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Editorial

Mirror, mirror on the wall...

Pierandrea Lo Nostro

Department of Chemistry "Ugo Schiff", University of Florence, 50019 Sesto Fiorentino (Firenze), Italy
Email: pierandrea.lonostro@unifi.it

While seeking for newer and wider horizons in science and technology, some scientists appear to be challenging common life in a way that - in time - may eventually destroy life on Earth and therefore mankind. For the moment this risk is still far away, but it may become one of the worse scenarios on the planet.

To introduce this discussion, we need a mirror.

"Mirror, mirror on the wall, who's the fairest of them all?" was the resounding question that the Evil Queen uttered when consulting her magic mirror to be reassured that she was still the most beautiful lady in the land. (At least until Snow White entered the scene).

But "our" mirror will be used in another way.

We know that a chiral molecule can exist in two different forms, which are perfectly specular (here is the mirror) but they cannot be superposed. Hands and feet are the most common example we teach chirality to our students. In fact in Greek χειρ means hand.

Most of biomolecules such as amino acids and sugars possess at least a chiral center and produce R and S enantiomers. And what is particularly intriguing is that their biological activity is totally different. So, most of natural proteins are composed of L-amino, although some contain D-amino acids or after some time this homochirality is lost in aged organisms.[1]

These weird D-proteins pave the way to unique applications in molecular biology, structural biology, bioactive compound discovery, and pharmacology. In fact according to Lander "D-enantiomers of protein drug targets can be used in mirror-image phage display allowing discovery of non-proteolytic D-peptide ligands".[2] Similarly, the biologically active form of ascorbic acid is the levo isomer (vitamin C), while its epimer D-isoascorbic acid retains only 5% of the biological activity, perhaps because of different hydration properties.[3]

On the other hand, Nature builds up polysaccharides such as amylose, glycogen and cellulose from D-sugars. While it is still possible to synthesize L-glucose, it does not have any function in living organisms as a source of energy because it cannot be phosphorilated by hexokinase, however we know since 1979 that the plant pathogenic bacterium *Burkholderia caryophill* can oxidize L-glucose.[4] Thus, natural exceptions exist but they are extremely confined to tiny environments and they are not healthy.

DNA and RNA homochirality, which is essential for life, is based on the presence of D-nucleotides in these macromolecules.[5]

Uppalapati and coworkers found that a D-protein is much more stable in different animals (including humans). In particular they synthesized a variant of a D-protein antagonist of natural vascular endothelial growth factor A (VEGF-A) with an extra receptor blocking capability.[6] Now, while the L-protein triggers a massive immune response, the D-protein was found to be nonimmunogenic in mice. Hence, its potential use as an alternative to therapeutic antibodies.

With these premises, mirror-molecules do have some potential interesting applications, for example in pharmacology due to their specific pharmacokinetic features.

However, a very recent paper, published in December 2024 and authored by 38 experts is not only an informative review on the business but also a superb alert of what may occur if this kind of biotechnology research is not guided, controlled and monitored by appropriate authorities.[7] An issue that lately has become particularly pressing. The authors belong to quite different fields, particularly synthetic biology, human, animal, and plant physiology, immunology, microbial ecology,

evolutionary biology, planetary life detection, biosecurity global health, and policy-making groups.

In that paper the authors state:

> *Driven by curiosity and plausible applications, some researchers had begun work toward creating lifeforms composed entirely of mirror-image biological molecules.*

Our immune defenses are strongly based on chiral recognition, but in the presence of a mirror bacterium our "normal" immune recognition would be significantly weakened if not completely useless. And

> *even partial impairment of either innate or adaptive immunity can leave patients vulnerable to bacterial infection. Similar evidence is seen in a wide variety of animal and plant immune systems.*[8]

The number of potential harms that may derive from such laboratory activities are scary indeed. Accidental or deliberate misuse, leakage of contaminated material, spillover, uncontrolled infections and particularly the lack of effective and timely countermeasures are part of the nightmare we may have to confront soon or later. Particularly because we have almost no idea of what would happen, the relevant literature is extremely poor and once a catastrophic accident occurs, we have no history or memory to refer to.

Apparently at this moment we do not even have a clear idea of what we are really looking for and for sure the real serious risks that we may be facing in the future are quite uncertain.

The perspective is definitely challenging. It seems that the collaboration of different players at different level is absolutely necessary. But this is another story and, given the current circumstances, more unrealistic that Snow White and the Seven Dwarfs.

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