Science in One Health 4 (2025) 100096

Contents lists available at ScienceDirect

Science in One Health

journal homepage: www.journals.elsevier.com/science-in-one-health

Review

Fieldwork on animals living in extreme conditions as a source of biomedical innovation

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ARTICLE INFO

Keywords:
Biodiversity
Biomimetics
Nature roadmap
Evolutionary biology
Physiological/molecular adaptations

ABSTRACT

Most biomedical research on animals is based on the handful of the so-called standard model organisms, i.e. laboratory mice, rats or *Drosophila*, but the keys to some important biomedical questions may simply not be found in these. However, compared with the high number of molecules originating from plants in clinical use, and with the countless unique adaption mechanisms that animals have developed over the course of evolution to cope with environmental constrains, there is still few investigations on wild animals with biomedical objectives, and field studies are far fewer. A major limitation is insufficient funding, the main causes of which we analyze. We argue, however, that fieldwork is a key driver in generating new scientific knowledge as part of a One Health approach, by observing/documenting and understanding the diverse and largely unexplored biological processes evolved by animals adapted to unusual environmental conditions, which would be extreme conditions for humans. These conditions do not only refer to extreme temperatures, since lack of food or water, high pressures or lack of oxygen, are clearly extreme constraints. To conduct this research, there are serious limitations we propose to address. Specific techniques and methods are requested, not only to work in extreme environments, but also to minimize the ecological footprint of field work. The erosion of biodiversity is a major threat. The reduction of animal disturbance, a key issue, requires specific technologies and expertise. An ethical approach is requested, for the sake of transparency and to comply with the Nagoya Protocol on genetic resources. An interdisciplinary expertise and a meticulous planning are requested to overcome the field constraints and interface the associated laboratory work. We recommend focusing on the major threats to global human health today, which wild animals appear to resist particularly well, such as antibioresistance and diseases associated with lifestyle and senescence.

1. Introduction

Global health is increasingly challenged by lifestyle-related diseases that accumulate with age [1]. Zoonotic diseases, which result from interspecies transmission between humans and other vertebrates, are moreover emerging more frequently [2]. The risk of human exposure is notably increased by biodiversity loss, as animal taxa that are much more likely to be zoonotic hosts often proliferate in human-dominated landscapes [3]. In parallel, biodiversity loss threatens our ability to draw inspiration from nature. Over millions of years of evolution, Nature has indeed developed many solutions to physiological problems in both plants and animals [4]. It therefore offers a huge opportunity, through the One Health concept that is emphasizing the common denominator between human, animal, plant, and environmental health, to discover new biomolecules and design new therapeutic treatments.

Plants as a major source of bioactive products have played a key role in drug discovery including in the need of anti-infectious substances. About 70,000 plants have been used for medicinal applications. The advancement in metabolomics, genomics, transcriptomics and proteomics has enhanced the contribution of natural products in the discovery of novel drugs/therapeutics [5]. Drugs originating from plants have had a major role in important therapeutic areas, such as for cancer, infectious and cardiovascular diseases and multiple sclerosis. After technical barriers, which contributed to a decline in their pursuit in the 1990s, the interest in natural products has been recently revitalized by new technological and scientific developments, particularly for tackling antimicrobial resistance [6].

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https://doi.org/10.1016/j.soh.2024.100096
Received 3 October 2024; Accepted 19 November 2024

Considering wild animals, of the over eight million eukaryotic species on our planet, many wild species have successfully adapted through natural selection to extreme environmental conditions due to, for example, seasonality, thermal stress (hot or polar), salt and metal concentrations, anoxia, and low pH [7]. Thus, there are countless unique adaption mechanisms that animals have developed over the course of evolution to cope with environmental constraints, and which cannot always be mimicked in the laboratory. Despite a recent surge of interest for biomimetics as a means of accelerating innovation by drawing inspiration from Nature [8], its development in biomedical sciences has however been limited. The limitations imposed by molecular resources, such as antibodies, and/or by gene editing or whole genome sequencing technologies, have led to the emergence of the mouse as the premier mammalian so-called standard model organism [9]. Mice, fish, nematodes, and flies retain the strong advantage of their rapid generation times and ability to facilitate rapid genetics, but it calls into question their suitability as models for, e.g., research into aging [10]. We acknowledge that standard laboratory models may provide the necessary frameworks for understanding disease mechanisms and testing therapeutic strategies. However, as pointed out by John Sedivy in his *Proceedings of the National Academy of Sciences of the United States of America* (PNAS) editorial [9], “the mainstream biological model systems sure shine a powerful light, but the keys to some really interesting (and important) questions may simply not be found under it”.

The anti-cancer mechanisms developed by naked mole-rats have been described using the classical cell culture laboratory approach, which has also proven useful to unravel additional anti-cancer processes in the elephant and the bowhead whale [11]. More will for sure result from the investigation in the laboratory of other wild animals, which have developed traits to avoid senescence and age-associated burden of lifestyle diseases [7]. However, working with animals in laboratory can have confounding effects, due to the lack of interaction of individuals with their environment and the possible alteration of healthy mental development and metabolic physiology induced by captivity [12,13]. If we want to exploit these mechanisms, we need to move investigations from the laboratory to the natural environment, where conditions are often extreme. By reviewing investigations where field work has been or still is the condition to open innovative biomedical perspectives for new therapeutics, we find that the number of such studies remains limited. We therefore examine the reasons for this situation, the challenges to be met, the various ways of overcoming these limitations, and propose recommendations for future research priorities.

2. Field work opening new biomedical perspectives

The review published by Stenvinkel et al., in 2020 [7] followed a Nobel conference organized by the Karolinska Institute in Stockholm (September 2019) on “Bioinspired Medicine: unlocking access of Nature to opportunities in health”. Its objective was to gather leading biomedical researchers working in the interdisciplinary field of biomimetics to improve human health. This conference allowed to identify several species that are of interest considering the lifestyle diseases that accumulate in aging human populations. Hibernating bears are protected from osteoporosis, muscle disuse, cardiovascular and kidney disease, obesity and diabetes; hummingbirds are protected from diabetes and fatty liver; elephants and naked mole-rats from cancer and; despite severe hypertension, giraffes from stroke. But this 2019 conference also illustrated that the scientific community involved in this research relies on a maximum of 100–120 scientists. Moreover, only a handful of these projects involved fieldwork conducted for biomedical purposes. This is obviously very few considering most biomedical researchers focusing on standard laboratory models. To the best of our knowledge, the situation has not significantly evolved since then. We will consider here the four research projects which, to our knowledge at least at a stage, have requested the conduction of an intensive fieldwork and are well documented. Note that the mere collection of samples, such as of soil to get bacteria, is not considered here as a field investigation. These four examples are linked to wild animals living in totally different environments between aquatic and aerial life: a marine worm which has to cope with extreme intertidal conditions, a marine worm living in deep sea, where conditions are extremes regarding pH, pressure and temperature, a pelagic seabird breeding on land where he cannot feed, and a forest mammal facing a severe winter cold.

The marine lugworm *Arenicola marina* inhabits the intertidal area and is therefore exposed to a lack of oxygen at low tide. The initial work to explain its survival under such extreme conditions has been conducted in the field and has been followed by laboratory investigation. The 450 million years old worm's extracellular hemoglobin (M101) can transport up to 156 O_2 molecules (*versus* four for human hemoglobin) in a saturated state, giving it a greater capacity to fix O_2 and antioxidant properties. Since it is not antigenic, it has been presented as an efficient O_2 carrier with potential anti-inflammatory, antibacterial and antioxidant properties of great interest for conditions involving massive hemorrhage or for graft preservation and transport [14,15]. It has recently obtained the approval from some countries to be used in clinical practice to solve the problems of most commercially available O_2 carriers as graft preservatives for transplantation procedures, namely increase in oxidative stress among other adverse effects. The fact that the same molecule not only enables a worm to cope with an extreme environmental condition but also efficiently improves the preservation of human grafts for transplantation, a critical issue, is clearly in accordance with the concept of One Health.

The extreme conditions faced by the marine lugworm at low tide are readily accessible and can be easily mimicked in the laboratory. It is obviously not the case for deep-sea worms, which also proved to be of great biomedical interest. Their study requires a logistics and an expertise that very few countries have developed. It has been well described by Liang et al. [16]. While the bacteria and archaea of hydrothermal vents have been studied for years [17], the animals that live there however remained under-explored as a reservoir of innovative bioactive molecules. Until the oasis of life was discovered in the 1980s, life was not expected in such conditions: no light (meaning no carbon source from photosynthesis), wide range of pH and thermal variations, salt, heavy metals, high pressure. The most emblematic species inhabiting such an environment are worms, which constitute a massive biomass. One of them is the most eurythermal and thermotolerant animal known on Earth: *Alvinella pompejana* (Fig. 1), also called the Pompei worm because of its ash-covered appearance [18,19]. To survive in this extreme habitat, *A. pompejana* lives in vital symbiotic association with giant filamentous bacteria (mostly proteobacteria) that cover the dorsal region of its skin. The epidermis cells of *A. pompejana* produce an original natural antimicrobial peptide (AMP), named Alvinellacin, that is released on the surface of the skin to select and limit the overproliferation of bacterial symbionts [20,21]. We have provided evidence that the gene region encoding Alvinellacin has remained unchanged for hundreds of millions of years [22]. Years of evolution of deep-sea hydrothermal vent worms have shaped and selected unique molecules naturally optimized to ensure the functioning not only of a single cell, but also of multicellular organisms, whatever the extreme conditions [23]: (i) high spatial and temporal variations of environmental conditions, and especially pH (3–8), temperature (4 to $>$ 100 °C) and (ii) high density of Gram negative (G-) bacteria, a bacterial community that contains most of the actual top listed multi-drug resistant (MDR) strains by the World Health Organization (WHO) [24]. In addition to their unusual sequences, our data on deep-sea worm AMPs show that they can kill G- bacteria under a wide range of physical and chemical conditions that normally inhibit conventional antibiotics and other AMPs [25]. Due to their original physicochemical properties and sequence diversification, AMPs from extremophilic worms may therefore be considered as new and promising novel antibiotics.

Of the many other marine molecules of biomedical interest, such as the antifreeze glycoproteins whose emergence has enabled fish to survive at sub-zero temperatures [26], most only require laboratory work.

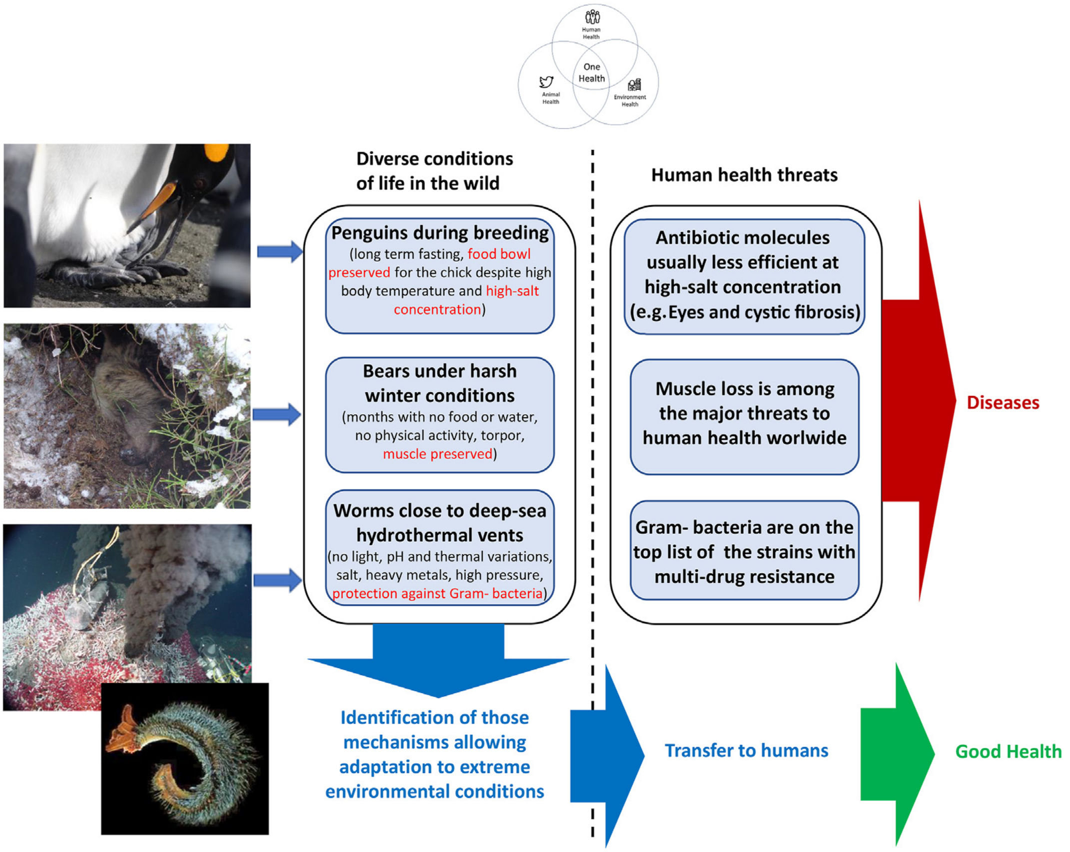

Fig. 1. Exploring the diversity of extreme environmental conditions as a key “One Health” approach. Images of king penguin feeding its chick and of hibernating bear: @Fabrice Bertile. Images of hot chimney and *Alvinella pompejana: @Wikipedia*.

However, there is at least one example at this stage where a discovery of biomedical interest would not have been made without a field investigation. King penguins (*Aptenodytes patagonicus*) (Fig. 1) breeding in the sub-Antarctic Crozet archipelago during the austral summer are regularly undertaking long foraging trips since they essentially rely on myctophid fish located at the southern polar front, i.e. the limit between the sub-Antarctic sea and the colder Antarctic sea. Importantly, the localization of the front fluctuates according to an interannual variation in sea temperature, ranging between 400 km south of Crozet archipelago in cold years and 600 km south in warmer years [27]. Both mates alternate in the task of incubating the egg. Since they only feed at sea, they are drawing on their body's fuel reserves. The male generally assumes the last 2–3 weeks of the incubation and the female is in principle back from her foraging trip to feed the newly hatched chick by regurgitating prey stored in her stomach. She comes back in due time when the polar front is at a shorter distance, i.e. in cold years, but may be delayed in warmer years when the distance to come back is much larger. We have demonstrated that the male is then able to feed the newly hatched chick for about one week by regurgitating marine prey he has preserved in its stomach and not digested. If the delayed female then returns, this food therefore will have ensured the chick's survival [28].

It takes about one week for king penguins to come back from the polar front with food in their stomach. Thus, including the 2–3 weeks of the last shift of incubation, the male can preserve intact food for 3–4 weeks despite his high 37 °C body temperature. We have shown that the bacteria are stressed in the stomach environment of food-preserving birds, which is unfavorable to bacterial multiplication [29]. Searching for a molecule involved in food preservation, we have then isolated and fully characterized in the stomach content of king penguins two AMP members of the avian β-defensins, namely Spheniscin 1 (Sphe1 or AvBD103a; UniProtKB entry P83429) and Sphe2 or AvBD103b (UniProtKB entry P83430). We found an increase in their concentration during food preservation, which supports the hypothesis that they are at least one of the molecular keys to this physiological process. Moreover, by studying the antimicrobial properties of a synthetic version of AvBD103b, we demonstrated that this molecule secreted by the penguin's stomach is active against a large spectrum of micro-organisms (Gram-positive/G+ and G- bacteria, yeast and filamentous fungi) that are pathogenic to humans and animals and may be associated to foodborne diseases. The molecule moreover remains active and efficient against *Staphylococcus aureus* and *Escherichia coli* when increasing salt concentration to values close to those of sea water (approx. 1000 mOsm/L) or measured for the king penguin stomach content [30]. This is of a particular interest for infections in high-salt environments such as ocular infections and cystic fibrosis, as antibiotic molecules from fungi usually lose their efficacy in these environments [31].

Clearly, Spheniscins would not have been discovered in the stomach of king penguins breeding in zoological gardens. They are daily fed and therefore do not face those extreme conditions encountered by king penguins in their natural environment. Even wild birds kept in captivity in their natural environment but not incubating eggs do not show a plasma molecular profile similar to that of incubating birds feeding their chicks when the female is delayed, despite a similar metabolic state [32].

Considering terrestrial animals, field research based on biomedical objectives is mainly carried out on black and brown bears, particularly when they are hibernating (Fig. 1). Seasonal environments can present a significant challenge to the survival of animals. In response to the deterioration of their environmental conditions at certain times of the year (e.g. cold ambient temperatures and drastically reduced food availability), they employ one of three main strategies: migration, adaptation or hibernation. Hibernation corresponds to a lethargic state involving torpor, where energy savings are generally achieved through physical inactivity, reduced food intake, lower core body temperature, slower heart and respiratory rates and a drastic reduction in metabolic rate [33]. Contrary to what would occur in humans under comparable conditions, that involve physical inactivity, fasting and a metabolism geared towards high utilization of lipid substrates, no organ damage and adverse effects were ever observed in hibernating animals.

In hibernating bears, specific mechanisms [34] and various molecular and cellular changes [35] notably help to explain the protection of cells and organs in the torpor state, and could well feed innovation in the treatment of, e.g., bone disease [36], cardiac failure [37] or muscle atrophy [38] in humans. In this respect, the example of muscle maintenance in hibernating black and brown bears is striking and deserves to be described in more detail. It is indeed remarkable that, depending on the bear muscle considered, protein content is reduced by a maximum of 15%–20 % during the first month of hibernation, but does not worsen thereafter [39], and that muscle strength appears to be conserved [40]. Various mechanisms have been reported to possibly contribute to muscle protein sparing in hibernating bears, including periodic muscle contractions (shivering), nitrogen recycling via urinary urea or specific organic cycles, an antioxidant strategy, a myogenic microRNA response, and the possible role of increased docosahexaenoic acid or testosterone levels [38]. In addition, an earlier study has suggested the existence of anti-atrophy factors circulating in the blood of hibernating black bears (*Ursus americanus*) by showing that winter bear plasma was able to induce a 40 % decrease in the net proteolytic rate of isolated rat muscles [41]. Ten years later, the existence of such anti-atrophy factors was confirmed in the serum of hibernating brown bears (*U. arctos*), and it was shown that they could act on human muscle cells to make them grow faster [42]. This effect involves a reduction in protein turnover in human myotubes, with spectacular inhibition of proteolysis involving both the proteasomal and lysosomal systems, leading to an increase in the protein content of incubated human muscle cells. As suggested elsewhere, the brown bear circulating anti-atrophy factors may involve agonists or antagonists of the transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP) pathways [43]. Another study later showed similar results using serum of Japanese black bears (*U. thibetanus japonicus*) and suggested that the effect could result from the modulation of protein kinase B/forkhead box O3 (Akt/FOXO3a) signaling [44]. Hibernating brown bear serum also revealed recently its ability to protect mouse cardiomyocytes against hypoxia-reoxygenation stress, offering a potential source for the identification of new therapeutic molecules against myocardial reperfusion injury and cell death in general [45]. Finally, it has also been shown recently that the serum of winter Japanese black bears can inhibit osteoclastogenesis *in vitro*, opening the way to promising new approaches for better treatment of osteoporosis in humans [46]. In-depth studies of the composition of bear blood during hibernation could therefore lead to a multitude of potential therapeutic applications. Identifying the circulating compounds responsible for the musculoskeletal effects described above could pave the way for transferring the properties of hibernating bear serum to humans, to develop new tools for better care and treatment of sedentary people, patients immobilized for long periods or suffering from catabolic disorders, the elderly or astronauts subjected to the absence of gravity. The case of hibernating bears, which adapt to difficult environmental conditions in their natural habitat, is thus a perfect illustration of the extent to which field studies can inspire biomedical progress.

Investigating bears hibernating under natural conditions is dangerous because they may get out of their lethargy very quickly. It therefore requires a particular expertise, but is still needed. This is because captive bears, which are generally fed continuously, are known to skip hibernation and have hormone profiles that differ from those of free-ranging bears, while showing fluctuations in their behavior and body condition that resemble those of bears in their natural environment [47]. We can therefore expect the composition of serum in winter to differ largely between captive non-hibernating bears and wild bears hibernating in their natural environment, at the risk of preventing the identification of the molecules likely to be responsible for the above-described beneficial muscular effects.

3. Limitations in fieldwork and how to overcome them

While extreme habitats are home to a unique fauna with an incredible capacity for adaptation, and for which there much remains to be discovered, sustainable methods must be developed to reduce the number of missions (and the resulting carbon emissions) and limit disturbance to the fauna and flora. We are currently facing major societal and industrial challenges, such as the urgent need to find new molecules to combat bacterial pathogens that are becoming increasingly deadly as they become more resistant to existing drugs. Simultaneously, there is a pressing need to adopt new, sustainable, and less polluting working methods in industry, in research laboratories/vessels and in fieldwork. Moreover, conducting studies on wild populations often remains challenging, primarily due to logistical and regulatory factors, including ethical approvals and specificities of certain geographical regions. When it comes to field work, especially in underdeveloped countries, the ethical use of genetic resources must also be in line with the Nagoya Protocol and the fair and equitable sharing of benefits.

One of the most serious challenges to conduct fieldwork in all conditions, even if they are not extreme, is the effect of disturbance. For standard laboratory animals, it is generally not considered to be an issue, investigations being based on a comparison of the data obtained with similarly disturbed experimental *versus* control animals. In contrast, for a wild animal under natural conditions, any disturbance or impact of instrumentation may have a serious impact, e.g. induce a failure in breeding or have an impact on survival. In addition to the ethics and possible impact on the population of the species, it may obviously introduce a bias and jeopardize any possibility to get data. Even marking individuals, which is the very first step of any field research, may have a serious impact on the breeding success and survival of some species and introduce a bias in the data [48]. Since in most investigations, data must be collected at regular times in the same individuals, the study is usually conducted during a specific activity that is localized, such as on a breeding or hibernating site, but the animal may not come back if disturbed.

Ideally, to investigate wild animals without disturbing them, a key issue is therefore to get data while they are ranging freely and undisturbed in their natural environment. In this context, the development of instrumentation and techniques has been essential. Indeed, from the 1960s, with other colleagues, Knut Schmidt–Nielsen [49] and another most influential organismal biologist of that time, George Bartholomew [50], remarkably pioneered the way to understand how wild animals adapt to the very diverse and often constraining living conditions of our planet. They were obviously aware that particular procedures had to be developed to elucidate those successful mechanisms that enable wild animals to cope with extreme conditions. However, at that time, those methods that enabled to investigate wild animals ranging freely in their natural environment were essentially very limited. This has changed during the last decades, thanks to the rapid development of microelectronics, microcomputers and satellite technologies. Today, with animal-attached or inserted remote sensing, or bio-logging, scientists can examine wild animals behaving normally in their natural environment, and this with the same rigor that is normally used in the laboratory [51, 52]. For individual identification, the ultraminiaturisation of the tags for radio frequency identification (RFID) allows their implantation under the skin and therefore an automatic identification without the impact that bands have on some species [48]. Robots enable collecting data without the disturbing presence of humans [53].

Considering the measurement of metabolic rate, a key parameter to determine how a wild animal may cope with environmental constrains, the only way until the 1980s was by measuring its O_2 uptake and CO_2 production using a face mask, either in a controlled temperature room [54] or under natural conditions [55]. The development of the so-called doubly-labelled water method, which is based on the utilization of stable isotopes, allows today to determine the metabolic rate of an animal ranging freely in its natural environment whether it is extreme or not [56]. In large species, the use of data loggers implanted in an animal allows recording heart rate without disturbance, which can then be used as an indicator of metabolic rate [57].

The implantation of loggers in the animal body may be the only way to get key data in the long-term. It also avoids the disturbance resulting from its more usual fixation on the skin [58]. However, in addition to the anesthesia for the implantation, the risk of not finding again the animal to remove the instrument with its battery is a potential ethical dilemma. The procedures for implantation and localizing the animal have therefore to be seriously secured, which hopefully involves more and more frequently veterinarians together with research scientists. Another difficulty is that the way to minimize disturbance may require a completely different expertise according to the species investigated. For example, to demonstrate that king penguins preserve food in their stomach [28], we had to collect stomach samples of individual king penguins at different times of the incubation without any disturbance. The key was to mask their eyes from behind so that they would not realize they were handled by humans. We did experience no breeding failure but, obviously, such procedure of handling which is appropriate for birds would not work for example with primates. Considering the collection of blood samples in a Scandinavian hibernating bear, the ecophysiologist is only allowed to approach the bear once it has been securely anesthetized into its den by veterinarians with the appropriate expertise. In addition, to avoid any risk of reproductive failure, only non-breeding sub-adult individuals are captured, and a bear captured in a given year is generally not recaptured later in its life. Finally, although plantigrades are fairly large animals, only tiny samples are taken using the least invasive sampling procedures possible and sampling is performed on a very limited number of individuals per year.

Fieldwork imposes sometimes to work with animals for which important information is not known, such as the age, sex, lineage, breeding and/or feeding status, and the number of sampled individuals can be rather limited. Cutting-age methodologies nowadays allow to circumvent such difficulties, for example the so-called epigenetic clock to evaluate the age of individuals with good accuracy [59], genotyping methods to assign sex and parentage [60] or mass spectrometry-based analysis to better predict the breeding status [61].

The first step of field research under extreme conditions therefore involves the development of a particular expertise in logistics, ecology, ethology, anesthesiology and ecophysiology. It is obviously followed by long-lasting research in the laboratory, which requires the usual biomedical expertise in genetics, physiology, biochemistry, molecular biology and proteomics. Altogether, therefore, such a project requires a huge interdisciplinary expertise to succeed [10]. Concerning cruises to access deep-sea vents ecosystems, they remain scarce. New sensitive technologies that can be used in the field need to be developed to optimise and reduce sampling while getting the maximum amount of data from each sample and from each mission [56]. In general, field work is time consuming as we must consider the life cycle of the animals and the season, and this lengthy work may seem less productive than obtaining data from laboratory models.

As indicated by the participants of the 2019 Nobel conference on Bioinspired Medicine in Stockholm, the main limitation in all countries to investigate wild animals is poor academic funding. Most of the members of academic committees reviewing and selecting grant applications usually are involved in standard research on laboratory animals and are hard to convince of the value of conducting research on “exotic” animals. One reason might be that the One Health concept of a common health denominator is not so widespread. Considering all the projects reviewed in this paper, it took years, sometimes decades, to get an appropriate funding, including for the marine worm project [14,15] which is the most advanced in practical clinical application as indicated above. In this context, if the bear, penguin or deep-sea worms have emerged, it is thanks to specific funding sources such as space agencies or polar institutes. Thus, investigations in the field might often remain at the preliminary stage, simply because of insufficient funding.

4. Recommendations

To enable the investigation of those mechanisms of biomedical interest that allow wild animals to cope with conditions which are extreme for humans, such as in the deep sea or in polar regions, the pursuit of the development of new technologies or methodologies suited for extreme conditions is obviously needed. Moreover, as shown in this review, the reduction or, even better, the suppression of disturbance in field work through innovative techniques and methods is also a major goal. Importantly, it will not only be beneficial to the research conducted in extreme conditions but also to field research in general. This is obviously of a particular importance not only to avoid scientific bias but also to minimize the ecological footprint of field work.

Concerning the biomedical objectives which should be addressed, since it is much more difficult to conduct field research than research in the laboratory, as we illustrate in Fig. 1 with some undergoing projects as examples, we recommend focusing on the major biomedical questions that have seen little progress in the last decades and for which a pronounced threat to human health is currently ongoing worldwide and is expected to worsen in the coming decades. Then, clearly, considering that antibiotic resistance is one of the most prevalent threats to global health today, the search for natural antimicrobial peptides as a source of new compounds for future drug development is a major goal [62]. Since there is at this stage no efficient clinical solution to avoid muscle loss, a major human health threat worldwide today [63], the quite unique ability of the hibernating bear to preserve its muscles deserves an appropriate focus for future innovative prevention or therapy in elderly, sedentary people or during prolonged immobilization.

Obviously, as was pointed out by Stenvinkel et al. [7], given the very small number of field projects conducted with an ultimate biomedical objective and the countless adaptations facilitating survival in animals, a novel strategy is needed to identify models relevant to human health. In this context, the establishment of collaborations with local experts to facilitate field access is a guarantee of high efficiency. Another important consideration is the need for a field ethics. Once the scientific question has been clearly defined and the commitment respected, ethical biological fieldwork requires a holistic approach that combines respect, meticulous planning and transparency.

5. Conclusions

Model organisms will certainly remain of interest to test new molecules at a later stage. However, we clearly need to investigate non-model organisms under natural conditions if we are to benefit from all the innovative mechanisms of biomedical interest that enable wild animals to cope with extreme conditions. Similarly, considering the extreme conditions of hydrothermal vents, they overcome limitations of terrestrial AMPs in their stability and activity under certain physiological conditions (salinity, large pH range, and protease resistance). This again underlines that only strictly natural conditions are able to reveal some important biological processes. To reach this objective, an interdisciplinary/holistic approach is obviously mandatory [9,10].

In this context, considering the present gap in funding, a key issue is to convince academic agencies and foundations of the urgent need to enable the development of such a field work. While it seems widely accepted that plant biodiversity is a quite unlimited source of new molecules, it is paradoxical that the outstanding ability shown by many wild animals to cope with extreme environments has not so far generated the same interest. This could be explained by the general view that human health is apart and therefore by a still insufficient perception of what means the concept of One Health. The examples we have described in this review of molecules of biomedical interest originating from wild animals, such as the extracellular hemoglobin of the lugworm already used in clinical practice, should enable a better perception of the importance of this concept. Accordingly, it will then be easier to convince agencies and foundations that the wild environment should be investigated to address, as recommended above, major biomedical questions that have seen little progress in recent decades or for which there is no efficient clinical solution at this stage.

Then, the erosion of biodiversity is a major threat, which jeopardizes the chances of finding new molecules for future generations. The AMPs found in king penguins would not have been discovered if these birds had disappeared during the last century when they served as a fuel to melt seal blubber when seals were killed by millions. Today, the main menace for penguin populations is climate change. The gastric brooding frog *Rheobatrachus silus* disappeared soon after the discovery of its unique parental care of biomedical interest [64]. Mining issues are a major threat for the conservation of deep-sea ecosystems. The discovery of vent endemic animals below the visible seafloor underscores the need for protecting vents, as the extent of these habitats has yet to be fully ascertained [65]. The conservation of bears is challenged in livestock areas where they are considered as a major threat to sheep, and global change is already altering their hibernation patterns, with a serious risk of putting them at risk in the not-too-distant future. Altogether, therefore, wildlife as a reservoir of powerful bio-inspired chemicals is an argument to put on the table for the preservation of biodiversity.

CRediT authorship contribution statement

Yvon LE MAHO: Initial conceptualization of the topic of the review, writing part of original draft, supervision and coordination. **Aurélie TASIEMSKI:** Writing part of original draft and conceptualization. **Fabrice BERTILE:** Writing part of original draft and conceptualization. **Philippe BULET:** Writing part of original draft and conceptualization.

Declaration of competing interest

Prof. Yvon LE Maho is the Advisory Board Member of *Science in One Health*. The authors declare that they have no other competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

For the penguin antimicrobial peptide, PB, FB and YLM are funded by the project ANR ANTARBioTic (grant number ANR-22-CE18-0036) and FB by the project ANTARBIOTIC (IMSMedalis). For the bear molecules to fight muscle diseases, FB is funded by the projects ANR B-STRONG (grant number ANR-22-CE14-0018) and the project Bear2Man CNES (French Space Agency). For the antimicrobial molecules of deep-sea worms, AT is funded by the Université de Lille, the Total Foundation-Ifremer (PIONEER project) and the SATT Nord projet RedAMP.

References

[1] P. Stenvinkel, C.M. Avesani, L.J. Gordon, M. Schalling, P.G. Shiels, Biomimetics provides lessons from nature for contemporary ways to improve human health, J. Clin. Transl. Science 5 (e128) (2021) 1–14, https://doi.org/10.1017/cts.2021.790.

[2] K.E. Jones, N.G. Patel, M.A. Levy, A. Storeygard, D. Balk, J.L. Gittleman, et al., Global trends in emerging infectious diseases, Nature 451 (2008) 990–993, https://doi.org/10.1038/nature06536.

[3] F. Keesing, R.S. Ostfeld, Impacts of biodiversity and biodiversity loss on zoonotic diseases, Proc. Natl. Acad. Sci. USA 118 (17) (2021) e2023540118, https://doi.org/10.1073/pnas.2023540118.

[4] P. Stenvinkel, P.G. Shiels, R.J. Johnson, Lessons from evolution by natural selection: an unprecedented opportunity to use biomimetics to improve planetary health, J. Environ. Manag. 328 (2023) 116981, https://doi.org/10.1016/j.jenvman.2022.116981.

[5] N. Nasim, I.S. Sandeep, S. Mohanty, Plant-derived natural products for drug discovery: current approaches and prospects, Nucleus (Calcutta) 65 (2022) 399–411, https://doi.org/10.1007/s13237-022-00405-3.

[6] A.G. Atanasov, S.B. Zotchev, V.M. Dirsch, International Natural Product Sciences Taskforce, C.T. Supuran, Natural products in drug discovery: advances and opportunities, Nat. Rev. Drug Discov. 20 (2021) 200–216, https://doi.org/10.1038/s41573-020-00114-z.

[7] P. Stenvinkel, J. Painer, R.J. Johnson, B. Natterson-Horowitz, Biomimetics - nature's roadmap to insights and solutions for burden of lifestyle diseases, J. Intern. Med. 287 (2020) 238–251, https://doi.org/10.1111/joim.12982.

[8] E. Snell-Rood, Interdisciplinarity: bring biologists into biomimetics, Nature 529 (2016) 277–278, https://doi.org/10.1038/529277a.

[9] J.M. Sedivy, How to learn new and interesting things from model systems based on “exotic” biological species, Proc. Natl. Acad. Sci. USA 106 (2009) 19207–19208, https://doi.org/10.1073/pnas.0911232106.

[10] F. Bertile, S. Matallana-Surget, A. Tholey, S. Cristobal, J. Armengaud, Diversifying the concept of model organisms in the age of -omics, Commun. Biol. 6 (1) (2023) 1062, https://doi.org/10.1038/s42003-023-05458-x.

[11] D.D. Trivedi, S.K. Dalai, S.R. Bakshi, The mystery of cancer resistance: a revelation within nature, J. Mol. Evol. 91 (2023) 133–155, https://doi.org/10.1007/s00239-023-10092-6.

[12] J. Alfred, I.T. Baldwin, The natural history of model organisms: new opportunities at the wild frontier, Elife 4 (2015) e06956, https://doi.org/10.7554/eLife.06956.

[13] T.A. Markow, The natural history of model organisms: the secret lives of Drosophila flies, Elife 4 (2015) e06793, https://doi.org/10.7554/eLife.06793.

[14] F. Batool, E. Delpy, F. Zal, E. Leize-Zal, O. Huck, Therapeutic potential of hemoglobin derived from the marine worm *Arenicola marina* (M101): a literature review of a breakthrough innovation, Mar. Drugs 19 (2021) 376, https://doi.org/10.3390/md19070376.

[15] Y. Le Meur, L. Badet, M. Essig, A. Thierry, M. Büchler, S. Drouin, et al., First-in-human use of a marine oxygen carrier (M101) for organ preservation: a safety and proof-of-principle study, Am. J. Transplant. 20 (2020) 1729–1738, https://doi.org/10.1111/ajt.15798.

[16] J. Liang, J.-C. Feng, S. Zhang, Y. Cai, Z. Yang, T. Ni, et al., Role of deep-sea equipment in promoting the forefront of studies on life in extreme environments, iScience 24 (2021) 103299, https://doi.org/10.1016/j.isci.2021.103299.

[17] T. Laemthong, A.M. Lewis, J.R. Crosby, R.G. Bing, W.H. Schneider, D.J. Willard, et al., Enzymes from extremely thermophilic bacteria and archaea: current status and future prospects, Extremozy. Ind. Appl. (2022) 41–84, https://doi.org/10.1016/B978-0-323-90274-8.00004-6.

[18] D. Desbruyères, P. Chevaldonné, A.-M. Alayse, D. Jollivet, F.H. Lallier, C. Jouin-Toulmond, et al., Biology and ecology of the “Pompeii worm” (*Alvinella pompejana* Desbruyères and Laubier), a normal dweller of an extreme deep-sea environment: a synthesis of current knowledge and recent developments, Deep Sea Res. Part II Top. Stud. Oceanogr. 45 (1998) 383–422, https://doi.org/10.1016/S0967-0645(97)00083-0.

[19] J. Ravaux, G. Hamel, M. Zbinden, A.A. Tasiemski, I. Boutet, N. Léger, et al., Thermal limit for metazoan life in question: in vivo heat tolerance of the pompeii worm, PLoS One 8 (5) (2013) e64074, https://doi.org/10.1371/journal.pone.0064074.

[20] A. Tasiemski, S. Jung, C. Boidin-Wichlacz, D. Jollivet, V. Cuvillier-Hot, F. Pradillon, et al., Characterization and function of the first antibiotic isolated from a vent organism: the extremophile metazoan Alvinella pompejana, PLoS One 9 (4) (2014) e95737, https://doi.org/10.1371/journal.pone.0095737.

[21] B. Bruno, M. Maresca, S. Canaan, J.-F. Cavalier, K. Mabrouk, C. Boidin-Wichlacz, et al., Worms’ antimicrobial peptides, Mar. Drugs 17 (2019) 512, https://doi.org/10.3390/md17090512.

[22] C. Papot, F. Massol, D. Jollivet, A. Tasiemski, Antagonistic evolution of an antibiotic and its molecular chaperone: how to maintain a vital ectosymbiosis in a highly fluctuating habitat, Sci. Rep. 7 (2017) 1454, https://doi.org/10.1038/s41598-017-01626-2.

[23] P.J. Shukla, V.D. Bhatt, J. Suriya, C. Mootapally, Marine extremophiles, adaptations and biotechnological applications, in: S.-K. Kim (Ed.), Encyclopedia of Marine Biotechnology, John Wiley & Sons Ltd., 2020, https://doi.org/10.1002/9781119143802.ch74.

[24] WHO Bacterial Priority Pathogens List, 2024. Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1. (Accessed 2 October 2024).

[25] R. Bruno, C. Boidin-Wichlacz, O. Melnyk, D. Zeppilli, C. Landon, F. Thomas, et al., The diversification of the antimicrobial peptides from marine worms is driven by environmental conditions, Sci. Total Environ. 879 (2023) 162875, https://doi.org/10.1016/j.scitotenv.2023.162875.

[26] I. Bista, J.M.D. Wood, T. Desvignes, S.A. McCarthy, M. Matschiner, Z. Ning, et al., Genomics of cold adaptations in the Antarctic notothenioid fish radiation, Nat. Commun. 14 (2023) 3412, https://doi.org/10.1038/s41467-023-38567-6.

[27] C.A. Bost, C. Cotte, P. Terray, C. Barbraud, C. Bon, K. Delord, et al., Large-scale climatic anomalies affect marine predator foraging behaviour and demography, Nat. Commun. 6 (2015) 8220, https://doi.org/10.1038/ncomms9220.

[28] M. Gauthier-Clerc, Y. Le Maho, Y. Clerquin, S. Drault, Y. Handrich, Penguin fathers preserve food for their chicks, Nature 408 (2000) 928–929, https://doi.org/10.1038/35050163.

[29] C. Thouzeau, G. Froget, H. Monteil, Y. Le Maho, C. Harf-Monteil, Evidence of stress in bacteria associated with long-term preservation of food in the stomach of incubating king penguins (*Aptenodytes patagonicus*), Polar Biol. 26 (2003) 115–123, https://doi.org/10.1007/s00300-002-0451-2.

[30] C. Thouzeau, Y. Le Maho, G. Froget, L. Sabatier, C. Le Bohec, J.A. Hoffmann, et al., Spheniscins, avian β-defensins in preserved stomach contents of the king penguin, *Aptenodytes patagonicus*, J. Biol. Chem. 278 (2003) 51053–51058, https://doi.org/10.1074/jbc.M306839200.

[31] P. Reginatto, G.d. Agostinetto, R.d. Fuentefria, D. Ruschel Marinho, M.D. Pizzol, A. Meneghello Fuentefria, Eye fungal infections: a mini review, Arch. Microbiol. 205 (2023) 236, https://doi.org/10.1007/s00203-023-03536-6.

[32] F. Bertile, L. Fouillen, T. Wasselin, P. Maes, Y. Le Maho, A. Van Dorsselaer, et al., The safety limits of an extended fast: lessons from a non-model organism, Sci. Rep. 6 (2016) 39008, https://doi.org/10.1038/srep39008.

[33] H.V. Carey, M.T. Andrews, S.L. Martin, Mammalian hibernation: cellular and molecular responses to depressed metabolism and low temperature, Physiol. Rev. 83 (2003) 1153–1181, https://doi.org/10.1152/physrev.00008.2003.

[34] B. Chazarin, A. Ziemianin, A.L. Evans, E. Meugnier, E. Loizon, I. Chery, et al., Limited oxidative stress favors resistance to skeletal muscle atrophy in hibernating Brown bears (*Ursus arctos*), Antioxidants 22 (2019) 334, https://doi.org/10.3390/antiox8090334.

[35] S. Giroud, C. Habold, R.F. Nespolo, C. Mejías, J. Terrien, S.M. Logan, et al., The torpid state: recent advances in metabolic adaptations and protective mechanisms, Front. Physiol. 11 (2021) 623665, https://doi.org/10.3389/fphys.2020.623665.

[36] S.W. Donahue, Bone adaptation and osteoporosis prevention in hibernating mammals, Comp. Biochem. Physiol. Mol. Integr. Physiol. 280 (2023) 111411, https://doi.org/10.1016/j.cbpa.2023.111411.

[37] P.G. Jørgensen, A. Evans, J. Kindberg, L. HøierOlsen, S. Galatius, O. Fröbert, Cardiac adaptation in hibernating, free-ranging Scandinavian Brown Bears (*Ursus arctos*), Sci. Rep. 10 (2020) 247, https://doi.org/10.1038/s41598-019-57126-y.

[38] F. Bertile, C. Habold, Y. Le Maho, S. Giroud, Body protein sparing in hibernators: a source for biomedical innovation, Front. Physiol. 12 (2021) 634953, https://doi.org/10.3389/fphys.2021.634953.

[39] T.D. Lohuis, H.J. Harlow, T.D. Beck, Hibernating black bears (*Ursus americanus*) experience skeletal muscle protein balance during winter anorexia, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 147 (2007) 20–28, https://doi.org/10.1016/j.cbpb.2006.12.020.

[40] T.D. Lohuis, H.J. Harlow, T.D. Beck, P.A. Iaizzo, Hibernating bears conserve muscle strength and maintain fatigue resistance, Physiol. Biochem. Zool. 80 (2007) 257–269, https://doi.org/10.1086/513190.

[41] G. Fuster, S. Busquets, V. Almendro, F.J. Lopez-Soriano, J.M. Argiles, Antiproteolytic effects of plasma from hibernating bears: a new approach for muscle wasting therapy? Clin. Nutr. 26 (2007) 658–661, https://doi.org/10.1016/j.clnu.2007.07.003.

[42] S. Chanon, B. Chazarin, B. Toubhans, C. Durand, I. Chery, M. Robert, et al., Proteolysis inhibition by hibernating bear serum leads to increased protein content in human muscle cells, Sci. Rep. 8 (2018) 5525, https://doi.org/10.1038/s41598-018-23891-5.

[43] L. Cussonneau, C. Christian Boyer, C. Brun, C. Deval, E. Loizon, E. Meugnier, et al., Concurrent BMP signaling maintenance and TGF-beta signaling inhibition is a hallmark of natural resistance to muscle atrophy in the hibernating bear, Cells 10 (8) (2021) 1873, https://doi.org/10.3390/cells10081873.

[44] M. Miyazaki, M. Shimozuru, T. Tsubota, Supplementing cultured human myotubes with hibernating bear serum results in increased protein content by modulating Akt/FOXO3a signaling, PLoS One 17 (1) (2022) e0263085, https://doi.org/10.1371/journal.pone.0263085.

[45] L. Givre, C. Crola Da Silva, J.E. Swenson, J.M. Arnemo, G. Gauquelin-Koch, F. Bertile, et al., Cardiomyocyte protection by hibernating Brown bear serum. Toward the identification of new protective molecules against myocardial infarction, Front. Cardiovasc. Med. 8 (2021) 687501, https://doi.org/10.3389/fcvm.2021.687501.

[46] A. Nasoori, Y. Okamatsu-Ogura, M. Shimozuru, M. Sashika, T. Tsubota, Hibernating bear serum hinders osteoclastogenesis in-vitro, PLoS One 15 (8) (2020) e0238132, https://doi.org/10.1371/journal.pone.0238132.

[47] P. Dori, I. Anastasio, E. Macchi, I. Manenti, M. Hones, M. Carosi, Hibernating or not hibernating? Brown bears' response to a mismatch between environmental natural cues and captive management, and its welfare implications, PLoS One 19 (7) (2024) e0306537, https://doi.org/10.1371/journal.pone.0306537.

[48] C. Saraux, C. Le Bohec, J.M. Durant, V.A. Viblanc, M. Gauthier-Clerc, D. Beaune, et al., Reliability of flipper-banded penguins as indicators of climate change, Nature 469 (2011) 203–206, https://doi.org/10.1038/nature09630. Erratum in: Nature, 471 (2011) 254.

[49] R.M. Alexander, Obituary: Knut Schmidt-Nielsen (1915-2007),, Nature 446 (2007) 744, https://doi.org/10.1038/446744a.

[50] R.B. Huey, A.F. Bennett, Bart's familiar quotations: the enduring biological wisdom of George A. Bartholomew, Physiol. Biochem. Zool. 81 (2008) 519–525, https://doi.org/10.1086/589841.

[51] Y. Ropert-Coudert, R.P. Wilson, Trends and perspectives in animal-attached remote sensing, Front. Ecol. Environ. 3 (2005) 437–444, https://doi.org/10.1890/1540-9295(2005)003[0437:TAPIAR]2.0.CO;2.

[52] H.J. Williams, J.R. Shipley, C. Rutz, M. Wikelski, M. Wilkes, L.A. Hawkes, Future trends in measuring physiology in free-living animals, Phil. Trans. R. Soc. B 376 (2021) 230, https://doi.org/10.1098/rstb.2020.0230.

[53] Y. Le Maho, J.D. Whittington, N. Hanuise, L. Pereira, M. Boureau, M. Brucker, et al., Rovers minimize human disturbance in research on wild animals, Nat. Methods 11 (2014) 1242–1244, https://doi.org/10.1038/nmeth.3173.

[54] B. Pinshow, M.A. Fedak, D.R. Battles, K. Schmidt-Nielsen, Energy expenditure for thermoregulation and locomotion in emperor penguins, Am. J. Physiol. 231 (1976) 903–912, https://doi.org/10.1152/ajplegacy.1976.231.3.903.

[55] Y. Le Maho, P. Delclitte, J. Chatonnet, Thermoregulation in fasting emperor penguins under natural conditions, Am. J. Physiol. 231 (1976) 913–922, https://doi.org/10.1152/ajplegacy.1976.231.3.913.

[56] A. Ancel, H. Visser, Y. Handrich, D. Masman, Y. Le Maho, Energy saving in huddling penguins, Nature 385 (1997) 304–305, https://doi.org/10.1038/385304a0.

[57] J.A. Green, The heart rate method for estimating metabolic rate: review and recommendations, Comp. Biochem. Physiol. Mol. Integr. Physiol. 158 (2011) 287–304, https://doi.org/10.1016/j.cbpa.2010.09.011.

[58] M.-A. Forin-Wiart, M.R. Enstipp, Y. Le Maho, Y. Handrich, Why implantation of bio-loggers may improve our understanding of how animals cope within their natural environment, Integr. Zool. 14 (2019) 48–64, https://doi.org/10.1111/1749-4877.12364.

[59] R. Duan, Q. Fu, Y. Sun, Q. Li, Epigenetic clock: a promising biomarker and practical tool in aging, Ageing Res. Rev. 81 (2022) 101743, https://doi.org/10.1016/j.arr.2022.101743.

[60] A. Whalen, G. Gorjanc, J.M. Hickey, Parentage assignment with genotyping-by-sequencing data, J. Anim. Breed. Genet. 136 (2019) 102–112, https://doi.org/10.1111/jbg.12370.

[61] T. Shi, E. Song, N. Ehwang, R. Song, K.D. Rodland, T. Liu, et al., Advances in targeted proteomics and applications to biomedical research, Proteomics 16 (15–16) (2016) 2160–2182, https://doi.org/10.1002/pmic.201500449.

[62] S.J. Uddin, J.A. Shilpi, L. Nahar, S.D. Sarker, U. Göransson Editorial, Natural antimicrobial peptides: hope for new antibiotic lead molecules, Front. Pharmacol. 12 (2021) 640938, https://doi.org/10.3389/fphar.2021.640938.

[63] S. Ding, Q. Dai, H. Huang, Y. Xu, C. Zhong, C. An overview of muscle atrophy, Adv. Exp. Med. Biol. 1088 (2018) 3–19, https://doi.org/10.1007/978-981-13-1435-3_1.

[64] M.J. Tyler, D.B. Carter, Oral birth of the young of the gastric brooding frog *Rheobatrachus silus*, Anim. Behav. 29 (1981) 280–282, https://doi.org/10.1016/S0003-3472(81)80175-3.

[65] M. Bright, S. Gollner, A.L. de Oliveira, S. Espada-Hinojosa, A. Fulford, I.V. Hughes, et al., Animal life in the shallow subseafloor crust at deep-sea hydrothermal vents, Nat. Commun. 15 (2024) 8466, https://doi.org/10.1038/s41467-024-52631-9.