REVIEW

Novel insights on the effect of sclerostin on bone and other organs

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Abstract

As a key regulator of bone homeostasis, sclerostin has garnered a lot of interest over the last two decades. Although sclerostin is primarily expressed by osteocytes and is well known for its role in bone formation and remodelling, it is also expressed by a number of other cells and potentially plays a role in other organs. Herein, we aim to bring together recent sclerostin research and discuss the effect of sclerostin on bone, cartilage, muscle, liver, kidney and the cardiovascular and immune systems. Particular focus is placed on its role in diseases, such as osteoporosis and myeloma bone disease, and the novel development of sclerostin as a therapeutic target. Anti-sclerostin antibodies have recently been approved for the treatment of osteoporosis. However, a cardiovascular signal was observed, prompting extensive research into the role of sclerostin in vascular and bone tissue crosstalk. The study of sclerostin expression in chronic kidney disease was followed by the investigation of its role in liver–lipid–bone interactions, and the recent discovery of sclerostin as a myokine prompted new research into sclerostin within the bone–muscle relationship. Potentially, the effects of sclerostin reach beyond that of bone alone. We further summarise recent developments in the use of sclerostin as a potential therapeutic for osteoarthritis, osteosarcoma and sclerosteosis. Overall, these new treatments and discoveries illustrate progress within the field, however, also highlight remaining gaps in our knowledge.

Key Words

- sclerostin
- Wnt signalling
- therapeutic
- bone

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Introduction

Sclerostin is a 22 kDa secreted glycoprotein encoded by the *SOST* gene. It is primarily expressed by osteocytes and plays a major role in bone homeostasis, affecting bone formation and bone remodelling through its role as a negative regulator of the Wnt/β-catenin signalling pathway (reviewed by Holdsworth *et al.* 2019). Sclerostin achieves this through inhibition of wingless-related integration site (Wnt)–ligand interaction with low-density lipoprotein receptor protein 4/5/6 (LRP4/5/6) Wnt co-receptors (Leupin *et al.* 2011, Holdsworth *et al.* 2012). Changes in sclerostin expression mediates its function as a negative regulator of bone formation: *SOST* overexpression results in decreased bone formation, mass and strength, whereas disruption of sclerostin function or expression results in high bone mass conditions (Balemans *et al.* 2001, Van Wesenbeeck *et al.* 2003, Winkler *et al.* 2003, Loots *et al.* 2005, Niziolek *et al.* 2015, Zhang *et al.* 2016, Kim *et al.* 2017*a*). Thus, it is crucial that we continue to investigate this fascinating protein to better understand its biology and to provide future therapeutic options for disease modification.

The current review examines recent literature and expands on the earlier Holdsworth *et al.* (2019) review, which examined the structure and biological function

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of sclerostin as well as its role in disease (Holdsworth *et al.* 2019). We explore recent progress made in our understanding of both sclerostin biology and its mechanism of action in the skeleton and beyond (Fig. 1). We also examine recent evidence for its potential as a therapeutic and highlight areas where further research could expand our current understanding of this protein.

The Wnt/β-catenin signalling pathway

Wnt inhibitors such as sclerostin and Dickkopf-related protein 1 (DKK1) elicit their biological effects through interaction with the Wnt/β-catenin signalling pathway, which has been reviewed extensively and will not be discussed in depth herein (Ke *et al.* 2012, Nusse & Clevers 2017). Briefly, canonical Wnt signalling occurs via an autocrine or paracrine fashion presenting in either an on or off state (Fig. 2). The signalling cascade is activated when extracellular Wnt interacts with LRP5/6 and frizzled family (FZD) cell surface receptors, forming a ternary complex. This results in phosphorylation of the LRP5/6 cytoplasmic domain and subsequent translocation via recruitment of the destruction complex consisting of axin, dishevelled (DVL), adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1). Localisation to the cellular membrane disrupts the destruction complex activity, allowing non-phosphorylated β-catenin to accumulate in the cytoplasm. Here it is translocated to the nucleus to initiate transcription of Wnt target genes through interaction with TCF/LEF transcription factors (Ke *et al.* 2012, Nusse & Clevers 2017). The Wnt signalling pathway is switched to its off state when Wnt antagonists such as sclerostin and DKK1 interact with LRP5/6 surface receptors, preventing Wnt LRP5/6 interaction and subsequent formation of the Wnt/FZD/LRP5/6 ternary complex (Semënov *et al.* 2001, Ai *et al.* 2005, Balemans *et al.* 2008, Choi *et al.* 2009, Holdsworth *et al.* 2012, Ke *et al.* 2012, Bullock *et al.* 2019). The destruction complex remains active and ubiquitinates cytoplasmic phosphorylated β-catenin for degradation by the proteasome. β-catenin does not translocate to the nucleus, and Wnt target gene transcription is repressed due to the association of Groucho instead of β-catenin with TCF/LEF (Nusse & Clevers 2017).

Sclerostin and bone

Activation of the Wnt/β-catenin signalling pathway promotes mesenchymal cell differentiation into preosteoblasts and subsequent osteoblasts, which lay down an organic matrix that is mineralised to form bone (reviewed by Holdsworth *et al.* 2019). Osteoblasts either remain on the bone surface as quiescent bone lining cells, undergo apoptosis or become embedded in the bone matrix to eventually become osteocytes, the primary source of sclerostin in the adult skeleton (Poole *et al.* 2005, Capulli *et al.* 2014). In addition to negatively regulating the above processes, sclerostin contributes to

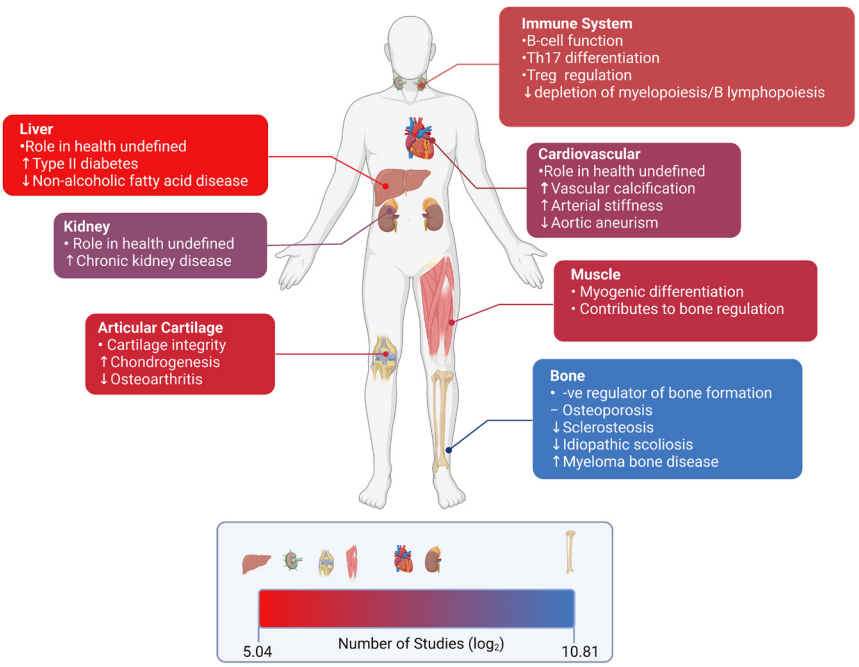

Figure 1
Current knowledge on the role of sclerostin in the body. Primary research article searches of sclerostin and tissue type published between 2001 and 2022 were carried out on PubMed with review articles excluded. The number of hits were converted into log base 2 to generate a scale, with hits for each tissue highlighted on the scale. Arrows in the tissue detail boxes indicate direction of altered sclerostin levels in disease with colour of box reflecting the volume of data published based on the scale generated. The number of studies per tissue excluding review articles: bone (2312), kidney (282), cardiovascular (213), muscle (115), cartilage (88), immune system (61) and liver (44). Created with https://www.biorender.com/.

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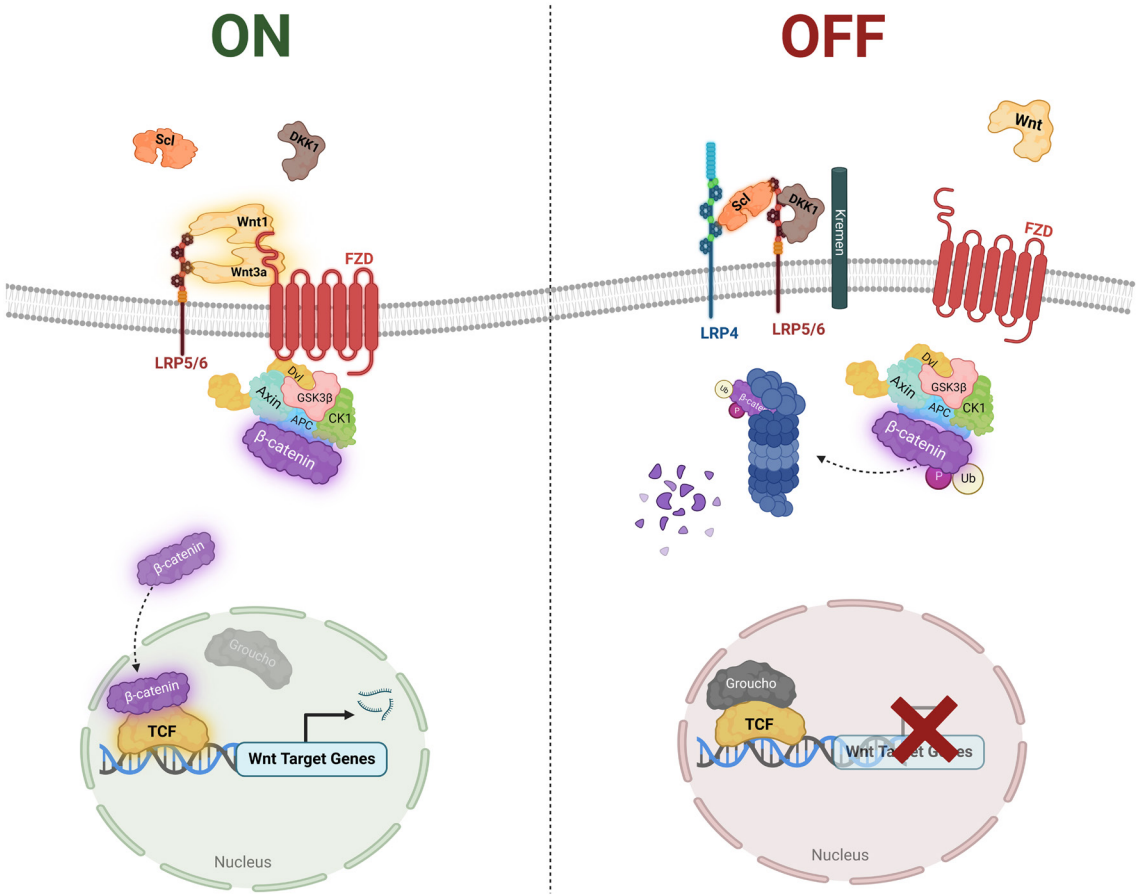

Figure 2
Wnt/β-catenin signalling pathway. During the 'on' state of the pathway, Wnt binds to LRP5/6, resulting in localisation of the destruction complex to the membrane and disruption of destruction complex activity. Non-phosphorylated β-catenin accumulates in the cytoplasm and is translocated to the nucleus where it interacts with TCF/LEF to initiate transcription of Wnt target genes. During the 'off' state, sclerostin (Scl) binds to LRP4/5/6 and DKK1 interacts with LRP5/6 and Kremen, preventing Wnt from interacting with the Wnt receptors. Phosphorylated β-catenin is ubiquitinated by the destruction complex for degradation by the proteasome, resulting in repression of Wnt target gene expression. Created with https://www.biorender.com/.

maintaining the bone lining cells in a quiescent state and inhibits differentiation of late osteoblasts into osteocytes via inhibition of canonical Wnt signalling (Atkins *et al.* 2011, Kim *et al.* 2017*b*, Hong *et al.* 2022). Sclerostin also plays an important role in the regulation of bone marrow adiposity and bone marrow adipose tissue (reviewed by Holdsworth *et al.* 2019). Furthermore, sclerostin indirectly affects bone resorption by upregulating osteocyte-expressed receptor activator of nuclear factor-κB ligand (RANKL), an essential cytokine for osteoclast development and activity, and decreasing expression of osteoprotegerin (OPG), a decoy receptor for RANKL, in mature osteoblasts and osteocytes, thereby increasing osteoclastogenesis (Simonet *et al.* 1997, Glass *et al.* 2005, Nakashima *et al.* 2011, Wijenayaka *et al.* 2011). Indeed, administration of anti-sclerostin antibodies to oestrogen-deficient osteocytes decreases osteoclastogenesis and resorption, highlighting the importance of sclerostin in the upregulated pro-osteoclastogenic signalling between osteocytes and osteoclasts in the absence of oestrogen (Allison *et al.* 2020). Moreover, the presence of osteoclasts in trabecular bone reduces sclerostin expression in osteocytes, suggesting that osteoclast-mediated reduction in sclerostin facilitates trabecular bone formation (Koide *et al.* 2020). Overall, these results demonstrate the importance of sclerostin in modulating the RANKL/OPG ratio, a major determinant of bone mass and strength (reviewed by Holdsworth *et al.* 2019).

Osteoporosis

Postmenopausal (type I) osteoporosis is the most common form of the disease and is characterised by increased bone fragility and susceptibility to fractures. These symptoms

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result from low bone mass and reduced bone structural integrity caused by aging and menopause-related decrease in oestrogen levels, which has been shown to increase sclerostin expression (Dobbs *et al.* 1999). Despite this link, studies have shown serum and bone sclerostin levels to be positively correlated with bone mineral density (BMD) in osteoporosis, which may be explained by the decreased osteocyte number in low BMD disorders such as osteoporosis (Ueland *et al.* 2019, Gorter *et al.* 2022). Osteoporosis is treated with either antiresorptive or bone-anabolic drugs. The major antiresorptives are bisphosphonates and denosumab, a humanised monoclonal anti-RANKL antibody (Storm *et al.* 1990, Pols *et al.* 1999, McClung *et al.* 2006, Brown *et al.* 2009, Baron *et al.* 2011). The anabolic agents teriparatide (parathyroid hormone (PTH) 1-34) and abaloparatide (parathyroid hormone-related protein (PTHrP) 1-34) are used in patients with more severe and established osteoporosis (Yu *et al.* 2014, Leder *et al.* 2015, Eastell *et al.* 2019). In 2019, an additional anabolic agent, romosozumab (EVENITY™), was approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating postmenopausal women at a high risk of osteoporotic fractures. Romosozumab, a humanised monoclonal anti-sclerostin antibody, blocks sclerostin-mediated Wnt inhibition, resulting in increased bone formation whilst inhibiting bone resorption. Phase III clinical trials have shown therapeutic effectiveness in reducing fractures in elderly osteoporotic patients (Cosman *et al.* 2016, Saag *et al.* 2017, Lewiecki *et al.* 2018). However, there are concerns regarding the effect of romosozumab on the cardiovascular system (discussed in more detail later in this review). Alternative anti-sclerostin antibodies are also in various stages of development including setrusumab, a sclerostin neutralising human IgG2λ monoclonal antibody which is being investigated for the treatment of moderate osteogenesis imperfecta and hypophosphatasia (Glorieux *et al.* 2017, Seefried *et al.* 2017). Additionally, blosozumab, a recombinant humanised antibody, has shown promising results as a potential treatment for postmenopausal osteoporosis and is currently in phase I clinical trials in China (Recker *et al.* 2015).

Idiopathic scoliosis

Idiopathic scoliosis (IS) is a low bone mass disorder often characterised by spinal deformities (Cheng *et al.* 2007). Zhang *et al.* reported lower *SOST* gene expression and serum sclerostin levels that were negatively correlated with plasma miRNA-145 in adolescent IS (AIS), the most common type of scoliosis (Zhang *et al.* 2018). Moreover, osteocyte secretion of sclerostin was reduced in AIS patients due to reduced osteocyte numbers as well as augmented osteocyte function caused by aberrant miRNA-145/β-catenin expression. Overactive canonical Wnt signalling in IS inhibits osteoblast differentiation to osteocytes and negatively affects matrix mineralisation in AIS instead of yielding the expected high bone mass phenotype (Rodda & McMahon 2006, Regard *et al.* 2011). This defect in mineralisation results in inferior bone mechanical properties which might increase the susceptibility of bone to asymmetrical forces, leading to spinal column deformities (Vasiliadis *et al.* 2021). Vasiliadis *et al.* hypothesised that stimulating osteocyte sclerostin secretion and restoring normal function of the Wnt/β-catenin signalling pathway during growth could, in theory, increase bone strength and prevent deterioration of the scoliotic deformity. However, Zhang *et al.* noted that further study of osteoclastogenesis and osteoclast resorption activity is required to give a more comprehensive picture of bone remodelling in AIS (Zhang *et al.* 2018). Further investigation of miRNA-145 effects on osteoblast and osteocyte development and function may provide clarity on AIS-related changes in *SOST* expression.

Myeloma bone disease

Myeloma bone disease (MBD) is characterised by a plasma cell malignancy that forms in the bone marrow, often leading to severe bone destruction, pathological fractures, osteolytic bone lesions and debilitating bone pain (Delgado-Calle *et al.* 2014, Paton-Hough *et al.* 2019). The condition is caused by imbalance and uncoupling of the bone-remodelling process, whereby sclerostin is suggested to contribute to increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation (Paton-Hough *et al.* 2019). Indeed, MBD patients have increased serum sclerostin, correlating with disease stage and degree of bone destruction (Eda *et al.* 2016). The source of this sclerostin is contentious, with multiple studies reporting that multiple myeloma (MM) cells secrete sclerostin with other osteoclast activating factors and osteoblast inhibitory factors, including DKK1 in the bone marrow micro-environment (Tian *et al.* 2003, Brunetti *et al.* 2011, Colucci *et al.* 2011, Habibi *et al.* 2013, Eda *et al.* 2016). Conversely, McDonald *et al.* reported that *SOST* was not expressed in MM cells isolated from myeloma patients or in numerous myeloma cell lines (McDonald *et al.* 2017). However, MM cancer cells have been

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shown to alter osteocyte (the primary source of sclerostin) viability and gene expression (Atkinson & Delgado-Calle 2019). Liu *et al.* showed that sclerostin is upregulated by histone acetyltransferase major histocompatibility complex (MHC) class II transactivator (CIITA) expressed in osteocytes, resulting in decreased osteoblastogenesis and increased osteoclastogenesis (Liu *et al.* 2022). Furthermore, MM cells increase osteocyte death through upregulation of activated Notch signalling-mediated apoptosis and autophagy, which triggers osteoclast formation and activity (Giuliani *et al.* 2012, Delgado-Calle *et al.* 2016, Toscani *et al.* 2018). Notably, Mabille *et al.* showed that DKK1 and sclerostin are increased 4 months prior to relapse from treatment (Mabille *et al.* 2018).

There is a positive correlation between circulating sclerostin and osteolytic fractures, disease stage and bone remodelling markers in MBD patients, with mounting evidence for the benefit of bone anabolic agents in treatment of MBD (Gau *et al.* 2022). Mice injected with myeloma cells showed significant bone loss (Lawson *et al.* 2015). Interestingly, *Sost* deletion or treatment with anti-sclerostin antibodies increased osteoblastogenesis and bone formation rate. Additionally, anti-sclerostin antibodies prevented myeloma-induced bone loss, increased fracture resistance and decreased osteolytic bone lesions without interfering with MM chemotherapy (Delgado-Calle *et al.* 2017). Co-treatment with the antiresorptive agent zoledronic acid (Zol) increased bone mass and fracture resistance when compared with Zol alone in preclinical models of myeloma and may prevent the onset of MBD whilst increasing resistance to fractures (McDonald *et al.* 2017). Furthermore, combined inhibition of sclerostin and DKK1 (DKK1 levels are elevated in MM cells and rodents treated with anti-sclerostin antibodies) with a bi-specific antibody or a combination of anti-sclerostin and anti-DKK1 antibodies has a synergistic effect on increased bone formation and bone strength in mice and might be a potential therapeutic strategy for treating MBD (Stolina *et al.* 2014, Nioi *et al.* 2015, Florio *et al.* 2016, Taylor *et al.* 2016, Holdsworth *et al.* 2018, Witcher *et al.* 2018).

Sclerosteosis

In contrast to osteoporosis and IS, sclerosteosis is a high bone mass condition. It is autosomal recessive and is caused by loss of function mutations in *SOST* and *LRP4*, the latter causing sclerosteosis 2 (Beighton 1988, Balemans *et al.* 2001, Balemans *et al.* 2002, Fijalkowski *et al.* 2016). This condition is associated with increased bone formation and has been studied intensively in *Sost*$^{-/-}$ mice, a mouse model of sclerosteosis (Li *et al.* 2008). It has recently been shown that due to lack of sclerostin-mediated upregulation of RANKL expression, remodelling-based bone formation likely accounts for two-thirds of bone formed in 12-week-old *Sost*-deficient mice (Koide *et al.* 2022). Importantly, sclerosteosis has no pharmacological treatment with symptoms managed through surgery. However, efforts have been made to develop potential new treatments through protein replacement therapy (Dreyer *et al.* 2021).

Sclerostin and cartilage

Chondrocytes produce and maintain the cartilage extracellular matrix (ECM) present on the articular surface for healthy joint function (reviewed by Akkiraju & Nohe 2015). These stable, mature chondrocytes are derived from mesenchymal cells that differentiate down the chondrogenic lineage. Differentiation is halted once the mature chondrocyte stage is reached and cells remain in a steady state, maintaining cartilage homeostasis. In contrast, during endochondral ossification (observed during long bone growth and fracture repair), mature chondrocytes undergo hypertrophic differentiation leading to the catabolism of ECM components. This degeneration of the cartilage ECM includes mineral deposition and paves the way for subsequent bone formation (Goldring 2012). Sclerostin has been shown to be expressed in chondrocytes *in vitro*, facilitating early chondrogenic differentiation through suppression of Wnt/β-catenin signalling (Yamaguchi *et al.* 2018). This expression is lost during hypertrophic differentiation resulting in high levels of Wnt/β-catenin signalling (Ma *et al.* 2013, Yamaguchi *et al.* 2018). Interestingly, *Pinch2* knockout mice have been shown to express high levels of sclerostin in their hypertrophic zone chondrocytes and phenotypically display low bone mass and shortened limbs, providing further evidence that sclerostin may be a negative regulator of endochondral ossification (Lei *et al.* 2020).

Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease characterised by progressive loss of articular cartilage, in addition to subchondral bone exposure and remodelling, synovial inflammation and osteophyte formation. During OA development, mature chondrocytes continue to differentiate into a hypertrophic and catabolic state

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which leads to degeneration of the cartilage matrix (Goldring 2012). Sclerostin expression is elevated in articular chondrocytes following surgically induced OA and is reduced in subchondral bone in association with bone sclerosis, suggesting that sclerostin might play a role in preventing articular cartilage degradation (Chan *et al.* 2011). Additionally, an increase in miRNA-218-5p, a *SOST* inhibitor, was reported to be upregulated in moderate to severe human OA and has been suggested as a potential therapeutic target (Lu *et al.* 2017). During OA development sclerostin expression is reduced in human subchondral bone from OA subjects undergoing total knee arthroplasty (Wu *et al.* 2016). This has been replicated *in vivo* with *Sost*-deficient mice displaying increased subchondral bone sclerosis and subsequent OA development (Li *et al.* 2019*a*). It is suggested that OA osteoclasts secrete higher levels of the sclerostin-negative regulator, leukaemia inhibitory factor (LIF), resulting in increased Wnt/β-catenin signalling. This leads to subsequent abnormal bone remodelling, further exacerbating cartilage destruction. Interestingly, inhibition of osteoclasts with alendronate attenuates LIF expression and cartilage degeneration (Zhao *et al.* 2022). These data suggest that sclerostin depletion may play a role in OA development and is therefore a plausible therapeutic target for targeting early to moderate OA as a means to prevent disease progression.

Sclerostin and the cardiovascular system

Increasing data suggests a role for Wnt signalling in the pathophysiology of vascular diseases and ageing (Catalano *et al.* 2020). Wnt signalling also interacts with endothelial dysfunction, affecting both the proliferation and migration of vascular smooth muscle cells (VSMCs) and intimal thickening.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arterial wall (Libby *et al.* 2019). Research suggests that sclerostin is linked to subclinical atherosclerosis and is inversely associated with carotid intima-media thickness (CIMT) in postmenopausal woman with type II diabetes mellitus (Morales-Santana *et al.* 2013, Gaudio *et al.* 2014). Leto *et al.* reported *SOST* expression at the vascular level in humans. Sclerostin production was identified in atherosclerotic plaques of patients that had carotid endarterectomy, with significantly greater quantities in the media compared to intima. Vascular smooth muscle cells (VSMCs) also displayed higher sclerostin levels than infiltrating macrophages (Leto *et al.* 2019). Excess sclerostin has been shown to be protective against the progression of both atherosclerosis and inflammation in the Apolipoprotein E (ApoE) mouse model (Krishna *et al.* 2017). Decreased sclerostin may therefore be related to higher susceptibility to atheroprogression. Turk *et al.* further evaluated the relationship between sclerostin and atheroprogression with nonclinical toxicology and safety packages and found no significant correlation between sclerostin inhibition and atheroprogression in two ApoE models (Turk *et al.* 2020). Similarly, Holdsworth *et al.* observed little or no sclerostin in human plaques. Sclerostin intensity was decreased compared to normal aorta and was found in deeper areas of the plaque and aorta wall, but not in regions known to be relevant to plaque stability, such as the fibrous cap and the endothelium. These data indicate little association of sclerostin involvement with the stability of an atherosclerotic plaque (Holdsworth *et al.* 2021).

Vascular calcification

Sclerostin has been discovered in the aorta of patients undergoing aortic valve replacement and found to be increased in both calcified vascular plaques and calcifying VSMCs (Didangelos *et al.* 2011, Zhu *et al.* 2011, Koos *et al.* 2013). Sclerostin serum levels were positively correlated with the presence of thoracic aorta calcification and positive *SOST* expression in the vascular system (Li *et al.* 2019*b*). Evidence also exists that sclerostin could differentially affect vascular calcification (VC) in distinct vascular beds. Sclerostin was linked to an increased risk (1.61×) of coronary artery calcification (CAC) whilst there was no link to aortic artery calcification (AAC) in recent work performed by Kuipers *et al.* (2015). However, calcified aorta in rats with chronic kidney disease (CKD) secreted increased amounts of sclerostin and displayed impaired bone metabolism (Mace *et al.* 2021). Further *in vitro* analysis with calcified aorta rings co-incubated with UMR-106 osteoblast-like cells showed detrimental effects of the calcified aorta on bone mineralisation, suggesting crosstalk between vascular and bone tissue (Mace *et al.* 2022). De Maré *et al.* showed that *SOST*$^{-/-}$ mice with adenine diet-induced CKD had significantly higher calcium content in their aorta compared to wild type (De Maré *et al.* 2022). DBA/2J mice on a warfarin diet were treated with an anti-sclerostin antibody and displayed significantly more calcification in both the aorta and renal arteries, suggesting that sclerostin offers a protective role during the development of vascular

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calcifications (De Maré *et al.* 2022). The bone–vascular axis should thus be a key consideration when developing new therapeutics for vascular calcification and augmented bone metabolism (De Maré *et al.* 2019*a*).

Romosozumab and cardiovascular events

Romosozumab has been compared to alendronate, an oral bisphosphonate that effectively suppresses osteoclast-mediated bone resorption and lowers fracture risk in postmenopausal women with osteoporosis (Schenk *et al.* 1986, Liberman *et al.* 1995, Chavassieux *et al.* 1997, Saag *et al.* 2017). Moreover, bisphosphonates have previously been linked to cardioprotection; however, a recent review by Fuggle *et al.* suggests that this might not be the case (Kim *et al.* 2015, Kranenburg *et al.* 2016, Fuggle *et al.* 2020).

Data collected from BRIDGE (placebo-controlled double-blind study evaluating the efficacy and safety of romosozumab in treating men with osteoporosis) and ARCH (active-controlled fracture study in postmenopausal women with osteoporosis at high risk) phase III randomised control trials (RCTs) using romosozumab showed a disproportionate occurrence in serious cardiovascular events (CVEs) (Saag *et al.* 2017, Lewiecki *et al.* 2018). This caused regulatory bodies to issue warnings on the product labels for the increased risk of heart attack, stroke and cardiovascular deaths. As such, romosozumab is not indicated for patients who have suffered such an event in the past year.

The increased adverse CVEs observed when comparing romosozumab to alendronate (2.5% vs 1.9%) during the ARCH phase III RCT could not be explained by baseline cardiovascular risk or concurrent use of cardiovascular medication (Saag *et al.* 2017). The FRAME (fracture study in post-menopausal women with osteoporosis) study did not produce similar results; however, this trial did enrol a study population with different criteria and was placebo controlled (Cosman *et al.* 2016). A meta-analysis by Lv *et al.* showed that romosozumab treatment was not associated with an increased risk of a three-point major adverse cardiovascular event composite (cardiovascular death or death, myocardial infarction and stroke), composite cardiovascular outcomes (including stroke, atrial fibrillation, heart failure and coronary heart disease) or any specific cardiovascular outcomes in patients with osteoporosis (Lv *et al.* 2020). However, there was a significant increase in the risk of four-point major adverse cardiovascular event composite (cardiovascular death, myocardial infarction, stroke and heart failure) with romosozumab treatment. Results from another meta-analyses of both published and unpublished (FRAME data made available to the U.S. FDA Drugs Advisory Committee) cardiovascular outcome trial data from romosozumab suggested that *SOST* genetic variants were also at a higher risk of myocardial infarction and/or coronary revascularisation and major adverse cardiovascular events, and concluded that sclerostin inhibition could elevate the risk of cardiovascular disease (CVD), necessitating a review of the cardiovascular safety of anti-sclerostin therapies (Bovijn *et al.* 2020).

However, the meta-analyses received criticism from Holm *et al.* who found fault with both the analysis and interpretation of the results (Holm *et al.* 2021). This study indicated that the analysis used a non-suitable significance threshold and use of the suggested *P*-value would require significant backing by data, which was not provided. The meta-analysis of all the RCTs also showed no association with cardiovascular incidences. It was also noted that coronary artery disease had been examined extensively within genome-wide association studies (GWAS), yet no *SOST* variants were seen (Buniello *et al.* 2019). Furthermore, there was disagreement with reporting the *P*-values of the combined markers when these are not independent, thus exaggerating the significance (Holm *et al.* 2021). Holm *et al.* noted that any potential relationship between the *SOST* BMD variant and CV risk has not been established as a driver by Bovijn *et al.* There are other *SOST* variants found in these vascular regions, thus making it impossible to undertake colocalisation analyses with the CVD phenotype (Holm *et al.* 2021). Bovijn *et al.* rebutted the comments, cautioning that the data from the RCTs of romosozumab did not show any relationship determined by their choice of *P*-value (Buniello *et al.* 2019). Additionally, the scale of a GWAS variant is not a correct illustration of the magnitude of biological effect seen when augmenting the protein produced by the same gene with a therapeutic agent (Bovijn *et al.* 2021). Regardless, despite contradictory data or the lack of evidence that inhibiting sclerostin has a detrimental effect upon the cardiovascular system, it is recommended that romosozumab should be carefully prescribed, weighing up the cardiovascular risk to the patient (Langdahl *et al.* 2021).

Work conducted by Yu *et al.* examined the role of sclerostin in cardiovascular protection as well as bone formation by targeting different loops of the sclerostin structure. *In vitro* and *in vivo* studies demonstrated that loop 3 deficiency, either by pharmacologically targeting loop 3 with Apc001PE or by genetic truncation, maintained protective features on the cardiovascular system. Interestingly, both loop 2 and loop 3 targeting

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in MC3T3-E1 cells diminished the inhibition of bone formation by sclerostin, which was mirrored *in vivo* in mice. Of note, the authors did not provide comparative data to sclerostin neutralisation through the use of an approved therapeutic antibody. As such, the decrease in cardiovascular risk could not be entirely quantified. Nevertheless, these data could inform on the creation of novel sclerostin inhibitors for future bone therapeutics coupled with decreased cardiovascular risk (Yu *et al.* 2022).

Other cardiovascular events

The function of sclerostin in aortic aneurysms was examined *in vitro* as well as in mouse models and human specimens (Krishna *et al.* 2017). This study revealed that sclerostin expression in the aorta was downregulated in human aortic aneurysms, possibly due to epigenetic silencing. Interestingly, sclerostin prevented angiotensin II-induced aortic aneurysms in the thoracic and abdominal aorta in *SOST* transgenic *ApoE*$^{-/-}$ mice, suggesting a potential therapeutic strategy via upregulation of sclerostin (Krishna *et al.* 2017). Arterial wall stiffness is a hallmark of arterial ageing, and interestingly sclerostin has been identified as an independent marker of arterial stiffness in healthy adults. However, DKK1 did not show a similar correlation (Gaudio *et al.* 2017). These two Wnt signalling inhibitors have very similar roles in vascular cells yet show a significant difference in behaviour in this process, which could account for their differing expression throughout the body (Gaudio *et al.* 2014, Desjardins *et al.* 2014, Hsu *et al.* 2016).

Interestingly, Javaheri *et al.* found that bone loss in a mouse model of glucocorticoid excess was not rescued by *Sost* haploinsufficiency (Javaheri *et al.* 2019), contradicting previous studies which reported that genetic deletion of *Sost* and anti-sclerostin antibody treatment rescued glucocorticoid-induced low bone mass (Marenzana *et al.* 2011, Sato *et al.* 2016, Yao *et al.* 2016, Javaheri *et al.* 2019). However, sclerostin deficiency combined with glucocorticoid excess resulted in sporadic, sudden, unprovoked and nonconvulsive death caused by peracute hemopericardium and cardiac tamponade. The authors speculate that glucocorticoid excess may also result in increased cardiac risk in situations of sclerostin suppression. They suggest that the developmental effect of excessive glucocorticoids and *Sost* haploinsufficiency, as well as differences in experimental design and analysis, could be potential reasons for the inconsistency between this study and studies that rescue glucocorticoid induced bone loss through *Sost* deletion and antisclerostin antibody treatment (Javaheri *et al.* 2019). However, a link from this preclinical study to the clinical situation has not been demonstrated.

Sclerostin and the immune system

Many signalling pathways, including the Wnt/β-catenin pathway, contribute to regulation of haematopoiesis in adults (Geest & Coffer 2009, Luis *et al.* 2011, Huang *et al.* 2012). Sclerostin depletion has been shown to affect B-lymphopoiesis and myelopoiesis, as well as other changes within the bone marrow cavity that could affect haematopoiesis (Donham *et al.* 2021, Sun *et al.* 2021). Furthermore, lack of sclerostin results in increased B-cell apoptosis and decreased *CXCL12* (an important B-cell growth stimulating factor) expression (Cain *et al.* 2012). Impaired B-lymphocyte survival causes a reduced number of B-lymphocytes in *Sost*$^{-/-}$ (MGI:3797839) bone marrow, an effect that is mediated in an indirect cell-extrinsic manner. Conversely, B-lymphocyte development was not affected by deletion of *Sost* (using *Dmp1-Cre*) in osteocytes; however, decreased B-cell precursors and immature B-cell subsets were observed when *Sost* was deleted (using *Prx1-Cre*) in mesenchymal stem cells (MSCs) (Yee *et al.* 2018). However, this decrease was not as pronounced as in global *Sost*$^{-/-}$ mice, suggesting that another sclerostin expressing cell is involved in B-cell development (Cain *et al.* 2012, Yee *et al.* 2018). You *et al.* demonstrated that sclerostin is necessary for inducing T helper 17 (Th17) cell differentiation, which are responsible for bone resorption by promoting the levels of interleukin (IL)-6 and transforming growth factor (TGF)-β. In addition, it has been shown that sclerostin inhibits the differentiation of regulatory T (Treg) cells by reducing the expression of IL-10 and Foxp3, which play essential roles in Treg cell development (You *et al.* 2018). These findings suggest that further research is warranted to determine whether sclerostin-depleting therapies could result in similar alterations in B-cell dynamics.

Sclerostin and other organs

Muscle

Muscle and bone are both endocrine target tissues and endocrine organs (Brunetti *et al.* 2017, Giudice & Taylor 2017). Previously it was believed that locomotion was the singular method of crosstalk between muscle and bone. However, crosstalk also occurs when muscle and bone interact with each other through paracrine and endocrine

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signals, which play key roles in modulation of their mutual development and function (Brotto & Bonewald 2015, Tagliaferri *et al.* 2015). Many tissue-specific factors released by osteoblasts and osteocytes, such as osteocalcin and insulin-like growth factor 1 (IGF1), appear to have a potential impact on skeletal muscle. Similarly, a number of factors released by muscle with bone-modulating properties have been identified (Magarò *et al.* 2021). Skeletal muscle cells (myocytes) release myokines, a panel of proteins and cytokines which exert paracrine or endocrine regulatory functions on bone, among other distant organs and tissues (Gomarasca *et al.* 2020). Myogenic media from differentiating C2C12 myoblast cells altered the functional maturation of osteoblasts and was shown to have inhibitory effects on bone cell differentiation. Sclerostin was identified as a myokine expressed by C2C12 muscle cells and primary murine myoblasts (from C57BL/6J mice) in all stages of differentiation and was dynamically secreted in the myogenic medium during myogenic lineage progression (Magarò *et al.* 2021). It appears that myoblast sclerostin secretion does not affect circulating sclerostin levels and myokines may affect adjacent bones through a paracrine mechanism, relying on their diffusion across muscle and bone tissues. This suggests that sclerostin released by bone might synergise with sclerostin released by skeletal muscle to inhibit osteogenesis (Magarò *et al.* 2021). Magarò *et al.* showed that both muscle- and bone-secreted sclerostin reduce bone formation. Overexpression of sclerostin by myocytes induced trabecular bone loss, but did not influence cortical bone parameters. Interestingly, sclerostin has been found to be expressed by metastatic breast cancer cells. Treating cancer bearing mice with anti-sclerostin (setrusumab) decreased osteolytic bone destruction and muscle weakness (Hesse *et al.* 2019). Muscle fibre atrophy was reversed by inhibiting the osteoclast-mediated increase in TGF-β1, suggesting cross talk between bone and muscle (Hesse *et al.* 2019). Although existing evidence shows that sclerostin secreted by both bone and skeletal muscles regulates bone homeostasis, further research is required to fully uncover the processes underlying sclerostin-mediated regulation of bone–muscle interaction. Understanding of these processes could be used to develop innovative therapeutics for diseases such as osteoporosis and sarcopenia.

Liver

Increasing evidence exists concerning the relationship between liver and bone metabolism. Sclerostin is known to be involved in metabolic abnormalities and is possibly increased in patients with impaired glucose regulation, correlating with insulin resistance in skeletal muscle, adipose tissue and the liver (Daniele *et al.* 2015). Remarkably, higher sclerostin levels are seen in type II diabetes as well as in men with excessive alcohol use (Gennari *et al.* 2012, Napoli *et al.* 2018, Martín González *et al.* 2022). Circulating sclerostin levels were lower in non-alcoholic fatty liver disease (NAFLD) patients and were negatively correlated with multiple metabolic parameters whilst showing no significant correlation to controls (Zou *et al.* 2020). Evidence suggests that NAFLD is a multisystem disease that affects several organ systems other than the liver and interacts with the regulation of multiple metabolic, endocrine, and pro-inflammatory pathways (Younossi *et al.* 2018). Significant differences in whole-body or lumbar BMD *Z* scores between children or adolescents with and without NAFLD have been described, suggesting that liver–bone interaction and the underlying mechanism should be further investigated (Mantovani *et al.* 2019). Zhou *et al.* observed reduced bone mass as well as lower sclerostin expression levels in the bone and liver tissues of mice fed on a high-fat diet. These results suggest that liver–lipid–bone interactions may play a key role in the abnormal bone metabolism in NAFLD (Zhou *et al.* 2021). These studies focused primarily on serum sclerostin levels, sclerostin mRNA expression and changes to bone parameters, thus further research is needed to clarify any effects of sclerostin on liver biology and function and to understand the link between liver and bone cells.

Kidney

Serum sclerostin is increased in patients with chronic kidney disease (CKD), with sclerostin hypothesised to originate from the skeleton and vasculature (Zhu *et al.* 2011, Brandenburg *et al.* 2019). The increase in sclerostin with CKD progression is most notable in stage 3 CKD, indicating that sclerostin is inversely proportional to glomerular filtration rate (Pelletier *et al.* 2015). The heightened sclerostin expression seen in CKD patients is thought to be a result of many factors, including sclerostin renal retention (Sabbagh *et al.* 2012, Bruzzese *et al.* 2016). However, it has been reported that urinary sclerostin excretion increases simultaneously with declining estimated glomerular filtration rate (eGFR) and increasing sclerostin secretion from osteocytes (Sabbagh *et al.* 2012, Bruzzese *et al.* 2016). The importance of sclerostin for cardiovascular and bone health in CKD patients is not fully understood. Studies have shown that CKD patients are at a higher risk of CVEs. Additionally, sclerostin is

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expressed within their vasculature with highly active vascular calcification processes. Within this patient population, anti-sclerostin antibody treatments have a weakened efficacy on bone, coupled with an increased rate of hypocalcaemia (Cejka 2021). The function of sclerostin in the uremic arteries is unknown; however, it may be postulated that its expression within the vasculature could be a marker for uremic damage (Marchand *et al.* 2011). In patients undergoing peritoneal dialysis, low serum sclerostin was related to an increased survival rate as well as a lower chance of a CVE. This relationship does not correlate with haemodialysis patients (Zou *et al.* 2020). Sclerostin may have utility as a clinically relevant marker of disturbed bone metabolism in end-stage kidney disease patients (De Maré *et al.* 2019*b*). However, further *in vitro* and *in vivo* cause–effect studies are required to better understand the role of sclerostin in the kidney and how it relates to both bone and vasculature.

Sclerostin as a therapeutic

An increased understanding of sclerostin and its function in bone biology has resulted in the investigation of sclerostin as a therapeutic. Here, we focus on the latest advances in sclerostin as a treatment for sclerosteosis, OA and osteosarcoma.

Sclerosteosis

Sclerostin replacement therapy has recently been investigated as a potential treatment for sclerosteosis by replacing absent sclerostin with recombinant wildtype or sclerostin fusion constructs (Dreyer *et al.* 2021). Dreyer *et al.* demonstrated that wildtype murine sclerostin, sclerostin human immunoglobulin G1 (IgG1) fragment crystallisable (Fc) fusion protein (mScl-hFc) and sclerostin human Fc fusion with a bone targeting C-terminal poly-aspartate motif (mScl-hFc-PD) bound with high affinity to the extracellular domain of the LRP6 Wnt co-receptor and inhibited mineralisation in a murine osteoblast-like cell line. Fusing sclerostin with IgG1 human Fc increased protein half-life from minutes to longer than a day in WT and *Sost*$^{-/-}$ mice. Modest but significant reductions in trabecular volumetric bone mineral density (vBMD) and bone volume fraction (BV/TV) of 20% and 15%, respectively, were observed after 6 weeks in *Sost*$^{-/-}$ mice treated with mScl-hFc-PD. It is thus possible that the bone-targeting moiety may have been beneficial. Cortical bone and bone formation markers remained unchanged and anti-sclerostin antibodies were observed. Although these antibodies are the most likely cause of modest efficacy, increased DKK1 concentrations have been reported in mice and rats treated with anti-sclerostin antibodies (Taylor *et al.* 2016, Holdsworth *et al.* 2018). It is possible that increased DKK1 levels are also present in the *Sost*$^{-/-}$ mice and potentially contributed to the modest effects from sclerostin constructs (Dreyer *et al.* 2021). This study indicates that a protein replacement approach might not be effective for long-term use and alternatives, such as small molecules, should be considered.

Osteoarthritis

Suppression of Wnt signalling by upregulated *SOST*/sclerostin in cartilage derived from biopsies of OA patients and elevated sclerostin in traumatic OA models suggest that sclerostin might play a key protective role in the maintenance of articular homeostasis (Karlsson *et al.* 2010, Chan *et al.* 2011). Indeed, Chang *et al.* found that sclerostin inhibits cartilage degradation after traumatic injury by downregulating catabolic enzymes/activity of proteolytic enzymes, such as matrix metalloproteinases (MMP and MMP2/3), in osteopenic *SOST* transgenic mice (Chang *et al.* 2018). MMP activity was also significantly decreased in both *SOST* transgenic and *Sost* knockout mice after intra-articular administration of recombinant sclerostin, immediately after joint injury. These findings suggest that elevated levels of sclerostin immediately post-injury can aid the joint in maintaining its articular cartilage integrity in post-traumatic settings (Chang *et al.* 2018). In addition, sclerostin overexpression may protect OA joints from excessive osteophyte formation, whilst lack of sclerostin could protect the femur from bone loss that results from disuse or injury (Chang *et al.* 2018). Sclerostin treatment of ATDC5 cells, a well-established *in vitro* model of chondrogenesis, promoted chondrogenic gene expression and suppressed hypertrophic differentiation (Atsumi *et al.* 1990, Yamaguchi *et al.* 2018). Moreover, addition of sclerostin following IL-1β treatment repressed the upregulation of Wnt/β-catenin signalling and inhibited progression of chondrogenic differentiation and terminal calcification promoted by IL-1β addition to ATDC5 cells (Miyatake *et al.* 2020). As with the Chang *et al.* study, these results suggest that suppression of Wnt signalling by sclerostin might be key for the maintenance of articular homeostasis. Furthermore, treatment with the anti-malarial drug dihydroartemisinin has been shown to enhance sclerostin expression and subsequently reduce subchondral bone remodelling in a surgically induced OA mouse model (Ma *et al.* 2021). Interestingly, sclerostin

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has been shown to be upregulated by OA chondrocytes in end-stage disease, which may be an attempt to prevent further destruction by slowing down Wnt-driven catabolic responses (Chan *et al.* 2011). There is evidence that sclerostin modulates cartilage homeostasis and may be of therapeutic benefit in early stage disease; however, its application as a sole therapy for advanced disease is likely insufficient to reverse the plethora of pathological structural changes observed.

Osteosarcoma

Osteosarcoma has one of the lowest survival rates of all paediatric cancers as it is highly resistant to treatment, partially due to its highly diverse and heterogeneous nature (Gill & Gorlick 2021). New treatments are thus urgently needed. The Wnt/β-catenin signalling pathway may play an important role in osteosarcoma tumourogenesis (Inagaki *et al.* 2016). Indeed, Ideta *et al.* recently reported that sclerostin inhibits the Wnt/β-catenin pathway as well as proliferation and migration in both murine (LM8) and human (143B) osteosarcoma cell lines (Ideta *et al.* 2021). Sclerostin also inhibited tumour growth in mice with transplanted osteosarcoma cells, extending overall survival rate. *SOST* expression was significantly decreased in tumour-bearing bones from 15-week-old osteoblast-specific Wntless (Wls) loss-of-function OS mice ($Wls^{\Delta OB}$-OS mice) (Matsuoka *et al.* 2020). These results corroborate the findings by Zou *et al.* that *SOST* gene silencing activates the Wnt/β-catenin pathway, resulting in decreased apoptosis, increased proliferation, and invasion and migration of osteosarcoma cells collected from primary tumour tissues of osteosarcoma patients (Zou *et al.* 2017). Taken together, these findings suggest that local treatment with drugs that increase local sclerostin concentration or reduce Wnt expression/activity by mimicking sclerostin function could be effective for the treatment of osteosarcoma whilst avoiding systemic negative impacts on bone.

Future

As discussed in this review, sclerostin has a potential role in regulating and maintaining homeostasis in many organs beyond that of the bone, with associations to the immune system, kidney, liver, muscle, cartilage and cardiovascular system. However, it is important to note that regulated expression is essential to ensure controlled balance of canonical Wnt signalling. Many reports suggest that an imbalance in sclerostin expression/function may be linked to metabolic diseases, musculoskeletal disorders and cardiovascular events. However, it is not yet understood whether dysregulation of sclerostin is a causative event in all these conditions, as observed in sclerosteosis, or whether sclerostin expression is affected during disease progression. Nevertheless, sclerostin levels are altered and more research (e.g. mechanistic *in vivo*) is required to underpin its role and aid therapeutic development. Research is well underway regarding the modulation of sclerostin function as a therapeutic approach, with romosozumab for post-menopausal osteoporosis already approved by multiple regulators. However, as seen with romosozumab, changes in bone mineral density might become smaller following prolonged treatment with canonical Wnt-signalling pathway targeting therapeutics (McClung *et al.* 2018). Novel approaches including sclerostin replacement therapy, small molecule intervention, epigenetic modulation and aptamer targeting of sclerostin may shed light on the future of sclerostin-based therapeutics and offer exciting avenues in novel drug development approaches.

Declaration of interest

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