Novel treatment strategies for chronic kidney disease: insights from the animal kingdom

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Abstract

Many of the >2 million animal species that inhabit earth have developed survival mechanisms that aid in the prevention of obesity, kidney disease, starvation, dehydration and vascular ageing; however, some animals remain susceptible to these complications. Domestic and captive felids, for example, show susceptibility to chronic kidney disease (CKD), potentially linked to the high protein intake of these animals. By contrast, naked mole rats are a model of longevity and are protected from extreme environmental conditions through mechanisms that provide resistance to oxidative stress. Biomimetic studies suggest that the transcription factor NRF2 may offer protection in extreme environmental conditions and promote longevity in the animal kingdom. Similarly, during months of fasting, immobilization and anuria, hibernating bears are protected from muscle wasting, azotaemia, thrombotic complications, organ damage and osteoporosis — features that are often associated with CKD. Improved understanding of susceptibility and protective mechanisms of these animals and others could provide insights into novel strategies to prevent and treat several human diseases, such as CKD and ageing-associated complications. An integrated collaboration between nephrologists and experts from other fields, such as veterinarians, zoologists, biologists, anthropologists and ecologists, could introduce a novel approach for improving human health and help nephrologists to find novel treatment strategies for CKD.

The evolution of species — mediated by genetic and epigenetic modifications over the past 3.8 billion years — has given rise to a wide variety of adaptations to different environments. This observation has led to the proposal that insights into adaptive mechanisms observed in nature could aid the development of therapeutic approaches for human disease (1). Comparative physiology — a subdiscipline of physiology that is based on Krogh's principle, which states "*for such a large number of problems there will be some animal of choice, or a few such animals, on which it can be conveniently studied*" — involves the comparison of organ systems within different taxa (2). Homer Smith's insightful work, for example, used a comparative physiology approach based on studies of fish and amphibians (3) to form the basis of many aspects of renal physiology. Similarly, Ivan Sperber (4) studied correlations between dietary habits, ecological distribution, urine-concentrating ability and kidney morphology in 1944. The emerging field of biomimetics explores adaptative mechanisms of a given species and imitates — or takes inspiration from — these mechanisms to solve human problems (**Table 1; Supplementary information S1 (table)**). Biomimetics is a particularly interdisciplinary field that can be used to identify new approaches to disease (**Figure 1**), such as the underlying mechanisms of longevity in naked mole rats (5), resistance to long-term renal hypoxia in seals (6) and preserved renal function in hibernating bears (7, 8). However, it is important to emphasize that when interpreting data from biomimetic studies, one should consider the likelihood of comparative animal data offering meaningful solutions when extrapolated to human disease. The physiological mechanisms that have evolved to enable healthy animals to adapt to extreme environments may not necessarily be the same mechanisms that should be harnessed to avoid disease in humans.

The prevalence of chronic kidney disease (CKD) is rising worldwide. Approximately 10–15% of the global population suffer from CKD and its associated complications (9), particularly cardiovascular disease, infectious complications, osteoporosis, muscle wasting, frailty and premature ageing (10) (11). Nephrologists are faced with limited treatment options for patients with CKD, and advances in dialysis technology have not yet translated into markedly better outcomes (10). As the majority of randomized controlled trials for CKD therapies have been negative (10), an urgent need exists to find novel treatment options for this patient group.

Here, we discuss some examples of renal biomimetics, and how studies of the mechanisms by which animals adapt to hypoxia, oxidative stress, food deprivation and conversely to high-protein, or high-phosphate diets, may result in a better understanding of the uraemic phenotype **(Figure 1).** Although biomimetic studies usually focus on the adaptive mechanisms that protect species from disease, changing environments — such as global warming, water availability or salinity in the oceans — can also lead to adaptations that may not offer full protection from these changes but may still shed light on disease mechanisms. Examples include the study of mechanisms that lead to the extinction of a species and the inability of that species to adapt to a changing environment.

[H1] High-protein diets and dehydration

High-protein diets that are rich in red meat accelerate the progression of both experimental and human CKD (12, 13). The link between a high-protein diet and CKD (**Figure 2**) suggests that one might obtain mechanistic insights from studying mammals that live almost exclusively on a high-protein diet, such as the Felidae family (felids) and Desmodontinae (vampire bats). Interestingly, one group (felids) seems to be susceptible to CKD, while the other (vampire bats) seems to be protected.

[H2] CKD in felids. Felids consist of 37 species in the wild. Although they are considered among the world's most successful carnivore families, they are particularly susceptible to kidney diseases, including polycystic kidney disease (14), glomerulonephritis (15), acute pyelonephritis, hypertension-associated CKD (16) and nephrolithiasis (17). The most common kidney pathology in domestic felids is chronic tubulointerstitial fibrosis, which is sometimes observed with glomerulosclerosis (14). The prevalence of CKD in domestic cats has increased 75-fold (from 0.04% to 3%) during the last four decades, although this increase might be partially due to improved diagnostics (18, 19) (22) and also due to increased nonsteroidal anti-inflammatory drug (NSAID) consumption in the last decade (20). Even so, CKD is thought to affect 35–80% of geriatric domestic cats and is the most common cause of death in domestic cats >5 years of age (19). Likewise, a necropsy study found renal lesions in 87% of big felids (mainly tigers, leopards and lions) held at zoos and safari parks in Germany (21). In the wild, free-ranging felids

experience a range of kidney diseases of differing origins, such as viral infections or amyloid deposition; however, free-ranging animals typically die from other causes before renal disese manifests or only show a mild form of disease (22). Extrinsic environmental or dietary factors that might promote the development of kidney disease among felids in captivity, seem to be absent among wild felids (22).

As mentioned above, the most common renal pathology among captive and domestic felids is chronic tubulointerstitial fibrosis, which is associated with minimal or mild proteinuria, normal blood pressure, hypokalaemia, hypo- or hypernatraemia, polydipsia and polyuria (18, 23) and an absence of diabetes mellitus (24). Hypertension, if present, is usually thought to be secondary to the renal disease (18). Microvascular lesions observed in chronic hypertensive renal injury are absent or only minimally present (25). The cause of this type of CKD remains unknown; however, it is unlikely that felids have evolved a selective susceptiblity to CKD. Hence, one might hypothesize that the dramatic increase in felid CKD might reflect a new environmental exposure to which felids are particularly susceptible. Insights into the underlying mechanisms might be gained from comparisons with populations of humans and other animals that are either affected by or protected from renal disease, as discussed in further detail below. As CKD among felids has been best described in domestic cats and felids in wildlife parks, one possibility is that this disease might reflect the contamination of meat with a nephrotoxic substance. This scenario is similar to the epidemic of renal disease that occurred in vultures in India and Pakistan, which was ascribed to the practice of treating cattle with NSAIDs that contaminated the cattle meat (26) .

[H3] *The effect of red meat intake.* Another potential mechanism of the high prevalence of CKD in felids might relate to their high intake of red meat (**Figure 2**). To meet the high energy demands of their brain, which is relatively large in comparison with body size (27), greater quantities of proteins are required, predominantly to generate glucose from amino acids through *de novo* gluconeogenesis. High-protein diets induce vasodilation of afferent renal arterioles, glomerular hypertension and hyperfiltration, which together accelerate the progression of pre-existing CKD in a variety of domestic and laboratory animals, including mice,

rats and dogs (28). A high consumption of salt and animal proteins has also been linked to progression of CKD in humans (12, 29), with increasing evidence indicating a greater effect of red meat consumption compared with that of other animal and vegetable protein sources (12, 13).

Whether high-protein diets can induce *de novo* renal disease is less certain. One study reported that a commercial diet low in potassium and high in meat (40% protein) and phosphoric acid led to the development of tubulointestitial lesions in five of nine domestic cats (30). In a human study, maintenance of a high-protein diet for 6 weeks increased estimated glomerular filtration rate (eGFR) by 4 ml/min/1.73 m^2 compared with a carbohydrate and unsaturated fat diet in healthy individuals (31); however, whether long-term consumption of a high-protein diet promotes CKD is unclear. Although felids are obligate carnivores, their dietary acquisition of protein in the wild is intermittent and separated by days of fasting (25). By contrast, domestic cats and felids kept in zoos are often fed high-protein diets on a daily basis.

An examination of published data on 12 biochemical parameters of serum that can be used to evaluate renal functions in 97 mammalian species shows that differences in patterns of these parameters result in a clustering of species, separating carnivorous mammals from omnivorous or herbivorous mammals **(Supplementary information S2 (figure)**). This clustering is mainly due to higher levels of urea (+57%), and chloride (+13%), as well as reduced levels of alkaline phosphatase (-56%) among carnivores compared with mean values of the other species. This finding highlights the importance of diet, including protein source, on parameters of renal function, and leads to the hypothesis that in humans, different types of diets (for example, vegetarian or highly carnivorous) might lead to similar differences in parameters of renal function(s).

Although the classic view is that renal injury induced by a high-protein diet is caused by changes in glomerular haemodynamics (32) (**Figure 2**), increasing evidence suggests that CKD risk is associated with protein originating from red meat and not with protein from dairy or vegetable-based sources (33). For example, epidemiological studies conducted in Singapore (34) and the USA (35) (36) have shown that among different protein sources (including red meat, poultry, dairy products, fish eggs and legumes) only red meat (beef, pork and lamb) and

processed meat increased the risk of CKD. In one study, individuals in the highest quartile of dietary red-meat intake had a 1.4-fold greater risk of end-stage renal disease (ESRD) than those in the lowest quartile of red-meat intake (34). Interestingly, diets rich in other protein sources, such as legumes and low-fat dairy products, were actually protective against CKD (35). Red and processed meat therefore seem to have direct nephrotoxic effects that increase the risk of CKD. Indirect support for differences in plant and animal proteins comes from studies in vegetarians. A study conducted in Taiwan showed that eGFR did not differ among 102 vegetarian Buddhist nuns compared with an equal number of age-matched omnivorous females (37) However, serum levels of sodium, glucose, urea and cholesterol, as well as blood pressure and urinary specific gravity, were lower among individuals in the vegetarian group (37). As vegetable proteins have different renal effects (lower GFR and renal plasma flow) than meat proteins (38), and plant-based diets might protect against the development of CKD (39) and its complications (40), patients with CKD should be encouraged to consider a vegetarian diet (41).

In addition to CKD, red and processed meat have been linked to an increased mortality (42) and risk of other chronic diseases, such as cancer (43), stroke (44), coronary heart disease (45) and type 2 diabetes mellitus (T2DM) (46). Moreover, one study reported that the withdrawal of red meat from the diet of patients with T2DM reduced albuminuria and improved their serum fatty acid profile compared with their usual diet (47). Another study in patients with T2DM showed that adherence to a chicken meat-based diet for 1 year reduced urinary albumin excretion to levels comparable to those achieved by treatment with an angiotensin-converting enzyme (ACE) inhibitor (48). These findings imply that renal toxicity is generated by red meat *per se,* and not total protein intake. Dietary management of CKD in domestic cats with a low-protein and low-PO_4 diet was associated with increased survival compared with that of cats that did not undergo the dietary change (49). Further investigation is required to elucidate potential differential effects of processed red meat, game meat and white meat (that is, chicken or fish) on renal function in felids.

[H3] Mechanism of red meat-induced CKD. Several factors have been proposed to be implicated in the disease-promoting effects of red meat (50) (**Figure 2**). These include an associated high

intake of NaCl (which increases blood pressure and stimulates vasopressin production and release by increasing serum osmolality), saturated fats (which drive mitochondrial oxidative stress), increased net acid production (which causes metabolic acidosis and acidic urine), the pro-oxidative effects of haem iron (which promotes oxidative stress), DNA damage caused by *N*-nitroso compounds , (which leads to purine degradation and uric acid formation), the incorporation of non-human sialic acid into tissue (which promotes interaction with inflammation-provoking antibodies) and changes in the composition and/or metabolism of gut microbiota. For example, trimethylamine-*N*-oxide (TMAO) - which is produced from the metabolism of red meat, eggs and fish by gut microbiota - induces renal fibrosis in animal models (51) and inflammation in endothelial cells (52). Although diminished renal function impairs the ability to eliminate TMAO, it predicts outcome in patients with CKD even after adjustment for other risk factors (53). Inhibition of gut microbial trimethylamine (TMA) production prevented the development of atherosclerotic lesions in *Apoe*$^{-/-}$ mice (54). Moreover, exposure to carnitine (a major nutrient in red meat) in mice affects the composition of gut microbiota via the proatherogenic intermediate γ-butyrobetaine that is converted into TMA and TMAO (55). Alterations in gut microbiota might also affect processes, such as haem-induced lipoperoxidation (56). Red meat consumption is also associated with increased intake of phosphate, which is associated with decreased renal function, inflammation and premature ageing (57). Moreover, phosphate activates nuclear factor-κB (NF-κB) signalling and promotes the generation of reactive oxygen species (ROS) in vascular smooth muscle cells (VSMCs) (58). This observation implies that the putative protective effects of antioxidative factors, such as nuclear respiratory factor (NRF2) (**Box 1**), on renal function should be investigated in the context of a diet rich in red meat.

The high content of nucleic acids in animal proteins probably also contributes to the nephrotoxic effects of red meat diets in humans and felids. Animal proteins are much more likely to raise serum uric acid levels than are proteins from vegetable and dairy sources (59). In domestic cats, a transient (up to 50-fold) increase in urine uric acid occurs following the ingestion of purine-rich animal proteins compared with a purine-free diet, despite the presence of a uric acid-degrading enzyme (uricase) (60). In humans, consumption of animal proteins

and/or purines also results in an acute rise in serum and urine uric acid levels (61, 62), which is accompanied with a substantial acid load in urine that leads to a decrease in urine pH (13). A urine pH of <5 is extremely common in cats with uraemic manifestations (23), and a low urine pH (5.0–5.5) predicts stage 3 CKD in humans (63). Although urate stones are relatively rare in cats (64), urate crystalluria is a common problem in felids (65). Coupled with dehydration and heat exposure, we propose that urate crystalluria and/or uricosuria resulting from high protein intake could facilitate tubulointerstitial injury. Both soluble and crystalline forms of urate have been shown to induce inflammation in rat tubular cells *in vitro* (66). Indeed, signs of dehydration in felids with CKD is common (23) and predictive for the development of CKD in domestic cats (67). In humans, although the aetiology of CKD in populations from Central America and Sri Lanka remains a subject of debate (68), we propose a role for heat stress and recurrent dehydration in the presence of high uric acid levels in disease pathophysiology (69) .

[H2] Protein metabolism in vampire bats. Vampire bats (*Desmodus rotundus*) feed mostly on the blood of warm-blooded mammals. However, in contrast to man and felids, they seem to be resistant to the detrimental metabolic effects of a high-protein intake. Their protein intake would be comparable to a daily intake of about 6 kg protein in a 70-kg man (as compared to a normal daily intake of 50–120 g in humans). As the consumption of >20 g of blood in a 20-min feed increases the body weight of vampire bats by 20–30%, they rapidly absorb the blood plasma and start urine production within 2 min of feeding (70). The blood urea concentration of vampire bats is 27–57 mmol/L (compared with 3–8 mmol/L in healthy humans), depending on the time point after feeding (71). Despite this high protein intake, the vampire bat does not have larger kidneys than mammals of similar size (72), which suggests no difference in glomerular number and glomerular capillary surface area. Indeed, indirect allometric calculations indicate that the vampire bat's GFR is not greater than that of similarly sized mammals (71); however, to our knowledge, GFR measurements have not been carried out. Of interest, mammalian blood has a lower relative purine content than does red meat (73); however, whether this difference accounts for the differential risk of CKD between felids and vampire bats is speculative.

[H1] Ageing and longevity

Ageing has been defined as an accumulation of deficits occuring in different individuals in different ways, and with varied rates in different organs (74). Ageing is an actively regulated process influenced by genetics, epigenetics, lifestyle, nutrition and psychosocial factors (75), which may act synergistically, independently or cumulatively. The ageing process is characterized by a series of hallmarks, including genomic instability, telomere attrition , epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, stem cell exhaustion, mitochondrial dysfunction, altered intercellular communication and cellular senescence (76), which are common across different taxa and affected by the uraemic milieu (75) (77) (78).

[H2] *Ageing and kidney disease.* In addition to the progressive loss of renal function, ageing in humans, rats and many other mammals is associated with the development of glomerulosclerosis and interstitial fibrosis (79, 80), which are linked to impaired autoregulation of renal blood flow and impaired angiogenesis, epigenetic modifications, endothelial dysfunction, oxidative stress and inflammation (75). Chronic inflammation (also known as 'inflammageing') is an important driver of premature uraemic ageing (81) and manifests with an increased frequency of age-related complications, such as vascular stiffening, osteoporosis, muscle wasting, depression, cognitive dysfunction and frailty (81). In addition, persistent mitochondrial dysfunction with increased generation of ROS features in both normative ageing (82) and progressive CKD (83).

Whether ageing-associated renal disease is inevitable (84) or modifiable (85) remains controversial. The use of senolytic agents , which selectively remove senescent cells , in pre-clinical models suggests that ageing-associated renal disease is modifiable (77), and direct improvement of physiological function following removal of these cells indicates causality. These cells are non-proliferative, resistant to apoptosis and are generated in response to genotoxic stress and resulting DNA damage, as part of normative ageing. Loss of age-related regenerative capacity in tissues and organs occurs as a direct consequence, and a senescence-associated pro-inflammatory milieu subsequently develops. The selective removal of senescent

cells from tissues and organs via immune-mediated clearance is dysregulated during normative ageing, and contributes to inflammaging (86). The accumulation of these cells has been observed across a broad spectrum of non-communicable diseases.

[H2] *Ageing in the animal kingdom.* One way to improve our understanding of ageing processes and senescence is to study animals with unusual longevity. Long-lived animals are found across the taxonomic spectrum, such as in certain mammals, birds, sea turtles and fish. For example, extreme longevity is observed in the ocean quahog (*Arctica islandica*; >500 years) (87) and the Greenland shark (*Somniousus microcephalus*; ~400 years) (88). The study on the ocean quahog supports the notion that chronic low-grade inflammation in the cardiovascular system is an ubiquitous feature of ageing (87). Other interesting candidates for studies of reduced senescence include the rougheye rockfish (*Sebastes aleutianus*) and the bowhead whale (*Balaena mysticetus*), both with documented life spans of >200 years. Interestingly, ageing rockfish do not show signs of organ degeneration or a decline in liver lysosomal function (89), which are typically observed in normative ageing. By contrast, examples of exceptionally short-lived species that exhibit an accelerated expression of ageing biomarkers are found in the family of Cyprinodontidae (killifish), which have a maximal lifespan of only 13 weeks (90). Thus, a better understanding of the mechanisms by which some animals have delayed or accelerated ageing processes (91, 92) may provide insights into not only the process of ageing in humans but also ageing-related kidney disease.

[H3] Insights from the naked mole rat. Naked mole rats (*Heterocephalus glaber*) have emerged as a good model organism to study ageing and ageing-related diseases. These subterranean rodents are rarely exposed to sunlight and have no obvious dietary source of vitamin D (93). However, despite having undetectable calcifediol levels (the precursor of vitamin D), their calcium phosphate homeostasis is adequately maintained (94). Although they have a small body size and are constantly exposed to hypoxia, oxidative stress and hypercapnia, they can live >30 years and maintain a healthy cardiovascular and reproductive status as well as body composition throughout their life (5). Interestingly, the structure and function of their proteins is not affected by their substantial exposure to oxidative stress (95), and they display high levels

of autophagy and efficient removal of stress-damaged proteins throughout life (96). In contrast to humans and other rodents, (97) these animals preserve normal vascular and cardiac function with ageing (98, 99) and are resistant to the development of cancer (100). Moreover, their bone mineral density, articular cartilage and nitric oxide sensitivity of VSMCs is not affected by ageing (101). Whereas most nephropathologies seem to be absent in naked mole rats, cases of nephrocalcinosis have been reported (102).

[H3] NRF2-mediated antioxidant activity. Some of the molecular pathways that protect these animals from cancer have been elucidated. For example, one study reported that the 5-fold higher production of high-molecular-weight hyaluronan in fibroblasts protects naked mole rats from cancer (103). High expression levels of the transcription factor NRF2, which stimulates intracellular antioxidant activity by regulating the expression of many target genes involved in the antioxidant response (**Box 1**), may also protect the naked mole rat from cellular damage. In addition to antioxidative activities, NRF2 has other important functions, such as regulating nuclear factor κB (NF-κB) activity, which may play a part in mitochondrial homeostasis (104) and may decelerate the ageing process (105). As NRF2 expression correlates positively with maximum lifespan in long-lived rodents (106), diminshed NRF2 activity may be important for the ageing phenotype of organisms as diverse as worms, flies and mammals (107) .

Evidence for a role of NRF2 in ageing has also been reported in humans. For example, children with the rare Hutchinson Gilford Progeria Syndrome (HGPS), which is caused by a mutation in prelamin A/C, age extremely prematurely, are subject to increased oxidative stress and have a repressed NRF2 pathway (108). As reactivation of NRF2 reversed the cellular ageing defects in HGPS patient cells and in an animal model of HGPS repression, NRF2-mediated transcription seems to have a pathogenic role in the progeric phenotype (108). As HGPS shares many features common to age-associated diseases it has been regarded as a model system to better understand ageing processes in chronic diseases (109). For unknown reasons at present, children with HGPS do not seem to have an increased risk of CKD despite a prematurely aged phenotype, which may reflect a feature of antagonistic pleiotropy (109). Despite apparent differences in the pathways underlying HGPS and CKD, we suggest that models of ageing and

longevity, such as HGPS and the naked mole rat, can be used to study factors that underlie progeric processes in CKD (**Figure 3**).

[H2] Vascular calcification and phosphate

[H3] Phosphate and calcification in vertebrates. The composition of seawater is similar to that of the human body in regard to the abundance of elements (110) (**Supplementary information S2** (**Table**)), consistent with the view that life originated from the sea (111). Of the 10 most abundant elements in the human body, only phosphorous is not among the 10 most abundant elements present in sea water (112), indicating that organisms selectively accumulated phosphorus (in form of phosphate within cells) at some point in time during evolution (**Supplementary information S4** (**figure)**). Phosphate is a major component of nucleic acids and membrane phospholipids, and has a key role in numerous intracellular functions, including ATP synthesis and function and kinase-mediated signal transduction (113). Phosphate is so fundamental to life that its deficiency can be fatal, which may be a reason for the evolution of 'phosphate appetite' (114).

Although intracellular phosphate is essential to all forms of life, accumulation of extracellular phosphate first emerged in bony fish during the evolution of skeletons (115). Unlike invertebrates, which have a calcium carbonate ($CaCO_3$)-based exoskeleton, most skeletons of vertebrates consist of calcium and phosphate, especially in the form of calcium hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) (116). This acquisition was likely required for terrestrial vertebrates to support their body weight on land. The extracellular fluid of vertebrates consists of a highly saturated solution of calcium and phosphate (117), which enables bone formation simply by controlling where to provide a 'cue' for nucleation of calcium phosphate, such as production and secretion of bone matrix proteins by osteoblast lineage cells. Undesired nucleation within the extraosseous tissues is achieved by maintaining extracellular phosphate concentration within a narrow range, in a process that is partially controlled by fibroblast growth factor 23 (FGF23) and its obligate co-receptor Klotho (encoded by *Kl*) (115). Interestingly, *Kl*-knockout mice have a 12-fold reduction in lifespan and a 2-fold increase in extracellular phosphate concentration compared with wild-type mice (118). Secreted Klotho

also exerts multiple functions independently of FGF23, such as inhibition of insulin-like growth factor 1 activity and upregulation of anti-oxidant enzyme expression levels. These additional functions may contribute to the anti-ageing properties of Klotho (119). Furthermore, Klotho induces NRF2 expression and subsequent anti-oxidant defence mechanisms (120), which links altered NRF2 expression to bone mineral metabolism and phosphate homeostasis (121).

[H3] Phosphate in ageing and calcification. Vascular calcification is a common feature of the progeric uraemic phenotype (122) and linked to senescence (123). High extracellular phosphate levels, which often occur in combination with elevated calcium levels, increase the risk of calcium phosphate deposition in the vasculature and vascular calcification (122). Cell culture studies have shown that a high phosphate concentration induces cellular senescence (124) and leads to the conversion of VSMC to osteoblastic cells (125, 126); a process that can be prevented by inhibiting calcium phosphate precipitation by pyrophosphate, phosphonoformic acid (127, 128) and phosphate-binders (129). Consistent with the observation that a high phosphate concentration induces cellular senescence and that accumulation of senescent cells accelerates ageing of the organism (130) a negative correlation exists between extracellular phosphate levels and longevity across mammalian species (131) (Supplementary information S4 (**figure**)). For example, children with HGPS have elevated phosphate levels, develop rapid vascular calcification and typically die of stroke or myocardial infarction as teenagers (132). Furthermore, expression of progerin (the mutated form of prelamin A associated with HGPS) in VSMCs leads to a decrease in extracellular pyrophosphate (133). As pyrophosphate protects VSMCs from calcification, high serum phosphate and low extracellular pyrophosphate may contribute to accelerated vascular calcification in HGPS. In the general population, high phosphate levels are associated with premature vascular ageing (134), shortened telomere length, reduced DNA methylation content and elevated IL-6 (57), which are all biological markers of ageing.

Studies from the past few years have provided insights into the mechanisms by which high extracellular phosphate levels lead to vascular calcification. Under conditions of inflammation, oxidative stress and high extracellular phosphate levels, nanoparticle calcium

phosphate precipitates can develop in the vasculature, despite the presence of multiple endogenous inhibitors of calcium phosphate deposition (135, 136) and can grow to form calciprotein particles (CPPs). CPPs are aggregates of serum protein fetuin A (also known as AHSG) loaded with calcium phosphate precipitates and dispersed as colloids in the blood. These CPPs may play a part in CKD progession, as recent clinical studies showed that serum CPP levels correlated with vascular calcification and/or stiffness (135, 137), and predict mortality in patients on dialysis (138). Of interest, tigers have particularly high levels of phosphate (1.7±0.3 mmol/L) and serum creatinine (265±62 μmol/L), suggesting it would be of interest to determine levels of serum CPP and FGF23 in these animals (139).

[H3] Therapeutic strategies to prevent vascular calcification in CKD. The best current approach to prevent vascular calcification in CKD is dietary phosphate restriction or chelation through the use of phosphate binders (140). However, a consequence of dietary phosphate restriction is reduced protein intake, which can lead to protein–energy wasting and inadvertently increased mortality (141). A major problem with phosphate binder therapies is patient non-adherence due to the high pill burden and gastrointestinal adverse effects (142). Alternative treatment strategies to prevent vascular calcification could potentially be derived from comparative physiology studies. For example, agents that stimulate NRF2 (**Box 1**), block mTORC1 signalling (143) or reduce phosphate absorption, such as by inducing calcium phosphate precipitation in the gut with magnesium (144), should be tested for their ability to decrease extracellular phosphate levels.

Of interest, a diet of highly fermentable carbohydrates (for example, starch) in captive ruminants, such as giraffes (*Giraffa camelopardalis*) — in combination with low calcium, high phosphate and low magnesium levels in the serum — is associated with premature death in these animals (145). Since introduction of a diet with lower starch content, led to higher magnesium and lower phosphate levels (145), one potential approach would be to use ‘resistant starch’, which is a complex carbohydrate fermented by gut microbiota that increases colonic absorption of minerals in animals. Indeed, resistant starch has been suggested to be a novel dietary method to prevent diabetic CKD (146).

[H2] Caloric restriction and ageing. Although dietary phosphate restriction is one mechanism to slow vascular calcification and ageing, a more effective approach to extend the lifespan of animals is by caloric restriction (147), which has demonstrated efficacy in both short-lived species, including flies, worms, rats, mice (148), and more long-lived species, such as primates (149). Fat stores, especially those generated during fructose metabolism, result in fructose-induced oxidative stress, which is associated with increased translocation of NRF2 to the nucleus, decreases in mitochondrial DNA content and mitochondrial dysfunction, with subsequent cellular apoptosis (150, 151). In most animals, excess fat stores are maintained as a protective mechanism for periods of food shortage (152). Thus, as long as food is available on a daily basis, caloric restriction would be expected to reduce mitochondrial oxidative stress and preserve mitochondrial metabolism. Other ways to mimic caloric restriction would be to administer agents that modulate cellular metabolism, including sirtuin agonists (153, 154) and AMPK agonists (155), the effects of which are mediated in part by the activties of FOXO family and the insulin signalling pathways (156). For example, resveratrol prolongs lifespan in the extremely short-lived killifish (90). We found that mice that cannot generate fructose, which are therefore protected from mitochondrial oxidative stress, were also protected from developing age-related renal disease (157). In theory, elevated expression of NRF2 also mimics caloric restriction, as knockdown of KEAP1 in mice results in accumulation of NRF2 and thus augments the activation of cellular stress responses, including fatty acid oxidation and lipogenesis (158) .

[H3] *Methionine restriction and ageing.* In addition to caloric restriction, dietary restriction of proteins — especially the sulphur-containing amino acid methionine — also promotes longevity in various animal models (159) (**Figure 4**). This effect is likely to be mediated through the cytoprotectant hydrogen sulphide (H_2S) gas and increased activation of the transsulphuration pathway , prevention of electron leakage from mitochondria, and possible hermetic effects on the mTOR pathway and NRF2 activity (160). Under conditions of cellular stress, H_2S-mediated *S*-sulfhydration of KEAP1 leads to its disassociation from NRF2 and enhanced NRF2 nuclear translocation. **(Box 1)** This increases mRNA expression of NRF2-targeted downstream genes,

such as glutamate cysteine ligase (GSH1) and glutathione reductase and upregulates a range of cellular defenses. In addition, methionine restriction increases expression of the transsulphuration pathway enzyme cystathionine γ-lyase (CTH), resulting in increased H_2S production, which leads to AMPK activation and mTORC1 repression, thus reducing cellular stress and promoting physiological longevity (161). H_2S also binds iron and captures electrons leaked from mitochondria, which reduces mitochondrion-mediated ROS formation (162, 163). In support of a role for H_2S activity in longevity, lower circulating methionine levels have been reported in naked mole rats compared with levels in shorter-lived laboratory rodents (164). The recent finding of low sulphide levels in naked mole rats and the inverse correlation between circulating sulphide levels and maximum longevity in six different species (165) add to complexity of understanding the role of H_2S in ageing. Thus, for prolonging life span, interconnections between methionine and caloric restriction in the context of comparative biology need to be investigated further.

Methionine restriction might be particularly important in preventing ageing and age-associated renal dysfunction (57). For example, an inverse correlation between methionine content in tissue proteins and longevity was reported in eight different species (166). Although circulating methionine levels do not differ between patients with CKD and healthy controls (167), oral methionine loading in patients on haemodialysis leads to an accumulation of homocysteine and other methionine metabolites in plasma and red blood cells, indicating impairment of the transsulphuration pathway. High doses of vitamin B6 and folic acid failed to mitigate this phenotype, indicating that it most probably was not due to a lack of these co-factors (168). Methionine restriction also increases the replicative lifespan and decelerates the accumulation of senescent cells across taxa from yeast to man (169). Consistent with these observations, we reported lower methionine levels in wild brown bears (*Ursus Arctos*) (8) and observed a 4-fold increase in the methyl donor betaine during hibernation (*P.S. et al., unpublished work*). Thus, it could be speculated that an increased production of H_2S protects the bears from ROS-mediated DNA damage. Moreover, dietary supplementation of H_2S in mice alleviates inflammation, abberant methylation and dysfunction in a model of hypertensive kidney disease (170), suggesting this cytoprotective gas should be investigated as a novel

treatment strategy in CKD. A diet rich in one-carbon methyl donor units relative to calories, such as betaine (found in fruits, cereals and vegetables) can be used as an epigenetic switch and, via DNA hypermethylation and transmethylation in the methionine cycle, promotes longevity (171). This mechanism merits further investigation, as low betaine levels have been observed in humans with poor renal function and accelerated biological ageing (P.G.*S. et al., unpublished work*).

[H1] Hypoxia and ischaemia

Naked mole rats survive constant exposure to hypoxic conditions by generating ATP through glycolysis. This process is mediated in part by using endogenously produced fructose, which preferentially stimulates glycolysis and lactate production (172). We have found that fructose metabolism commonly leads to glycogen accumulation in the liver in mice and rats (R. J. J. and M.L*., unpublished work*). This metabolic mechanism might also protect the kidneys of diving marine mammals that are subject to periods of prolonged hypoxia during deep dives. Harbour seals (*Phoca vitulina*) and whales (*Cetacea*) for example, have large amounts of glycogen in their proximal tubules, along with high levels of glycolytic enzymes to generate ATP during hypoxia (173, 174). The kidneys of Weddel seals (*Leptonychotes weddellii*) are protected from hypoxia despite severe renal vasoconstriction upon diving (175). Likewise, kidneys of hibernating squirrels are protected from ischaemic injury, in a process that is probably mediated via an abscence of caspase-3-like mediated activity (176).

One potential mechanism by which glycolysis protects against hypoxia could occur through the upregulation of antioxidants. Fasting seals have high expression levels of NRF2, (177) antioxidant enzymes (178) and glutathione levels (179) compared with the non-fasting state. In support of a protective role for antioxidants, hyperactivation of NRF2 prevents progression of tubular damage after renal ischaemic injury in mice (180). Thus, NRF2 might be a therapeutic target to prevent acute kidney injury and could activate a hypoxia survival pathway (**Box 1**). By contrast, very high intracellular concentrations of dietary or endogenously produced fructose leads to rapid and transient ATP depletion, resulting in a strong pro-inflammatory response and substantial oxidative stress in human proximal tubular cells (181). Indeed, a high-

fructose diet inhibits KEAP1–NRF2 antioxidant signalling and increases the risk of non-alcoholic hepatosteatosis in mice (182). Thus, high concentrations of fructose may be injurious whereas low concentrations may carry survival functions.

Last, although hypoxia and ischaemia usually occur in conjunction, some species, such as the turtle are tolerant to hypoxia but still sensitive to brain ischaemia (183). A better understanding of hypoxic tolerance in turtles and naked mole rats may provide novel therapeutic interventions to combat the harmful effects of cerebral, renal and cardiac ischaemia in humans.

[H1] Seasonal acclimatization and hibernation

[H2] Seasonal acclimatization of metabolic activity. Many small mammals escape food shortage during winter by hibernation or daily torpor (184). Other species that do not hibernate or go into daily torpor in the classical sense, such as red deer (*Cervus elaphus*) or Alpine ibex (*Capra ibex*), adopt a similar hypometabolic state during winter. The reduction in energy expenditure is therefore, similarly to hibernators and species undergoing daily torpor, mainly accomplished by lowering endogenous heat production and increasing the tolerance to a lower body temperature. Although the 2–3°C change in core body temperature is only moderate (185, 186) a substantially lower body temperature down to 15°C is present at the body's periphery (187), which is indicative of a substantial reduction in the mean temperature of the entire body mass. The winter phenotype of mammals further includes a shift from an anabolic metabolism during summer to the use of body fat reserves to fuel metabolism during winter (188, 189). As a result, many hibernators do not eat during winter (188), and non-hibernating species like red deer reduce their food intake substantially, even when fed *ad libitum* (190). The endogenous nature of the seasonal cycle of appetite and its entrainment by photoperiod has been shown experimentally for many wild species (191). Decreased food intake during winter leads to a reduction of the size of the gut and visceral organs, like the kidney (190, 192), which further contributes to lower energy expenditure.

Major differences exist in levels of serum biomarkers of microbiota metabolites between wild bears and bears in captivity (*P.S., unpublished work*), suggesting that nutrients and feeding patterns might contribute to the metabolic changes required for hibernation. A transition in

energy metabolism from carbohydrates during summer to lipids during winter is facilitated by a switch from insulin sensitivity in the summer to insulin resistance during hibernation (193). The observation that central administration of leptin to captive grizzly bears leads to reduced food intake in October, but not in August, implies that seasonal variations exist in the sensitivity of the bear brain to the anorexic effects of leptin (193). In addition, seasonal variations in gut microbiota might also contribute to changes in energy metabolism in hibernating bears, as transplantation of summer gut microbiota from wild bears promoted adiposity without affecting glucose tolerance in germ-free mice (194). Although humans do not hibernate, investigating the processes that trigger fat accumulation in the summer followed by the switch to reduced energy intake and a fat-burning state occuring immediately before animals hibernate (195) may help to understand the mechanisms driving obesity.

[H2] Seasonal changes in membrane composition. Seasonal variation in body temperature is preceded by changes in the composition of cellular membranes, which consists of the integration of nutritionally acquired polyunsaturated fatty acids (PUFAs) into phopsholipids during periods of cold acclimatization (196). In addition to seasonal changes, even daily rhythmic changes in the phospholipid fatty acid composition of membranes have been found in humans along with changes in body temperature (197). Furthermore, physical exercise can alter the lipid composition of membranes, for example by increasing the concentration of docosahexaenoic acid (DHA) in skeletal muscle phospholipids (198) and by enhancing insulin sensitivity, probably through increasing insulin receptor expression levels. Of interest, the composition of membrane phospholipids has also been reported to contribute to the outstanding longevity in naked mole rats (199).

The composition of membrane lipids influences the activity of membrane-bound enzymes, for example, sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity is increased in membranes that are rich in linolenic acid (LA). Therefore, incorporation of LA into phospholipids of cardiac myocytes can compensate for reduced SERCA activity due to low temperatures and enable adequate Ca^{2+} handling in cardiac myocytes even at body temperatures close to freezing point (196, 200). High concentrations of LA in membranes also improve muscle performance at a high body temperature, as suggested by a positive relationship between LA content of

membrane phospholipids of muscle cells and maximum running speed, found in a comparative study of 36 mammal species (201). By contrast, DHA incorporation into phospholipids decreases SERCA activity (200) but seems to increase the activity of key enzymes of the Krebs cycle and fatty acid ß-oxidation (202). Accordingly, an increase of the DHA content into phospholipids during hibernation in Alpine marmots is paralleled by an increase of thermogenic capacity (196).

As all PUFAs are of dietary origin in mammals and birds, uptake influences the fatty acid composition of membranes. However, the balance of ω-6 to ω-3 PUFA in phospholipids seems to be regulated more by deacylation/reacylation processes, that is, membrane remodelling, rather than directly by dietary intake (190, 203). The different effects of ω-6 and ω-3 PUFA on membrane-bound enzymes hint at intriguing molecular conflicts. There probably is no optimal "all-purpose" PUFA composition in tissues, which creates a trade-off between costs and benefits of each fatty acid that is influenced by metabolic state, for example fasting or fattening, and hence is subject to seasonal and even daily variations (190).

In rats with adenine-induced CKD, a pro-inflammatory fatty acid pattern (low PUFA and high saturated fatty acid concentrations) was associated with downregulation of NRF2 activity and increased activation of NF-κB and its downstream cytoprotective and anti-oxidant proteins (204). As oxidation of eicosapentaenoic acid and DHA generate concentrations high enough to induce NRF2-directed gene expression (205), this may explain the anti-oxidative and anti-inflammatory properties of ω-3 PUFAs. Burmese pythons (*Python molurus*) were reported to display 40% cardiac hypertrophy with increased cardiac output 48–72 hrs after large meals (206). Since consumption of these meals activates expression of fatty acid transport pathways and cardioprotecive enzymes, and injection of a combination of python fatty acids found in plasma promotes physiological hypertrophy in mammalian cardiomyocytes (207), targeted fatty acid supplementation may be a novel strategy to modulate cardiac gene expression and function in heart failure .

[H2] Circadian clock and kidney functions. Oscillating molecules that regulate circadian clocks is common in most if not all animal species (208). Disruptions of the circadian clock leads to metabolic syndrome with dyslipidaemia, hyperleptinaemia, hyperglycaemia and hepatic

steatosis in *Clock*$^{-/-}$mice (209). As the circadian clock activates NRF2–gluthatione-mediated antioxidant defense pathways and arrhythmic *Clock*$^{\Delta 19}$ mice have low NRF2 expression (210), this network might have an important role in regulating energy balance and anti-oxidative protection. Circadian fluctuations are also known to affect renal blood flow, glomerular filtration, blood pressure and water and sodium excretion (211). Thus, whether CKD progression is affected by circardian disruption and the potential benefits of chronotherapy should be investigated (212). In addition, further investigations are warranted into the reasons for seasonal variations in the incidence, progression and mortality of ESRD (213).

[H2] Insights from hibernating bears. Osteoporosis, poor wound healing, vascular disease, inflammation and muscle loss, together with substantial metabolic dysfunction (**Figure 1**), are common features of the uraemic phenotype (10). The metabolism of bears is suppressed to about 25% of basal rates during hibernation (195). Nevertheless, hibernating bears tolerate extended periods of an extremely low heart rate (~10 beats/min) (214) without developing congestive heart failure, atherosclerosis (215) thromboembolic events or cardiac dilation; which are common features in CKD. The protection against vascular disease may in part be mediated by changes in the coagulation pathway, in which traditionally intrinsic cascades (initiated when blood comes in contact with exposed collagen from damaged endothelial cells) are suppressed and extrinsic tissue factor pathways (initiated by vascular wall trauma) are maintained, to prevent thromboembolic events while enabling external injuries to be healed (216).

The fact that hibernating bears do not develop azotaemia or uraemic complications (8) is remarkable, considering that they have a 90% reduction in renal blood flow, anuria (70–180 ml of urine per day is reabsorbed through the urinary bladder wall (217)), mild hypothermia (30–36°C), a 50–70% reduction in GFR, and experience fasting and immobilisation for 5–6 months of winter sleep. It is even more intriguing that females are able to give birth to cubs and nurse them during hibernation. Although a histological study in Romanian brown bears reported signs of glomerular fibrosis after awakening from wintersleep (218) the reduced renal function is normalised within weeks (8). Thus, studies of the profound metabolic changes that occur in bears from summer to winter may provide clues that point towards novel therapeutic

strategies for patients with CKD (7) (**Figure 1**). Bears and marine mammals have a reniculated kidney system (renal lobulation) (Supplementary information S5 (**figure)).** Proximal convoluted tubules in multilobulated and reniculated kidneys are comparatively short, which decreases the resistance to intraluminal flow. The large body size in combination with the limitation of length of the proximal convoluted tubules (219), seem to be the most likely explanation for multilobulation of large terrestrial and marine mammalian kidneys. Similar to the protection from hypoxia during deep dives of seals, bears might benefit from reniculated kidneys during hibernation, when their blood flow is reduced.

[H3] Applications for transplantation. Kidneys are particularly susceptible to ischaemic injury because of their high metabolic rate and oxygen consumption. Ischaemia–reperfusion injury is common in donor organs used for renal transplantation, in part due to mitochondrial dysfunction, oxidative stress, ATP depletion and apoptosis following rewarming of the donor kidney. Despite extensive and repetitive periods of low metabolism, starvation and low cardiac output (220) bears return from hibernation without signs of persisting organ damage. Hence, studying the molecular changes in hibernating bears may lead to novel pharmacological approaches that could mimic hibernation and limit organ damage during renal transplantation (220). As active suppression of metabolism during hibernation preceeds the lowering the body temperature it can be speculated that lowering the basal metabolic rate may be more effective at preventing ischaemia–reperfusion injury to the donor organ than would therapeutic hypothermia (195). Intriguingly, the metabolic switch(es) that occurs in preparation for hibernation shares features with the metabolic changes associated with longevity in the animal kingdom (discussed in further detail below) (221). Indeed, hibernating species have an approximately 15% higher annual survival rate compared with non-hibernators of similar size (222). The observation that animals initiate hibernation due to a lack of food (or other environmental cues) and not because of a lower body temperature (223), and terminate hibernation due to physiological factors (214), can guide future research on the ”metabolic switches” that induce and terminate hibernation.

On the basis of metabolic pathways that are altered in hibernation and associated with longevity approaches that might preserve organ function during transplantation could be proposed: for example, the cytoprotective gas H_2S induces a torpor-like state in mice (224), protects against lethal hypoxia (225) and as mentioned earlier activates anti-inflammatory and anti-oxidant pathways via mTOR and Nrf2 (226). Thus, H_2S treatment might confer organ cytoprotection via creation of a hibernation-like environment (238). Furthermore, injection of the AMPK agonist 5'-AMP, induces torpor independently of H_2S (227), although the mechanism underpinning this observation remains to be defined. Therefore, pretreatment of donor organs with agents that inhibit inflammatory responses and activate anti-oxidant pathways, such as H_2S gas, sirtuin agonists, mTOR inhibitors and AMPK agonists, might prevent renal ischaemia–reperfusion injury more effectively than current approaches (228) (229).

[H3] Applications for muscle wasting. The loss of skeletal muscle mass that can occur in patients with CKD is caused by a combination of sedentary behaviour , anorexia and the activation of catabolic pathways in the uremic mileu. In contrast to humans — whose muscle mass and strength may be reduced by >90% during extended periods of immobilization — hibernating black bears show minor loss in skeletal muscle cell number or size (230). One mechanism by which bears retain muscle strength is by *de novo* amino acid and protein synthesis from urea (231), coupled with a unique ability to recycle urea during hibernation that has not yet been observed in other hibernating animals (7). Metabolic recycling of nitrogenous waste products seems to be a conceivable mechanism to prevent loss of muscle protein (**Figure 5**). In addition, the skeletal muscle of hibernating bears seems more resistant to denervation than skeletal muscle of non-hibernating bears (232), suggesting that hibernation is associated with changes in the neural regulation of skeletal muscle catabolic pathways, and that targeting these pathways could offer novel solutions for the treatment of disuse atrophy .

The plasma of hibernating bears has an anti-proteolytic effect that inhibits wasting of isolated skeletal muscle (233). Serum–glucocorticoid-regulated kinase 1 (SGK1) is activated by insulin and growth factors and helps prevent loss of muscle mass via downregulation of proteolysis and autophagy and increased protein synthesis (234). As high SGK1 expression

levels have been reported in hibernating ground squirrels (235), mice lacking SGK1 have muscle atrophy (234) and low SGK1 expression levels are found in patients with CKD (236) this serine/threonine kinase may be a novel therapeutic target to prevent uraemic muscle loss. Moreover, expression levels of peroxisome proliferator-activated γ-receptor coactivator 1α (PGC1α), which activates metabolic pathways associated with endurance exercise (such as running), are induced by cold exposure (237) and are elevated in hibernating squirrels (238). This master regulator plays a major part in renal recovery from acute kidney injury through regulation of NADH synthesis (239). Hence, stimulation of PGC1α, such as through exercise (240), might also promote skeletal muscle homeostasis in CKD. Since activation of NRF2 by sulforaphane also increases endurance exercise capacity (241) , multiple targets and pathways to prevent uraemic muscle loss exist.

[H3] Applications for bone loss. In addition to being protected from muscle wasting, hibernating bears are protected from poor wound healing and osteoporosis. Unlike humans and other mammals (including small hibernating mammals), hibernating bears can withstand physical inactivity (mechanical unloading) and nutritional deprivation for ≤6 months without any negative effects on bone strength (242). Maintenance of calcium homeostasis is considered the most important contributing factor in bone health, but many other factors, such as growth hormones and cytokines, also have a role. Hibernating bears maintain eucalcemia during immobilization (8) and have decreased markers of bone resorption and formation (243), which indicates precise balancing of bone remodelling activity. The suppression of bone remodelling during hibernation is likely an important mechanism to conserve energy during a long period of inactivity, decreased renal function and fasting (204). Other contributing factors probably include the differential reglulation of gene expression and hypothalamic control of hormones involved in bone remodelling, as higher expression levels of hormones that reduce bone formation, such as cocaine and amphetamine-regulated transcript (CART) (243). An elevated expression of anabolic genes but not bone resorption genes (244), have also been reported.

Changes in vitamin D metabolism may also preserve bone mass during hibernation (245). In contrast to humans, 25(OH)D-vitamin levels do not change between seasons in bears (246)

and bear kidneys continue to produce calcitriol ($1,25(OH)_2D_3$; the active metabolite of vitamin D) despite a marked reduction in renal function during hibernation (245). Black bear parathyroid hormone activates cAMP, mitigates apoptosis in osteoblast cultures and increases trabecular bone volume (247); hence, the anabolic effects of bear parathyroid hormone might also prevent disuse osteoporosis. In addition, NRF2 was reported to have a role in bone microarchitecture in a mouse model of osteoporosis (248) and inhibits receptor activator of NF-κB ligand (RANKL)-mediated osteoclastogenesis in osteolysis-induced mice (249). Given the fact that increased NRF2 expression plays a major part in the antioxidant defences that are required for hibernation success in ground squirrels (250), the potential role of NRF2 in maintaining skeletal mass in hibernating bears warrants investigation**.** Taken together, studies of hibernating bears can provide novel therapeutic approaches for the treatment of intracellular calcium disorders and prevention of bone loss during immobilization in humans.

[H3] Applications for wound healing. Bears also have the ability to heal wounds despite immobilisation, hypothermia and anuria — conditions that are usually unfavourable for wound healing (251). Elevated levels of δ-opioid receptor agonists and ursodeoxycholic acid have been linked to the wound-healing capabilities of hibernating bears (251), but further insights into the underlying mechanisms involved might provide strategies to enhance wound healing. Changes in the coagulation pathways that occur during hibernation (216) may also contribute to better wound healing.

[H3] Applications for azotaemia. The unique ability of hibernating bears to recycle urea back into proteins not only protects the bear from muscle wasting but also from azotaemia (**Figure 5**). Since little urea is generated during hibernation (252) minimal amounts of urine need to be excreted (231). When [14C] urea and heavy water (D_2O) were administered into the bladder of hibernating bears, reabsorption of both isotopes occured across urothelia with rapid appearance in plasma (253). Although small quantities of solute and water transport across urinary tract urothelia is a feature of most mammalian species (254), the mechanism(s) by which bears accomplish this transport during hibernation remains unknown (254). One hypothesis is that the passage of recycled urea from the intestine contributes to *de novo* amino

acid synthesis, since urease-expressing gut bacteria release ammonia that can be used by the host to synthetize glutamine for protein synthesis (252). In contrast to bears, humans cannot recyle urea, and urea degradation in the human gut does not stimulate the conservation of nitrogen (255). In addition, glycerol prevents azotaemia in hibernating black bears by serving as a carbon source for *de novo* amino acid synthesis (256). As urea levels decrease in the autumn before hibernation (257), a dietary shift may contribute to this change. The metabolic regulation of fasting is, in part, mediated by the activities of sirtuin 5 (SIRT5). SIRT5 exhibits deacetylase, desuccinylase and demalonylase activities and regulates the urea cycle enzyme carbamoyl phosphate synthetase 1 (CPS1) in liver mitochondria. Since *Sirt5*$^{-/-}$ mice fail to upregulate CPS1 and exhibit hyperammonaemia during fasting (258), this implies a role for SIRT5 in urea metabolism and the metabolic regulation of fasting. Thus, the long-term effects of sirtuin activators, such as resveratrol, on urea handling should be tested in patients with CKD.

[H3] Protective compounds in berries. Bears can ingest up to 200,000 berries per day in peak season, which occurs in late summer (259). There is a synchronous timing of food resources that triggers to switch from salmon to berries during the summer (260). Blueberries have potent anti-inflammatory and anti-oxidant properties (for example, through the actions of phenol-like antioxidants) and contain anthocyanins . Berries are also an important source of sirtuin agonists (such as pterostilbene and resveratrol), quercetin, vitamin K, vitamin C and fibers. In addition, berries contain fructose and linolenic acid that may stimulate fat storage in preparation for hibernation. Polyphenols are secondary metabolites in plants that are needed not only for plant growth but also as a defense mechanism against UVB exposure and agression by insects and fungal pathogens (261). In a mouse model of polygenic obesity, consumption of berries results in a shift in gut microbiota towards obligate anaerobes, which correlates with a decrease in gastrointestinal luminal oxygen and oxidative stress (262). Potential implications on human health of the nearly anoxic conditions observed in the mouse gut lumen after berry consumption should be investigated.

In addition, resveratrol preserves bone mass in old male rats (263), anthocyanins in berries increases serum alkaline phosphatase levels in obese male mice (264) and the

anthocyanin delphinidin inhibits excessive osteoclastogenesis in a mouse model of osteoporosis (265). Notably, delphinidin also prevents muscle atrophy in mice (266) and lowers fasting glycaemia in prediabetic individuals (267). Moreover, dietary supplementation with anthocyanins isolated from roselle (*Hibiscus sabdarrifa*) attenuated progression of adenine-induced CKD in rats (268). Since a causal role for senescent cells in ageing-related bone loss has been demonstrated in mice (269) nutritional compounds with senolytic effects , such as quercetin and fisetin (270) — found in fruits, capers, vegetables and berries — may also contribute to the capacity of bears to maintain their bone mass (242). Quercetin also blocks phosphate-induced apoptosis and VSMC calcification via inhibition of mitochondrial fission and oxidative stress (271). As polyphenols that stimulate sirtuins and PGC1α prevent muscle wasting induced by mechanical unloading (272) or in streptozotocin-induced diabetes in rats (273), their long-term effects should be tested in patients with CKD who experience muscle wasting. Resveratrol and grape seed proanthocyanidin extract facilitate VEGF expression and angiogenesis in different wound models (274). Hence, the long-term effects of sirtuin activators and antocyanins on wound healing require further investigation. In healthy humans and patients with the metabolic syndrome, blueberry supplementation decreases cardiovascular risk factors (275), increases HDL–cholesterol (276) and improves insulin sensitivity (277). Moreover, a study based on validated food-frequency questionnaires in 93,600 women (Nurses Health Study) showed that a high intake of anthocyanins (highest versus lowest quintile) was associated with a decreased risk of myocardial infarction (278). Finally, since many plants that are consumed by bears contain melatonin (279) the effect of plants, such as tall fescue (*Setvca arundinaces*), on the metabolic changes that occur between seasons in hibernating bears should be investigated further. Taken together, the potential beneficial effects of berries and other plants on the uraemic phenotype should be assessed.

[H1] Conclusions

Species living in extreme habitats have acquired adaptive mutations through natural selection and epigenetic calibration to survive in challenging environments. Environmental factors and stressors - such as infections, toxins, starvation, climate change and psychosocial factors - have modified the epigenetic landscape throughout evolution to enable dynamically responsive

changes in gene expression and associated biochemical networks to help mitigate the effects of these changes (75). Although humans have a common ancestry with mammals and share the same vulnerability to infections, environmental toxins and illnesses, most physicians have regarded animal diseases as different and of minor interest in the understanding of complex human diseases. However, almost all diseases that affect humans have an equivalent in the animal kingdom, although treatment options may differ. Thus, we propose a multidisciplinary approach to improve health care of patients with CKD by sharing new discoveries and tools from the fields of zoology, botany, ecology, veterinary medicine, anthropology and biology.

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Author contributions

P.S. and R.J.J. launched the idea of studying renal biomimetics. P.S., J.P., M.K., M.L., W.A., T.R., P.G.S. and R.J.J. researched the literature, discussed the article's content and wrote the text. All authors reviewed or edited the article before submission.

Competing interests

P. S. received grants and honararia from Baxter, Bayer, Astra Zeneca, Bristol-Myers Squibb, Pfizer, Akeiba and Corvidia. M. K. has received grants and honararia from Bayer, Astellas, Bristol-Myers Squibb and Kissei Pharmaceuticals. R.J.J. has grants from the National Institute of Health, Department of Defence and the Veteran's Administration. He also is a member of Colorado Research Partners, LLC that is developing inhibitors of fructose metabolism. The other authors declare no competing interests.

Publisher's note

Key Points

• Biomimetic studies of non-laboratory wild animals are useful for identifying mechanisms that protect or increase susceptibility to disease.

• Domestic and captive felids are vulnerable to chronic kidney disease (CKD), supporting the hypothesis that a high-protein intake — particularly from red meats and in combination with dehydration — is nephrotoxic.

• Extreme models of ageing, such as Hutchinson–Gilford Progeria syndrome and the naked mole rat, can be used to investigate the mechanisms of vascular progeric processes in CKD.

• Current evidence suggests that elevated serum phosphate levels promote ageing and cellular senescence.

• The transcription factor NRF2 may offer protection against diseases in extreme environmental conditions and may promote longevity in the animal kingdom; NRF2 agonists (such as resveratrol and sulforaphane) might improve the uraemic complications of CKD.

• Lipid composition of membranes has a role in seasonal acclimatization of metabolic activities in the animal kingdom.

• Hibernating wild bears with anuria are protected against many of the complications observed in humans with CKD, such as muscle wasting, osteoporosis and azotaemia; future studies should investigate the mechanisms behind these protective effects.

Box 1: The cytoprotective effects of the transcription factor NRF2

The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) upregulates the expression of cell-detoxifying enzymes in response to oxidative stress. Activators of NRF2 induce structural changes in Kelch-like ECH-associated protein 1 (KEAP1), which allows nuclear translocation of NRF2. In the nucleus, NRF2 initiates the transcription of >250 target genes, such as haemoxygenase, catalase and glucose-6-phosphate 1-dehydrogenase, which are important for antioxidant defences, through binding to antioxidant response elements (see the figure).

Nrf2-knockout mice have increased susceptibility to kidney damage. As impaired NRF2 activation is observed in renal fibrosis, focal segmental glomerulosclerosis and hypertensive kidney disease, NRF2-targeting therapies should be of interest for the study of CKD progression. Patients on haemodialysis have downregulated levels of NRF2 coupled with an upregulation of nuclear factor κB (NF-κB) (280), and display a phenotype characterized by persistent systemic inflammation (81) and increased oxidative stress (281). Given the potential contribution of a repressed NRF2 system in premature ageing, both synthetic compounds, such as bardoxolone methyl (282) and natural nutrigenomic compounds , such as sulforaphane (283), pomegranate polyphenols (284), curcumin (285), ethanol extract of *Alisma orientale* tubers (286) and cinnamon polyphenols (287) that restore NRF2 expression could slow progression and ageing-related CKD (288). Indeed, since sulforaphane (found in broccoli) inhibits restenosis by suppressing inflammation and proliferation of VSMCs in a carotid injury model (289) it has been suggested that dietary activators of NRF2 inhibit atherogenesis (290). Moreover, sulforaphane suppresses NRF2-mediated hepatic glucose production and attenuates exaggerated glucose intolerance by an order of magnitude similar to that of metformin in patients with type 2 diabetes mellitus (T2DM) (283). However, forced overexpression of NRF2 might not always be enough to restore adaptive responses (291). For example, the potent NRF2 agonist bardoxolone methyl increases the risk of heart failure compared with placebo in a clinical trial with patients with T2DM and stage 4 CKD (292), which highlights potential limitations of manipulating transcription factors. Although activation of NRF2 leads to improved anti-oxidant defences, whether this effect is independent of any influence on mitochondrial dynamics remains to be

determined. Sulforaphane, for example, modulates the KEAP1–NRF2 antioxidant element response signalling pathway, yet is a NRF2-independent inhibitor of mitochondrial fission (293). Whether such an effect for bardoxolone contributed to its failure due to excess mortality (292) remains to be proven. In future clinical trials of bardoxolone methyl, attention should be given to the dose-dependent effects on CKD progression (294). Whereas too little NRF2 activity can result in loss of cytoprotection, diminshed β-oxidation of fatty acids and lower antioxidant capacity, too much NRF2 activity may perturb the homeostatic balance and promote overproduction of reduced glutathione and nicotinamide adenine dinucleotide phosphate (NADPH) (295) .

Figure 1: Novel insights to treatment strategies of CKD from studies of wild animals. Several species in the animal kingdom have developed protective mechanisms against environmental stresses, and studying these mechanisms can provide insights into novel approaches to chronic kidney disease (CKD). For example, despite a long period of immobilization during hibernation, bears do not develop azotaemia, osteoporosis, thrombosis, atherosclerosis and muscle wasting, which could provide clues for better organ preservation. Naked mole rats (*Heterocephalus glaber*) are protected from oxidative stress, which could help to develop strategies to prevent or slow down premature ageing. As weddel seals (*Leptonychotes weddellii*) are protected against prolonged episodes of kidney ischaemia, they could provide insights to prevent acute kidney injury. Vampire bats (*Desmodus rotundus*) are protected against the consequences of a high-protein intake, whereas felids (such as tigers) are particularly susceptible to CKD, most likely due to their high intake of red meat.

Figure 2: Effect of red meat intake on kidney functions. Epidemiological studies suggest that red meat (but not other sources of protein) promotes chronic kidney disease (CKD). Several factors have been proposed to be implicated in the disease-promoting effects of a diet rich in red meat. Besides hyperfiltration due to a high-protein load (causing a haemodynamic insult), elevated levels of trimethylamine-*N*-oxide (TMAO) generated from gut microbiota and the metabolism of trimethylamine (TMA) in the liver could contribute to CKD via renal fibrosis and indirectly via atherosclerosis. Additional pathophysiological mechanisms linking a high intake of red meat to cardiovascular disease, cancer and CKD have been reported. Increased intake of salt, phosphate (PO_4), saturated fats, acid production, haeme iron, uric acid, nucleic acids and *N*-nitroso compunds with a high consumption of red meat may also contribute to the observed associations between increased red meat consumption and CKD. The intestinal microbiome represents a new potential therapeutic target for the prevention of CKD and for treatment of cardio-metabolic complications in CKD.

Figure 3: Extreme models of ageing with a marked discrepancy between chronological and biological age can be used to learn more about progeric processes in CKD. Children with the rare Hutchinson–Gilford progeria syndrome (HGPS) express truncated lamin (progerin) that

mediates premature ageing, especially in the cardiovascular system, resulting in premature death from stroke or myocardial infarction. On the other hand, naked mole rats undergo negligible senescence and can live for >30 years without signs of cardiovascular ageing. Integration of data from these two extreme models of ageing can reveal detailed mechanisms of the progeric phenotype. A high biological age is characterized by a premature ageing phenotype; which includes vascular stiffness, frailty, osteoporosis, sarcopenia, as well as high levels of inflammation, carbonylation and oxidative stress. CKD, chronic kidney disease; SASP, senescence-associated secretory phenotype.

Figure 4: Strategies to increase life span, protect organs and avoid renal ischaemia–reperfusion injury. Premature cardiovascular death and vascular progeria are prominent features of CKD. Based on insights from long-lived animals and basic research, several treatment strategies have been identified that could be tested for their effect on longevity. Activation of the cytoprotectant functions of hydrogen sulphide (H_2S), via restriction of the sulphur-containing amino acid methionine, is of major interest. Other potential treatment strategies that activate anti-inflammatory and anti-oxidant pathways include dietary restriction, senotherapies, sirtuin (NAD^+-dependent protein deacetylases) agonists, 5'-AMP-activated protein kinase (AMPK) agonists, mechanistic target of rapamycin (mTOR) agonists, extracellular secretory vesicles and H_2S-releasing salts. Studies suggest that activation of mTOR and nuclear factor (erythroid-derived 2)-like 2 (NRF2) signalling by such therapies may increase longevity, aid organ protection and decrease the risk for renal ischaemia and reperfusion injuries. Because hibernation shares some features and pathways associated with longevity, it can also be speculated that hibernation depends on these pathways.

Figure 5: Nitrogen metabolism in hibernating bears. To conserve mobility and muscle strength, hibernating bears minimize muscle protein loss and re-utilize the vast majority of urea produced, which is mediated by microbial ureolysis and urea-N resorption. Multiple mechanisms are responsible for the reduction in serum urea levels during hibernation. Lower urea production during hibernation leads to reduced amino acid degradation. Moreover, urea is

reabsorbed from urine via solute and water channels, such as urea transporters and aquaporin channels, in a leaky bladder wall. The reabsorbed urea is believed to be recycled back into skeletal muscle. Urea is also hydrolyzed by urease-expressing gut bacteria into ammonia, which is used by enterocytes to synthetize glutamine for incorporation into proteins. Other factors that may prevent muscle loss in hibernating animals include activation of peroxisome proliferator-activated γ-receptor coactivator 1α (PGC1α), for example by cold environmental temperature and the low-energy state, and serum-glucocorticoid kinase 1 (SGK1). Urea levels decrease in the autumn when food is still available, and the metabolic changes that determine urea metabolism may occur already before the bear enter hibernation. Since sirtuin (SIRT) stimulators, such as polyphenols in berries and plants, stimulate carbamoyl phosphate synthetase 1 (CPS1), which is the first and rate-limiting step of the urea cycle, this may decrease urea generation and prepare the animal for low urine output during hibernation.

Table 1: Selected animal models that are useful for comparative physiology studies.

Species/family	Area	Mechanisms and possibilities
Naked mole rat (*Heterocephalus glaber*)	*Gerontology* *Nephrology* *Oncology* *Cardiology*	These animals have developed protective mechanisms against cancer, hypoxia, cardiovascular ageing and oxidative stress (high NRF2 expression levels).
Vampire bat (*Desmodus rotundus*)	*Nephrology*	Blood-ingesting bats have a very high intake of proteins, which causes azotaemia (high serum urea levels). Studies of vampire bats may help to better understand how kidneys can be protected against protein overload.
Ursidae family (bears)	*Nephrology* *Endocrinology* *Cardiology* *Orthopedics* *Transplantology*	Bears do not develop insulin resistance during summer despite a 25-50% accumulation in body weight (fat mass) from spring to autumn. Moreover, despite prolonged fasting, anuria and immobilisation during hibernation, bears are protected from muscle wasting, pressure ulcers, thrombotic complications and osteoporosis. Studies of hibernating bears may help identify novel strategies to handle and prevent these complications as well as better ways of organ preservation.
Felidae family (cats)	*Nephrology*	Domestic and captive felids have a high incidence of CKD. As members of this family are obligate carnivores, studies of felids may provide information on links between red meat consumption, gut microbiota and renal disease.
Phocidae family (seals)	*Nephrology*	Seals can survive prolonged asphyxia during underwater dives up to 120 min. Although their kidneys are subjected to prolonged vasoconstriction during diving, seals do not develop acute kidney injury.
Elephantidae family (elephants)	*Oncology*	The risk of elephants developing cancer is only 5% compared with 25% in humans, although they have 100x as many cells. This protection may be due to the 20 copies of the tumour suppressor gene *TP53,* whereas humans only have 1 copy (2 alleles).
Chimpanzee (*Pan troglodytes*)	*Pharmacology*	Chimpanzees have developed ways to protect themselves against pathogens by

		self-medicating with various plant leaves. Since one of these plants (thiarubine A) contains an antibiotic, systematic studies of these plants may help us find novel antibiotics.
Trochilidae family (hummingbirds)	*Diabetology*	Hummingbirds can switch their energy source from glucose to fructose, which maximizes fat storage and optimizes energy use to power their high-energy lifestyle (their heart rate can reach >1200 beats/min). Despite hyperglycaemia, they do not seem to develop diabetic complications.
Testudine family (turtles)	*Neurology*	Turtles have a high anoxic tolerance and studies of these animals may help scientists to develop novel therapeutic strategies for cerebral ischaemia.
Wood frog (*Lithobates sylvaticus)*	*Physiology*	Frozen wood frogs have 10–13-fold higher glucose concentrations in muscle and heart than other frog species that have been frozen in the laboratory and have natural antifreeze glycolipids in muscle and internal organs to protect their cells. These mechanisms help them to survive over-wintering in average temperatures of -6.3°C (minimum -18.1°C) between October and May in the interior of Alaska. Studying wood frogs can help to understand limits to freezing tolerance.

Glossary terms

Uraemic phenotype
This phenotype includes several physical characteristics, such as vascular stiffness, sarcopenia, frailty, osteoporosis and left ventricular hypertrophy.

Chronic tubulointerstitial fibrosis
Diseases that affect the physiology of non-glomerular structures (tubules and/or the interstitium) in the kidney.

Glomerular haemodynamics
Regulation of efferent and afferent glomerular arteriolar resistance required to maintain a stable GFR.

Urinary specific gravity
A urine specific gravity test compares the density of urine to that of water.

N-nitroso compounds
Compounds found in processed meat and are formed endogenously from the intake of nitrite and nitrate.

Telomere attrition
Telomeres are the protective end caps of chromosomes. Attrition, or shortening, of telomeres is a form of tumour supression and may be due to inflammation, oxidative stress as well as exposure to infectious agents, resulting in limited stem cell function, regeneration and organ maintenance during ageing.

Uraemic milieu
The toxic internal milieu in patients with uraemia is characterized by accumulation of uraemic toxins and waste products that promote inflammation, oxidative stress, carbonylation, calcification and endothelial dysfunction.

Senescent cells
Cellular senescence is an irreversible cell cycle arrest mechanism that acts to protect against cancer. Senescent cells also have a role in complex biological processes, such as development, tissue repair, and age-related disorders.

Hypercapnia
Abnormally elevated carbon dioxide (CO_2) levels in the blood.

High molecular weight hyaluronan
A high-molecular-weight polysaccharide found in the extracellular matrix, especially in soft connective tissues.

Antagonistic pleiotropy

Scenarios in which one gene contributes to multiple traits, whereby at least one of these traits is beneficial and at least one is detrimental to the organism's health.

PO_4 appetite
A well-documented behaviour in animals that is induced by phosphate deficiency, which is especially common amongst herbivores.

Protein–energy wasting
A process characterized by a decline in body protein mass and energy reserves, including muscle and fat wasting and loss of visceral proteins. Protein energy wasting is often associated with inflammation and is a strong predictor of mortality.

Caloric restriction
A reduction in calorie intake without incurring malnutrition or a reduction in essential nutrients. In a variety of species, such yeast, fish, rodents and dogs, calorie restriction has been shown to slow the biological ageing process.

Sirtuin
Sirtuins (or NAD^+-dependent histone deacetylases) are a class of proteins that possess deacylase activity and regulate important biological pathways and cellular processes, including ageing, inflammation, transcription and apoptosis. Sirtuin agonists include pterostilbene and resveratrol.

Transsulfuration pathway
A metabolic pathway that involves the interconversion of homocysteine and cysteine via the intermediate cystathionine.

Protein sulfhydration
A post-translational modification that increases the catalytic activity of proteins. Physiological actions of sulfhydration include the regulation of endoplasmic reticulum stress signalling, inflammation and vascular tension.

One-carbon methyl donor units
DNA methylation influences the expression of some genes and depends upon the availability of methyl groups. Dietary methyl groups are derived from food sources that contain methionine, one-carbon units, choline or betaine (a choline metabolite).

Torpor
A state of reduced body temperature and metabolic rate in animals that enables them to survive periods of reduced food availability.

Circadian clock

The circadian clock regulates the internal and external activities of organisms, such as sleep and changes in metabolism, based on the day–night cycle.

Chronotherapy
The science of timing drugs according to the circadian clock. This approach is used in various clinical conditions, such as cancer, hypertension, seasonal affective disorder and bipolar disorder.

Renal lobulation
Carnivores and most small mammals have smooth-surfaced and uni-pyramidal kidneys, whereas primates and Suidae (hogs and pigs) have a smooth-surfaced and multi-pyramidal kidney system. Large terrestrial mammals have multi-lobulated and multi-pyramidal kidneys to keep the proximal convoluted tubules short. Most marine mammals and bears have each lobe separated into renules (reniculated kidney system).

Therapeutic hypothermia (also known as targeted temperature management).
The induction of mild hypothermia (32–35°C) after cardiac arrest for neuroprotection.

Sedentary behaviour
A type of behaviour that is characterized by an energy expenditure ≤1.5 metabolic equivalents while in a lying, reclining or sitting posture. Typical sedentary behaviours include watching TV, computer work, driving and reading.

Denervation
Loss of nerve supply to a part of the body, which can be due to multiple causes, such as surgery, physical injury, chemical toxicity or diseases.

Disuse atrophy
A type of muscle atrophy that occurs when a muscle is less active than usual. Disuse atrophy is a common feature in chronic debilitating diseases and immobility.

Mechanical unloading
A mechanical manoeuvre or therapy that decreases tissue growth and regeneration. Whereas mechanical loading of mammalian tissues is a potent promoter of tissue growth and regeneration, mechanical unloading in microgravity causes reduced tissue regeneration via stem cell tissue progenitors.

Eucalcaemia
The maintenance of normal and constant serum calcium levels.

Blueberries
Blueberries comprise all blue-coloured berries of the vaccinum genus, of which the most common is bilberries. Blueberries have a low glycaemic index and are a rich source of fibers,

vitamin K, manganese, >15 different anthocyanins (especially delphinidin and malvidin), quercetin, myricetin and resveratrol.

Anthocyanins

Anthocyanins (>600 molecular structures) belong to a class of molecules called flavonoids that are universal plant colorants responsible for the red, purple and blue colours in many fruits, berries, vegetables and flowers. Due to their contribution in multiple physiological activities, the consumption of these molecules is believed to have a substantial role in preventing lifestyle-related diseases.

Senolytic effects

Senolytic compounds selectively induce the death of senescent cells.

Nutrigenomic compounds

Bioactive nutrients that have an effect on or interact with the genome. Nutrigenomics also encompasses the effect of genetic variations on the absorption, metabolism, elimination or biological effects of various nutrients.

Biographies

• Peter Stenvinkel serves as a full professor and senior lecturer at Dept. of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden. He received hos MD and PhD from the Karolinska Institutet. His major research interests are vascular aging in CKD, risk factors for protein energy wasting and vascular calcification, inflammation, obesity in CKD, epigenetics and biomimetics.

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• Miguel A. Lanaspa is an Associate Professor of Medicine at the University of Colorado. He received his DVM and PhD from the University of Zaragoza, Spain. His research interest focus on the role of dietary and endogenously produce fructose in the development and progression of metabolic syndrome and kidney disease. He has also particular interest in the understanding of the interplay between nucleotide turnover and purine degradation in leptin signaling and food craving in hibernating animals.

• Walter Arnold is full professor at the University of Veterinary Medicine, Vienna, and head of the Research Institute of Wildlife Ecology. He received his PhD from the University of Munich, Germany. His major research interest is the ecology-physiology nexus. He studies in various large mammals, energetics, thermoregulation, seasonal acclimatization, hibernation, seasonal and circadian rhythms, and the physiological functions of polyunsaturated fatty acids.

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• Richard Johnson is a Professor of Medicine at the University of Colorado who practices clinical medicine as well as performs basic and clinical research on kidney disease, hypertension and diabetes, with a special interest in sugar (especially fructose) and uric acid. He has an interest in comparative physiology, climate change and the emerging epidemics of kidney disease worldwide.

TOC blurb

Some animals have developed mechanisms to protect them from environmental stresses, whereas others remain susceptible. Here, Stenvinkel et al. discuss how a better understanding of susceptibility and protective mechanisms could provide insights to novel strategies for the prevention and treatment of several human diseases, such as chronic kidney disease and ageing-associated complications.

Subject ontology

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