in live mice. These microrobots improved payload-retention rates by pressing the drug directly against the stomach wall. Or use local chemical gradients to generate thrust forces.

c) *Biohybrid designs* that take advantage of the self-contained energy and mobility of living cells, typically by coupling bacteria, sperm, or muscle cells to artificial structures and controlling them remotely by varying the surrounding temperature, acidity, lighting

d) *Optical actuation* that generate crawling locomotion on elastomer materials, which contract when directly heated by lasers.

However, the limitations with these methods can only work in controlled environments and require fine-tuning for applications in vivo.

2) **Control**:
Microrobots are too small to be easily incorporated or attached (on-board) to any power source, sensors, or computer circuitry and therefore can't be self-contained or self-propelled microrobot where all on-board components can operate autonomously or with a remote control.

Instead, these microrobots are more likely to be used as an off-board approach: The mobile, untethered component of the milli/microrobotic system is externally (off-board) actuated, sensed, controlled, or powered.

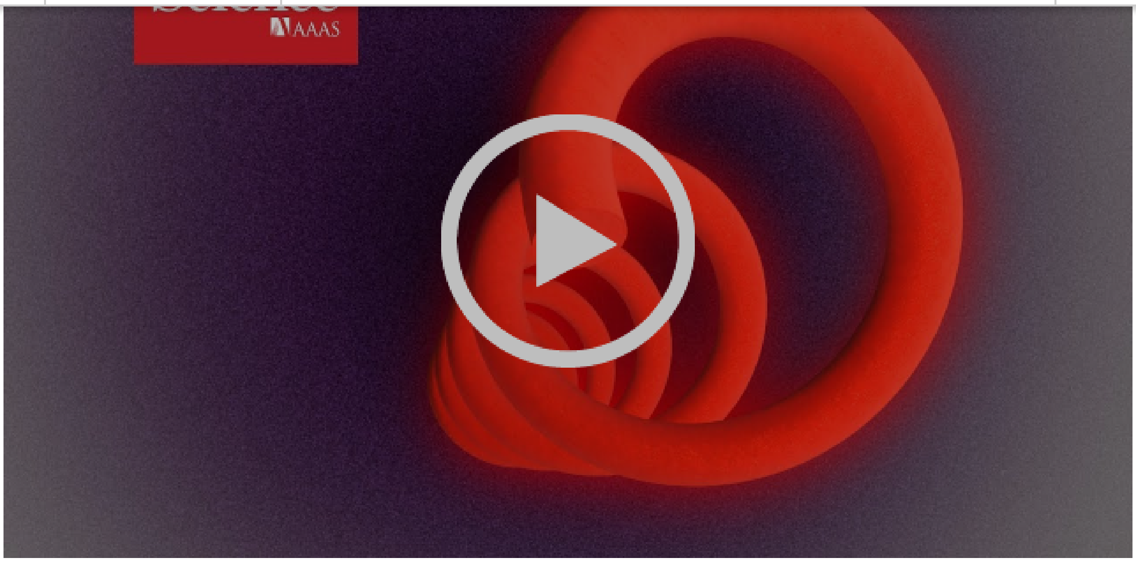
To date, the best form of microrobot actuation is magnetism and is well-suited for use in vivo. By embedding magnetic material inside or around its form, microrobots can be manipulate with external magnetic fields.

Locomotion Style:
In addition to activation, there are different locomotion styles. All organisms move under their own power by propelling themselves using nonreciprocating (one direction) motion with threadlike appendages known as *flagella*. Microswimmer that are flagella-based designs use *microhelices* that move with a screw-like motion driven typically by rotating magnetic fields. This design style works well in fluid but can't travel through pockets of air or rough and sticky surfaces in the body.

Solutions scientists have developed:

1) David Cappelleri and his team have developed microtumblers to overcome these issues. They found that rolling or tumbling a microrobot using magnetic torque is more effective than pulling it along a magnetic gradient. Similar to a rotating magnetic field this can be applied to spin artificial flagella and can be used to rotate block-like surface tumblers. See Figure 1 and title photo.

2) Li Zhang, a materials scientist from the Chinese University of Hong Kong in Shatin and his colleagues used miniature alga called *Spirulina platensis*, commonly used as a dietary supplement in the formed of a helical or spring-like shape design to solve the problem of locomotion and control. See video below.



Video: Spirulina platensis in the form of a helical design to solve the problem of locomotion and control. Credit: Li Zhang et el.

The key is to coat the Spirulina with iron oxide nanoparticles. These helical or spring-like shape magnetized alga provides maximum mobility when propelled by magnetic fields that pass through the body but remain harmless to the body. These synthetic microrobots are completely biocompatible and will degrade anywhere from a few hours to a few days, depending on how much magnetic coating they have without harming normal cells. The iron oxide however are toxic to cancer cells. In 48 hours the magnetized alga destroyed about 90% of tumor cells in a petri dish, a pleasant unexpected side-effect discovered by the researchers.

It is believed that these synthetic algae microrobots have the potential for delivering medical treatments to every corner of the human body and more efficiently; they can be easily controlled and monitored by either observing their fluorescence from the iron oxide or through nuclear magnetic resonance (NMR), a medical imaging tool when the algae travels deeper into the body.

The ability of the algae microrobots to carry cargo-load drugs inside the body still needs to be tested, “It’s still not ready for a doctor to use,” said Joseph Wang, a nanoengineer who’s developing a different type of medical microrobots. He thinks the technology might be available in the next ten years.

3) Eunpyo Choi at the Korea Institute of Medical Microrobotics in Gwangju, Korea, invented a magnetic microrobot that delivers stem cells to damaged knee cartilage in animals, a discovery that could lead to treating or preventing osteoarthritis.   He hopes to repeat his findings in human clinical trials.

Scientist are currently using mesenchymal stem cells, from the person’s fat or bone does one make the cells stick to the cartilage?

In order to achieve this the team used a polymer called PLGA to manufacture a spherical microrobot(bot) that looks a bit like a soccer ball full of holes, just a lot smaller. The bots are around 350 micrometres in diameter, half the width of a grain of sugar. See Figure 2.

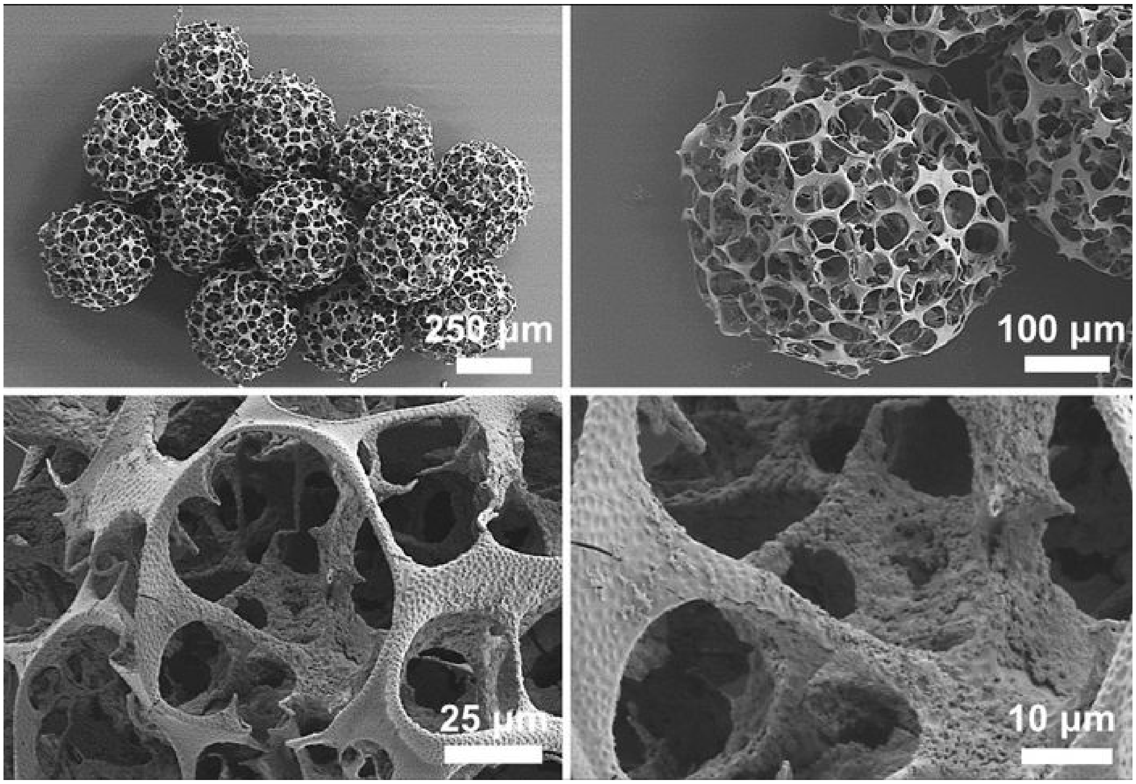


Figure 2: Close up images of the magnetic microrobots showing the porous structure and pore morphology. Credit: Go et al., Sci. Robot. 5, eaay6626 (2020)

Then to make them magnetic, biodegradable and non-toxic, the researchers coated the microrobot with a combination of ferumoxytol, an injectable iron supplement approved by the US Food and Drug Administration, and chitosan, a sugar found in the exoskeleton of shellfish and used to treat high blood pressure and cholesterol.

Then the magnetic mini-balls were impregnated with stem cells to be injected into a rabbit's knee. To prep the rabbit's knee for treatment, the knee was encased in a Star Wars-like contraption of electromagnetic coils housed in gleaming white cylinders. Then a hundred of the bots were injected while a video recorded the unfolding drama.

When the magnet was turned off, the microrobots fell away from the defect with gravity. When the magnet was turned on, almost all the microrobots were affixed to the injured zone for three weeks with the help of another magnet attached to the outside of the knee. A series of images shows significant healing of the defect at the three-week mark.

multitasking capability to suggest microrobots could one day be used for inner-body diagnostics or biomedical treatment at the cellular or molecular level.

They were able to program the microrobots to switch formation behavior as a robotic swarm by regulating the movement of each individual bot. By fine tuning the frequency and direction of a rotating magnetic field, each individual microrobot exhibited oscillating, rolling, tumbling and spinning movements.

Depending on the type of individual movement, the robots as a group self-organized into different formations of liquid (an evenly distributed pattern of robots), chains (robots connected in long and parallel rows traveling by the short end), ribbon (rows of robots traveling by the long end) and vortex (circular crowds of robots), respectively.

The researchers could also change the swarm's speed and direction, by tweaking the applied magnetic field and accomplish a variety of tasks by switching between conformations such as "chain" formation to cross narrow channels, then the "vortex" to lift heavy loads. see Figure 3.

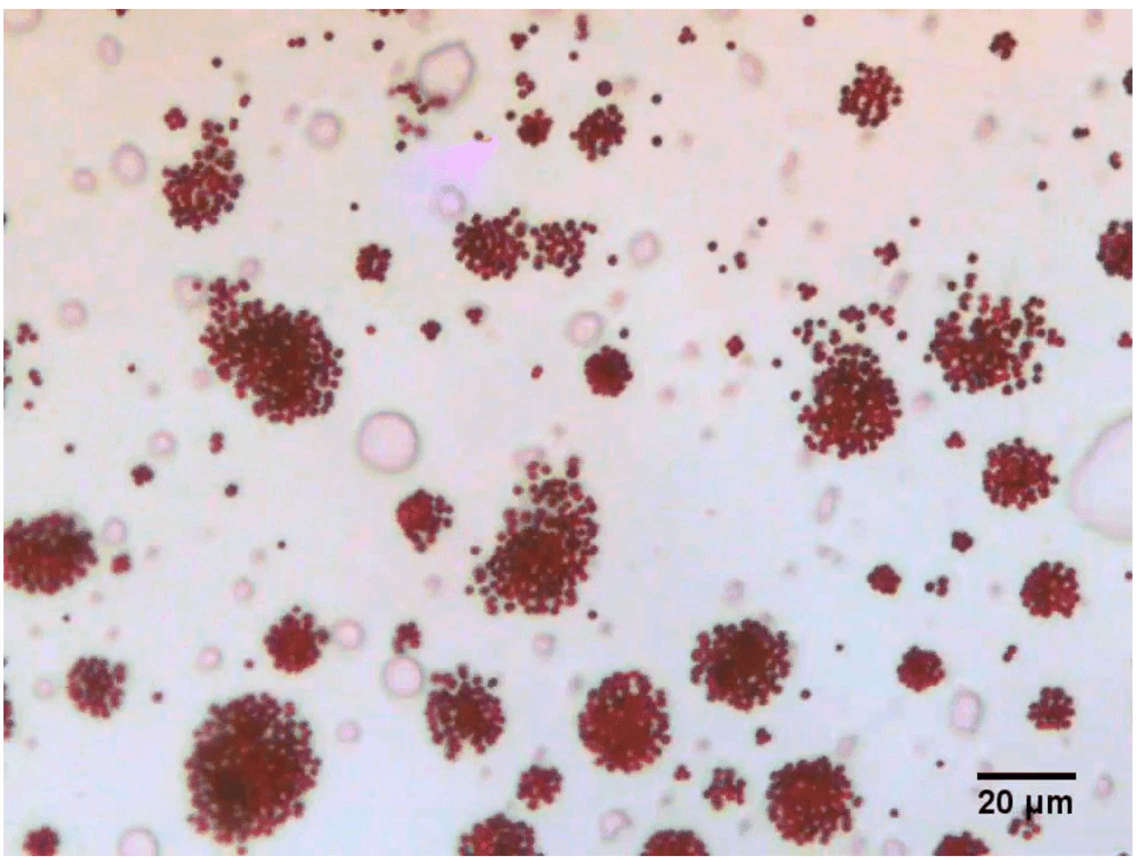


Figure 3: A vortex (circular crowds) was one of four different self-organized formations the magnetized microrobots created. Figure 3: credit: Xie et al., Sci. Robot. 4, eaav8006 (2019)

Xie and colleagues say their findings support and demonstrate the idea of achieving the

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Closing Thoughts

The advancement in medical device technology is incredible. If scientists and engineers can resolve all the challenges mentioned above, it will change the way medicine is practiced. The biggest challenge right now is the use of an external magnet house to control the microrobots which appear to be large and sometimes require external magnets on the body as described with Eunpyo Choi from Korea. Although details of how Hue Xie from China was able to manipulate the microrobots into different formations were not provided in the article, I assume since the microrobots were magnetic, an external magnet was also used.

When this technology does become available, surgical procedures to repair torn ACL of the knee or even knee replacement due to osteoarthritis may decrease because microrobots embedded with stem cells will repair or regenerate tissue, ligaments or even bone.

These microrobots could also be used to treat cancer as in the example of the Spirulina alga coated with iron oxide that is deadly to cancer cells yet leaves healthy cells unharmed. Or spherical microrobots embedded with cancer drugs are delivered to its target and then the drug is released. Could this be possible for use on solid tumors where the microrobots can change into different formation in surviving a hostile environment?

I'm sure scientist will come up with clever ways to develop and use this technology in medicine. Maybe films such as Star Trek and their futuristic ways of treating illnesses or

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Should you have any questions or need of assistance with your business due diligence, determining your product's value proposition, target product profile and economic value of your product for reimbursement, feel free to contact me at 781-935-1462 or regina@biomarketinginsight.com.
