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Viewpoint

Convergence of Liquid Metal Biotechnologies for Our Health

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INTRODUCTION: LIQUID METALS (LMS) FOR CONVERGENCE

Owing to the increasing public demand associated with health concerns, such as heart diseases, diabetes, and cancers, improved precision medical devices and highly effective therapeutic biomaterials are being explored. In addition to their unique properties, providing multifunctionality to these devices and materials is often crucial for achieving better performance, which simultaneously realizes the constant monitoring of health conditions as well as targeted therapy *in vitro* and *in vivo*. These multitasks might be assigned to an emerging concept, something born from "convergence" which combines exponential technologies with other research fields.[1]

Among various materials, transformable and easily handled liquid metals (LMs),[2] which have exceptional multifunctionality, might be suitable for creating the convergence concept with cutting-edge technologies, including optics, electronics, printing, robotics, and nanotechnologies. In particular, Ga- and Ga-based LM alloys are promising soft materials for various applications because of their low toxicity, excellent electrical and thermal conductivities, and fluidity at near-room temperature. More interestingly, Ga-based LM particles continue to exhibit both fluidic and metallic properties and are valuable for versatile functionalization in health monitoring devices and therapeutics.

For this Viewpoint, the important applications of LMs in achieving biotechnological strategies for the development of healthcare devices and medicines are outlined as milestones. The vision and future of LM-based biotechnologies as well as the implications of their convergence are also discussed.

EMERGENCE OF LMS AS A BIOTECHNOLOGICAL PLATFORM

LMs are metals and metal alloys that have low melting points and are formed in the liquid state at near-room temperature. In nature, pure traditional metals that are liquid at ambient temperature are mainly Hg, Ga, and Cs, with melting points of −38.87 °C, 29.8 °C, and 28.65 °C, respectively. In particular, LMs based on Ga and Hg and their alloys have been studied extensively, and between these two substrates, Ga is less toxic. Thus, Ga- or Ga-based LMs, especially eutectic gallium−indium (EGaIn) and gallium−indium−tin (Galinstan), are suitable and often used as building blocks for designing a blueprint for biotechnological strategies. Although the toxicity of LMs remains controversial, there is increasing evidence showing their high biocompatibility both *in vitro* and *in vivo*. For instance, Ga- or Ga-based LMs have been employed as implantable materials, such as restorative dental materials,[3] nerval reconnectors,[4] and photoexothermic anticancer agents.[5] Many research groups have systemically investigated the biocompatibility of Ga- or Ga-based LMs in mice; direct injection of LMs into mice resulted in no severe side effects on vital organ functions.[5−7] Furthermore, Ga ions (Ga^{3+}) have therapeutic effects against cancerous tumors and infectious microbes.[8] Additionally, radioactive ^{67}Ga and conventional Ga compounds comprising gallium nitrate and gallium citrate, which are approved by the United States Food and Drug Administration, have been clinically used as therapeutic agents for the diagnosis and treatment of patients with cancer.[9,10] Thus, it can be presumed that Ga- or Ga-based LMs have great potential for biomedical applications because of the excellent therapeutic efficacies of the solid or ion states of Ga in addition to the many original traits of LMs. Here, we highlight the Ga- or Ga-based LMs that are used in healthcare devices and medicines (Figure 1). They are likely to promote transformative convergence biotechnologies as a disruptive innovation for health and longevity. In fact, compared to rigid materials, nanoscale or structured LMs, either partially or completely soft, would provide various unconventional advantages, especially for their applications in biotechnology. For instance, in living cells, LMs can easily change shape, deform to pass through constrictions, or flow to wet or conform to surfaces. Thus, LMs might cause little physical damage to biological interfaces, such as cells, tissues, and organs, owing to their unique softness and flexibility. Furthermore, rigid materials may lead to mechanical friction and damage to biological bodies. These traits also help LMs to be readily rendered into nanomicroparticles by surface modifications and nanomicro fabrications. Furthermore, LMs have excellent properties that can be tuned based on the addition of other functional materials into the bulk or on the surface of the LM. At a minimum, the combination of softness and flexibility traits of LMs along with tunable properties suggests that the field of LMs is likely to evolve with their utilization in biotechnological platforms.

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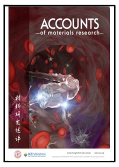

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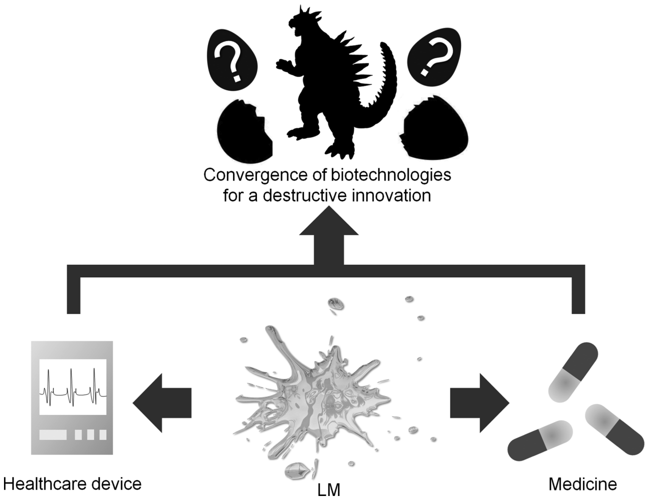

Figure 1. Schematic illustration of convergence of liquid metal (LM)-based biotechnologies for transformative innovation for our health and longevity. The kaiju (monster) and eggs present a conceptual cartoon of a future disruptive innovation and convergence of biotechnologies, respectively.

HEALTHCARE DEVICES

Diagnostic and monitoring devices are expected to contribute to the largest market share in healthcare at home and in hospitals. Flexible and stretchable electronic devices, such as flexible sensors, artificial electronic skins, stretchable displays, and wearable electronics, have attracted substantial attention in this market.[11] Current three-dimensional (3D) printing methods and microfluidics enable the preparation of a desired construction of LM-based flexible and wearable health care devices with self-healing ability, shape maintainability, biocompatibility, flexibility, conductivity, and piezoelectric properties.[12−14] For example, owing to their flexibility and adhesiveness, LM-based skin biosensors can dynamically detect external physicochemical signals, such as temperature, pressure, strain, gas, and light.

To be installed in the body, conventional implantable devices require surgery, wherein biological tissues and organs may treat devices as foreign invaders, leading to immunological responses. To avoid adverse immune reactions, devices must be modified with biocompatible materials via multiple steps. Moreover, there is also the issue of device design. Although the biological body is a flexible 3D environment, most current implants, such as brain stimulators and insulin pumps, are based on 2D inflexible devices with more in common with traditional solid silicon chips than anything that exists naturally in the body. Biocompatible Ga- or Ga-based LMs, which can be transformed into any shape and immersed in any space, would be suitable in biological 3D environments. In fact, Ga- or Ga-based LMs have already been applied in implantable materials such as photothermal heaters, artificial muscles, nerve connections, implantable sensors, and alternating magnetic field (AMF)-driven ingestible microdevices, because of their high biocompatibility and flexibility.[5,15,16] Among them, AMF-driven ingestible microdevices have unique spatiotemporal controllability for their mobility and drug delivery, which is expected to be effective in digestive organs (Figure 2).[5] Indeed, mobility of the device is wirelessly manipulated by electromagnetic levitation of EGaIn during AMF induction. In addition, upon AMF-induction, the EGaIn LMs were rapidly heated via an eddy current. The heating energy can then dissolve a thermally responsive hydrogel in the device. Eventually, this process promotes the release of drugs from the device at the target site.

These innovative applications are expected to accelerate related studies and translational applications with the aid of the inherent property of LMs. To expand the future clinical practices of new medical devices utilizing LMs, tremendous efforts are required to better understand their intrinsic properties and long-term performance. Nevertheless, LM-based healthcare devices are expected to integrate detection, monitoring, and therapeutic multifunctions. Inexpensive, multifunctional, and often tiny devices are widely distributed in practical scenarios. The convergence of LM multifunctionality and other technologies, such as brain−machine interface,[17] artificial intelligence,[18] high-throughput screening,[19] and single-molecule analyses,[20] might provide a new direction for transformative LM-based healthcare devices that can have high precision theranostic performance at single-cellular and single-molecular levels.

MEDICINES

Nanotechnology offers new solutions for the transformation of biological systems and a broad technical platform for various industrial applications, such as bioprocessing, molecular medicine, environmental improvements, improving food and agricultural systems, and human performance.[21] Nanotechnology serves as a technological platform for new developments in

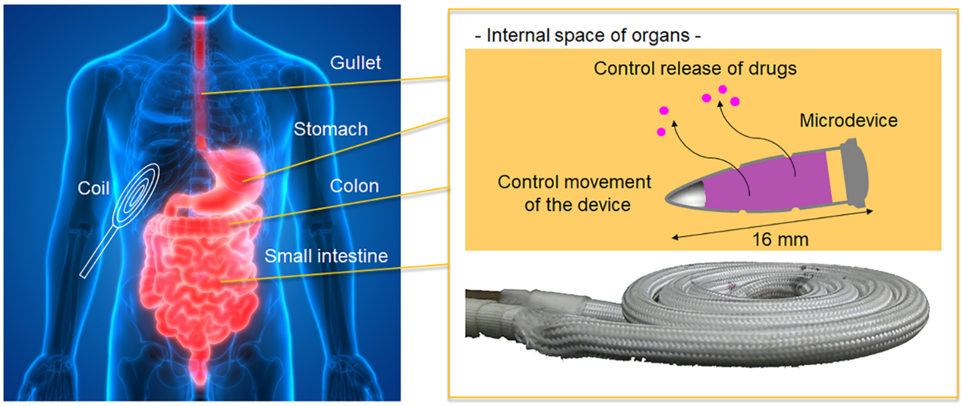

Figure 2. Application of a LM-based healthcare device. The schematic illustration represents the potential application of an alternating magnetic field-driven ingestible microdevice in digestive organs.

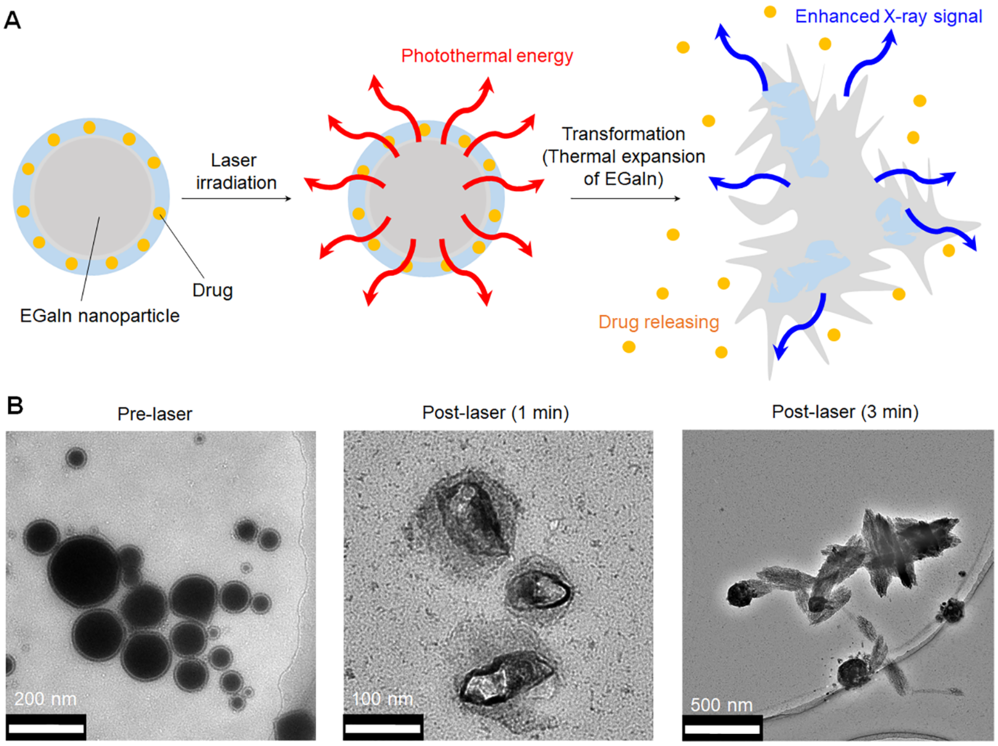

Figure 3. Medicinal application using the fluidity of LMsvia light energy. (A) Schematic illustration of light-induced transformable EGaIn LM nanocapsules. (B) Transmission electron microscopic images of light-induced transformable EGaIn LM nanocapsules before and after laser irradiation for 1 and 3 min. Reproduced with permission from ref 23. Copyright 2017 Springer Nature.

LM-based medicine. Ga-based LM nanoparticles have often been used in various theranostic applications, including drug delivery,[22] tumor ablation,[5,23] X-ray computed tomography imaging,[5,23] photoacoustic imaging,[23] magnetic resonance imaging,[24] and biosensing,[25] owing to their plasmonic effect and electromagnetic and electrochemical properties in addition to the aforementioned high biocompatibility.

Compared with other solid nanomaterials, Ga-based LM nanoparticles have various major advantages, especially their fluidic traits, the availability of free electrons and ions, and their interfacial electrical double layer. However, with maintaining both metallic and liquid states, a comprehensive understanding of the functionality, operability, and controllability of Ga-based LM nanoparticles is still lacking. In particular, the fluidity of LMs for expressing medicinal functions has not been sufficiently utilized. To date, only a few research groups have reported that tumor acidity- or light-inducible transformation of Ga-based LM nanoparticles can accumulate at targeted sites, contributing significantly to the release of drugs and enhanced X-ray signals because of the fluidity of LMs.[22,23] In particular, light-induced LM transformation is spatiotemporally controllable by simple laser irradiation through the destruction of nanoparticles, mainly caused by the thermal expansion of EGaIn owing to the powerful photothermal conversion efficiency of LMs (Figure 3).[23] This opto-physicochemical property would be useful for designing an active targeting strategy against a disease site such as a cancerous tumor in the biological body. Surface chemistry and modulation of the Ga oxide layer of LMs are important to leverage the advantage of the fluidity of LMs.[26,27]

Furthermore, many fundamental challenges remain to be explored, especially regarding the functionalization of the theranostic features of LM nanoparticles. Only a small subset of functional molecules (mostly polyethylene glycol moieties) has been used for functionalization of LM nanoparticles. The application of biocompatible and therapeutic biomaterials, such as proteins, genes, and cells, for functionalization of LM nanoparticles[28] might open new avenues and promote clinical applications, which may have unexpected effects, such as improved intracellular permeability and strong interactions with targeted receptors, on the characteristics of Ga-based LM nanoparticles. Self-assembly of functional molecules and biomaterials[29] might also aid in the creation of new LM-based biotechnologies that enhance the inherent properties of LMs. However, the current major challenge is the simple production and highly accurate remote control of nanomicrorobots.[30] The concept and mechanism of these studies might be useful for designing next-generation LM-based medicines.

■ CONCLUSION

To summarize, this Viewpoint outlines the properties and typical applications of LM-based biotechnologies in the field of healthcare devices and medicines. The development of LM-based biotechnologies holds great promise. Many research groups have indicated that progress in both devices and medicines is ongoing toward enhanced human healthcare and biomedical theranostics to maintain healthy physiological and psychological homeostasis and tackle various fatal diseases in the near future. These processes do not occur in isolation and in a vacuum.

Many LM-based biotechnologies will be developed, and in turn, be further improved through the integration of individual components for each goal and purpose. We envision that state-of-the-art technologies, such as brain−machine interfaces, artificial intelligence, high-throughput screening, single-molecule analyses, and traditional developments in chemistry and physics, would be involved in this new field. The unique abilities of natural biomaterials, such as proteins, genes, and cells, could also be exploited for the development of highly effective medicines while retaining the unique properties of LMs, which exist in both the metallic and liquid states. Molecular self-assembly and nanomicro robotics could offer an attractive route for the creation of new functions of LM conjugation in biotechnological applications. Although the application of LMs to biotechnologies has received much attention, challenges and limitations must be addressed. The exploratory research on emerging LMs has just begun. To achieve positive outcomes, we believe that large, multidisciplinary teams will be required to realize the anticipated revolution for good health and longevity using transformative LMs.

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Notes

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Biography

Eijiro Miyako received his PhD in Chemical Systems and Engineering from Kyushu University (Fukuoka, Japan) in 2006. During his PhD thesis, he worked as a Research Fellow of Japan Society for the Promotion of Science (JSPS) for a year. Shortly thereafter, he joined the National Institute of Advanced Industrial Science and Technology (AIST) (Takamatsu, Ikeda, and Tsukuba, Japan) to start his own works as an independent researcher in 2006. He also worked as a visiting scientist at the Centre national de la recherche scientifique (CNRS) (Strasbourg, France) from 2012 to 2013 and Nanyang Technological University (Singapore) from 2017 to 2018. He is currently an associate professor in Graduate School of Advanced Science and Technology, Japan Advanced Institute of Science and Technology (JAIST) (Nomi, Japan) from first of July 2019. He also works as the research director in the Research Center for Exponential-Biomedical Engineering (Research Core), JAIST, from first of April 2021. He has broad interests in bioengineering, materials chemistry, nanotechnology, and nanomedicine and in the interdisciplinary research area.

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