awareness: to identify emerging applications, diversify the supply chain and develop policy, strategy and implementation. Governments need to build and operate catalysts for innovation of time-based services such as demonstrators, testing sandboxes and complementary skills training.

In the United Kingdom, a National Position, Navigation and Timing (PNT) Office was set up in 2023 as part of a ten-point policy framework for national PNT resilience (see go.nature.com/3vaimtu). The measures also include developing a proposal for the building and maintenance of the National Timing Centre as an enduring asset to supply resilient time for the country's digital infrastructure assets. This could be initiated by government investment with subsequent private-sector involvement to develop commercially viable products and services. The policy framework highlights the importance of both space-based techniques and terrestrial radio-broadcast solutions, complementing the service provision by GNSS and reducing dependence on it. Developing a supply chain and skills base to support this infrastructure has been highlighted as essential to national adoption.

The ubiquity of GNSS has driven dependency without adequate protections in place in the event of a disruption or long-term loss. By ensuring interoperability with GNSS, and embedding traceability to UTC, the terrestrial delivery of time as a new utility can unlock industry co-investment, innovation, opportunity and economic growth across multiple sectors and domains while also delivering time resiliently — much as GNSS did.

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The authors declare competing interests; see go.nature.com/47jryu1 for details.

Should research on mirror-image molecular biology be stopped?

Ting Zhu

Amid growing debates about the benefits and risks of studying looking-glass versions of life's building blocks, there is an urgent need to bridge divergent views.

This week, experts in synthetic biology and microbiology, among other fields, are gathering in Manchester, UK, to explore the benefits and risks of building synthetic life. One of the topics that will be discussed is how research might be restricted to prevent the creation of organisms made of components that are the mirror image of those that make up life on Earth. Days after the Manchester meeting, the issue will be examined at a workshop organized by the US National Academies of Sciences, Engineering, and Medicine. And other meetings are planned.

Most of the biological molecules known to make up life on Earth have a specific handedness, or chirality. Amino acids have left-handed chirality, for example, whereas DNA is right-handed. Because mirror-image bacteria or other synthetic life forms would be made of molecules of opposite handedness (so with right-handed amino acids and left-handed DNA), the concern is that such organisms might represent a hazard to known life[1–3] (see also go.nature.com/3hshyst and go.nature.com/3vwuytw). For example, some of them might be capable of evading immune systems, confounding medicines, resisting predation and causing harms to humans, non-human animals, plants and ecosystems[2,3].

Prohibiting the creation of molecules or biological entities of either chirality that could endanger human health or environmental stability should be uncontroversial. And discussions early in the development of a field — as well as efforts to engage the public — can be constructive when it comes to ensuring that research is conducted responsibly and ethically.

But in the face of vast unknowns, the noble path of pre-emptively protecting humanity from potential risks in the distant future can be slippery. And we should tread cautiously.

The concept of a mirror-image biological world is not new. It was first proposed in 1860 by French chemist and microbiologist Louis Pasteur[4]. And the potential benefits and risks of mirror-image organisms have been discussed by the research community for more than 30 years[1–3] (see also go.nature.com/3hshyst and go.nature.com/3vwuytw). However, in the past few months, the conversation has abruptly shifted to calls for hard limits on basic research and funding[2].

At this point, there are divergent views (see go.nature.com/46tgjvf and eLetters by R. Derda *et al.* and D. Perrin in ref. 2) on how soon it might be possible to create mirror-image organisms; the potential benefits and risks of generating mirror-image life and of developing precursor technologies; whether moratoria on research should be imposed; and, if so, what areas of study should be restricted.

Given the countless unanswered questions, careful consideration of the scientific facts learnt so far — regarding what it would take to create a mirror-image life form, and the pros and cons of research on mirror-image molecular biology more broadly — is crucial for bridging divergent views and fostering rational and informed debate.

On the distant horizon

In December 2024, nearly 40 experts, including in synthetic biology, ecology and immunology, co-authored a Policy Forum article in *Science*[2] and released a separate 299-page technical report[3]. In both, the authors argued that were mirror-image life created, it would be very likely to present unprecedented risks to humans, animals, plants and ecosystems.

Multiple meetings have followed the *Science* publication, including in the United Kingdom, the United States, France and the Netherlands.

But how close are scientists to being able to

GETTY

In theory, all biological structures, functions and even organisms could be recreated in their mirror image, leading to endless possibilities.

create a mirror-image life form?

Dozens of research groups, including those at pharmaceutical companies, have been synthesizing and investigating mirror-image proteins, DNA and RNA for the past three decades to understand fundamental biology and develop therapeutics[5–14]. My colleagues and I have been exploring various mirror-image molecular processes, too. These include the replication of mirror-image DNA, the transcription of mirror-image DNA into mirror-image RNA and the translation of mirror-image RNA into mirror-image proteins – in other words, a mirror-image version of the central dogma of molecular biology[7–11].

Research in mirror-image molecular biology is still in its infancy. But scientists working in this field have been humbled by the tremendous challenges of exploring this unknown world[5–14]. The creation of mirror-image organisms, if it ever became feasible, would face monumental conceptual and technical barriers.

Hundreds to thousands of cellular components – including proteins, nucleic acids, membranes, metabolites and complex carbohydrates called glycans – would need to be synthesized chemically or enzymatically in their chirally inverted forms. Some of these are encoded directly by DNA. But many are synthesized or modified by other complex biological machinery, meaning their compositions and structures cannot simply be derived from DNA sequences. And many have not yet been characterized.

It took our group nearly four years to chemically synthesize a mirror-image protein fragment of up to around 470 amino acids[9] – the longest single-chain mirror-image polypeptide reported so far. Synthesizing longer polypeptides and membrane proteins that are rich in water-repelling (hydrophobic) domains would be even harder.

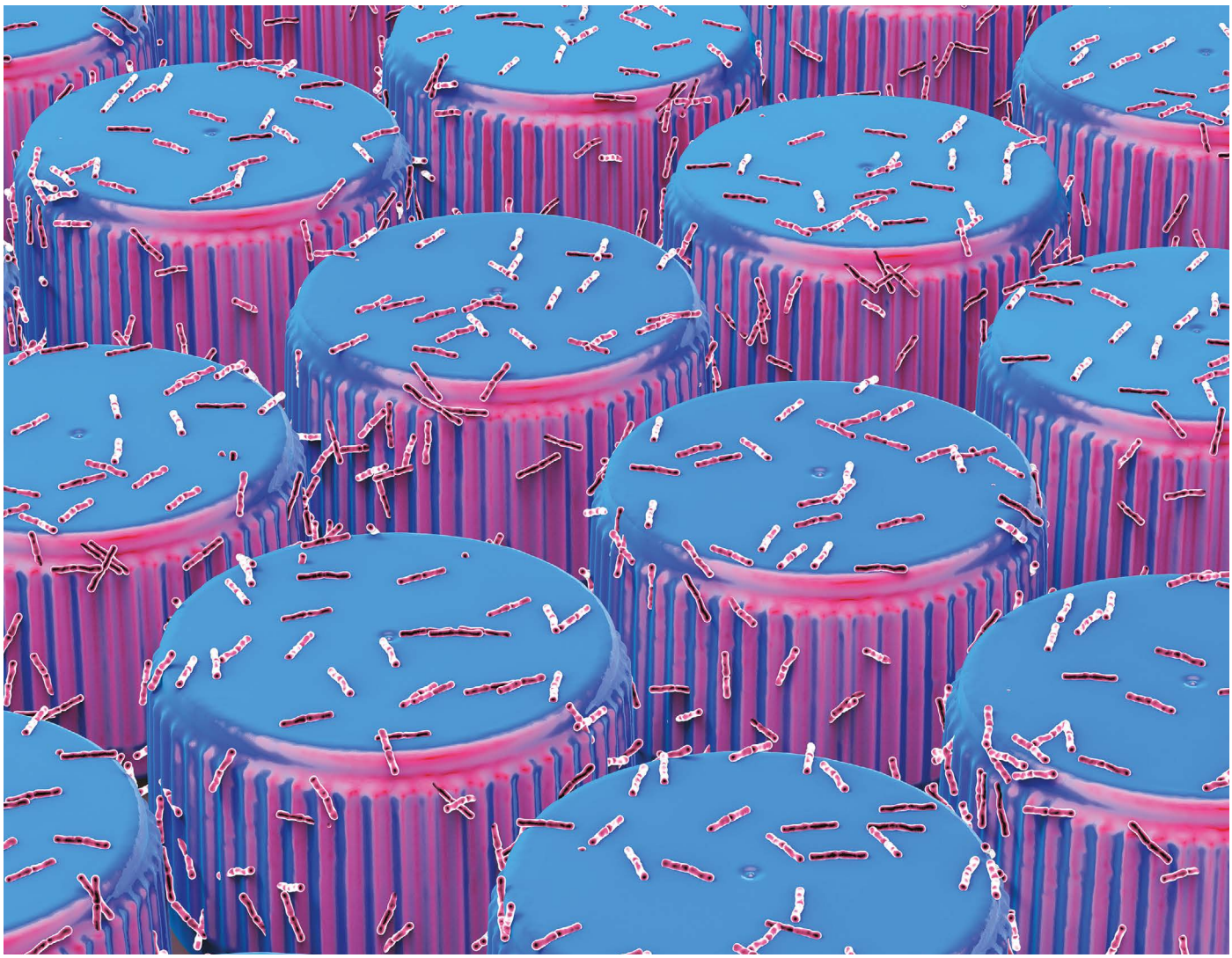
"The creation of a mirror-image organism lies well beyond the reach of present-day science."

Likewise, we have been trying to chemically synthesize a highly simplified version of a mirror-image ribosome since 2016, and are still years away from achieving it. Should we succeed, this ribosome will lack protein and RNA modifications and will not have aminoacyl-tRNA synthetases (the enzymes responsible for attaching specific amino acids to their corresponding transfer RNAs during protein biosynthesis)[8,11]. This means it will be able to produce only short peptides and small proteins (say, of about 300 amino acids)[8].

Even if all the constituent molecules of the simplest bacterium could be synthesized in their mirror-image forms, these would need to be folded correctly and assembled with spatio-temporal precision to create a mirror-image bacterium that functions as a complex, autonomously replicating cell.

Many laboratories have built non-living membrane-bound compartments, in which copies of DNA and RNA molecules can be made or in which RNA molecules can be translated into proteins. Although researchers have been able to isolate biologically derived ribosomes and other cellular machinery with natural chirality for decades, no lab has been able to use this machinery to produce all the essential cellular components *in vitro*.

Researchers don't yet know how to assemble a natural-chirality self-replicating cell from biologically derived building blocks – let alone how to chemically synthesize a mirror-image one from the ground up. And although other strategies for the creation of mirror-image life have been proposed (such as



THOMAS PARSONS/SPL

Plastic-consuming bacteria, shown in this artist's impression, contain enzymes that degrade plastics. Biostable mirror-image versions of these proteins could offer a solution to plastic pollution.

the stepwise conversion of a natural-chirality cell into a mirror-image cell[2,3]), there is insufficient evidence to support their feasibility.

In short, it is crucial to distinguish mirror-image molecular biology from the creation of mirror-image organisms. A self-replicating cell has molecular diversity, metabolic complexity and structural intricacy that are orders of magnitude greater than what's found in any currently synthesizable biomolecular system. And the creation of a mirror-image organism lies well beyond the reach of present-day science.

Endless possibilities

Because all biological structures, functions and even organisms could be recreated in their mirror image, the possibilities — good and bad — in a looking-glass world are endless. As well as considering the risks of hypothetical scenarios, such as the creation of mirror-image life, it is important to keep in mind the realized and potential benefits of the mirror-image molecular biology research that is already under way[5–14].

When given to animals or humans, mirror-image peptides and nucleic-acid drugs can trigger a much milder immune response compared with their natural-chirality counterparts[13]. They are also more resistant to biodegradation, which means a dose can stay in the body for much longer. The implications for drug discovery are profound.

"A synthesized mirror-image ribosome would probably drastically accelerate pharmaceutical discovery."

Dozens of mirror-image peptides, DNA and RNA molecules are already being developed as drug candidates for cancer, metabolic diseases, infectious diseases and inflammatory disorders[10,13]. Indeed, a synthesized mirror-image ribosome would probably drastically accelerate pharmaceutical discovery by enabling the high-throughput production of mirror-image peptides[8,11].

All sorts of other possible applications of mirror-image molecules or biological entities can be imagined, particularly in medicine and sustainability.

Mirror-image glucose tastes as sweet as its natural-chirality counterpart, but does not provide calories because it is not metabolized by the enzymes found in natural-chirality organisms[15]. This means that mirror-image glucose and other mirror-image sugars could serve as non-caloric sweeteners or other food additives.

Mirror-image DNA molecules have the same capacity to hold information as their natural-chirality counterparts do, but they are more resistant to biodegradation and easier to distinguish from contaminant (natural-chirality) DNA. As such, mirror-image DNA molecules can serve as robust information repositories[9].

Nanoparticles or nanocapsules, built using mirror-image proteins, could enable the safe

delivery of drugs by shielding them from the immune system. Mirror-image DNA or RNA molecules designed to detect the presence of certain human proteins and metabolites, such as thrombin[10] and guanine[11], could be used as diagnostic biosensors in clinical settings.

Meanwhile, mirror-image versions of enzymes that are capable of degrading plastics that have no chirality could offer a solution to plastic pollution[12]. Like their natural-chirality counterparts, such enzymes can break down plastics but are more resistant to biodegradation themselves. In principle, mirror-image versions of enzymes that can capture carbon might similarly be used to help address climate change.

As well as providing solutions for all sorts of practical problems, basic research on biology through the looking glass could offer insights into the structures and functions of biomolecules. It could shed light on the origin of homochirality (the dominance of one set of chiral molecules in known forms of life), and even on the origin of life[11]. It could guide searches for new life forms, for instance, on Earth as well as on other planets.

Of course, the very properties that promise to make mirror-image proteins and nucleic acids so useful in so many contexts — their biostability and tendency to induce only a mild immune response in humans and other organisms – could also make certain mirror-image organisms harmful[1–3] (see also go.nature.com/3hshyst and go.nature.com/3vwuytw).

The potential for harm needs careful consideration. But many questions remain. For example, a mirror-image bacterium would contain molecules such as glycans that, in known forms of life, exhibit less uniform chirality than do proteins, DNA and RNA. This might mean that a mirror-image bacterium could provoke a stronger immune response in humans and other organisms than do mirror-image proteins, DNA or RNA in isolation (see eLetter by R. Derda *et al*. in ref. 2).

Also, when it comes to considering the risks of mirror-image molecular biology, it is not just mirror-image life that we need to be concerned about. Mirror-image molecules that turn out to be toxic or pathogenic, or so useful that they become pollutants, could be hazardous too.

Paths through the looking glass

It would have been premature to ban the use of alternating current long before the electrification of cities, or to ban the use of molecular cloning far in advance of the production of recombinant insulin, owing to hypothetical dangers on the distant horizon. Some specialists in synthetic biology and biosecurity have cautioned that given so many unknowns, halting current progress in mirror-image molecular biology through funding restrictions and other means would be similarly premature (see go.nature.com/46tgjvf).

This view resonates. In fact, one could argue that if moratoria were to be imposed on basic research to safeguard against scientific possibilities as distant in the future as the creation of mirror-image life, precautionary regulations would be warranted to address all sorts of other dangers in biotechnology, chemistry, physics, computer science and beyond.

A better strategy for establishing ethical boundaries would be to comprehensively assess near-term challenges and long-term risks across multiple disciplines. For instance, a wide range of engineered biological systems might contain diverse unnatural amino acids and nucleotides, including but not limited to the mirror-image subset. Holistic guidelines could be developed for research on synthetic or semi-synthetic molecules, biological entities and modified organisms — irrespective of their chirality (see go.nature.com/3vwuytw).

"One intriguing scenario would be the discovery that mirror-image organisms have always existed in nature."

In an effort modelled after the Responsible AI × Biodesign initiative established by the protein-design community, more than a dozen investigators, including myself, are already coming together voluntarily to define ethical boundaries and commit to preventing the creation of molecules or biological entities of either chirality that could endanger human health or the environment (see https://responsiblesynbio.org).

When it comes to legal and regulatory restrictions on research, a more pragmatic path forwards could entail adaptive governance, whereby risk assessments and preventive policies are continually updated alongside the accumulation of knowledge and the development of technologies.

In this approach, the first assembly of a natural-chirality self-replicating cell from biologically derived building blocks could serve as a key checkpoint.

Because it would be much more difficult to chemically synthesize a mirror-image version of a cell from scratch, there would still be time after this milestone for the implementation of policies and regulations designed to prevent the creation of certain harmful mirror-image organisms. In fact, making this step a checkpoint would enable more knowledge to accumulate in mirror-image molecular biology, which might in turn enable more-effective policies and regulations to be established.

Such knowledge could include the development and improvement of surveillance and countermeasure tools, such as mirror-image enzymes that could detect and degrade mirror-image molecules or organisms in the environment[9,14].

Into the unknown

The word 'unknown' has long been a synonym for ignorance and risk — as intelligent beings, humans naturally fear what we cannot comprehend and control. However, the same word also invites us to seek evidence with humility and to remain open to all possibilities.

One intriguing scenario would be the discovery that mirror-image organisms have always existed in nature, and that they persist still.

Amid the race to take action, it is important not to let concerns and anxieties obscure our judgement of the underlying unknowns. Scientific exploration is not a glorious march towards increasingly precise understandings of a universal truth. It has a long and difficult history of trials and errors, uncertainties and risks, controversies and doubts. Yet through rational dialogue and objective analysis, a responsible, open and rich human adventure can be charted, for the world of the unknown is infinite.

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