Purpose of review
The aim of this article is to summarize and put into historical perspective current advances in research in otosclerosis, a disorder of the human temporal bone with a hereditary predisposition that is among the most common causes of acquired hearing loss.

Recent findings
Genetic studies have revealed that otosclerosis is heterogeneous, with evidence for defects in at least seven genes associated with six distinct chromosomal loci. Measurements of high levels of osteoprotegerin expression in the normal otic capsule and soft tissues of the cochlea provide the first molecular insight as to why the normal otic capsule remodels minimally, if at all. Osteoprotegerin knockout mice provide the best available animal model to date to study abnormal otic capsule remodeling that closely resembles otosclerosis. There is mounting evidence that the measles virus plays an important role in pathogenesis of otosclerosis although the mechanisms by which the virus results in otosclerosis remain unknown. Quantitative measures of angiogenesis can reliably distinguish between clinical and histological otosclerosis. Advances in the emerging field of osteoimmunology will likely impact and benefit from the research in otosclerosis.

Summary
Insights into molecular mechanisms that inhibit extensive remodeling in the normal otic capsule, and understanding of how these mechanisms are dysregulated in otosclerosis will allow future design of rational treatment strategies for otosclerosis.

Keywords
angiogenesis, bone remodeling, measles virus, osteoprotegerin, otosclerosis

Abbreviations
OPG osteoprotegerin
PTH parathyroid hormone
RANK receptor activator of nuclear factor κB
RANKL receptor activator of nuclear factor κB ligand

Introduction
Otosclerosis is a disorder of the human temporal bone with a hereditary predisposition that is among the most common causes of acquired hearing loss. It is estimated to occur histologically in 10% of Caucasians and produces hearing loss in 1% [1,2]. At a histological level, otosclerosis is a process of remodeling of the otic capsule. The usual initial manifestation is stapes fixation, leading to a conductive hearing loss, which is often bilateral. While most cases of conductive hearing loss can be effectively treated with either surgery or amplification, approximately 20–30% of patients develop a progressive, sensorineural hearing loss for which there are currently no efficacious medical or surgical therapies.

Remodeling in the otic capsule and otosclerosis
Otosclerosis is exclusively confined to the otic capsule of the human temporal bone [3,4], which implies that the otic capsule has some special features which predispose it to the development of otosclerosis. One unique feature of the otic capsule compared with other parts of the skeleton is that it exhibits very little or no bone remodeling [5,6]. Recent studies by Sorensen and colleagues quantified this lack of remodeling, and demonstrated that the greatest inhibition of bone turnover occurs in that part of the otic capsule that is immediately adjacent to the cochlea [5,6].

At a histological level, otosclerosis is simply the process of bone remodeling affecting the otic capsule. The initiation of otic capsule remodeling consists of an alteration in the composition of extracellular matrix that is produced by osteoblasts and osteocytes, which is seen histologically as a localized change in the staining pattern of otic capsule bone (termed ‘blue mantling’). As the disease evolves, these areas begin to actively remodel and give rise to otosclerotic foci. While considerable research has focused on etiological agents (genetic
mutations, measles virus infection, mechanical stresses, autoimmunity [3,7]) that might trigger otosclerosis, we have only started to understand the molecular factors which inhibit and promote remodeling within the otic capsule.

**Genetic heterogeneity**

Otosclerosis has a strong genetic component. Most studies on families with otosclerosis support a pattern of autosomal dominant transmission with incomplete penetrance [8,9]. The disease is genetically heterogeneous with evidence for defects in six loci [10–12,13*,14,15*], and in expression of the type I collagen gene, COL1A1 [16–18]. The identified loci associated with otosclerosis are OTSC1 on chromosome 15q25–q26 [10], OTSC2 on chromosome 7q34–q36 [11], OTSC3 on chromosome 6p21.3–p22.3 [12], OTSC4 on chromosome 16q21–q23.2 [13*] and OTSC5 on chromosome 3q22–q24 [14]. An additional locus was implicated in linkage analysis of monogenic nonsyndromic otosclerosis in a large Greek pedigree, which excluded linkage to OTSC1–3, OTSC5, and to the COL1A1 and COL1A2 genes [15*]. The identified loci include genes involved in collagen biosynthesis and metabolism, in the immune system, in cartilage and bone homeostasis, in growth suppression, and in intercellular communication. To identify specific disease-causing genes, refinement of the candidate regions and mutation analysis of candidate genes is required.

The evidence for involvement of COL1A1 gene in pathogenesis of otosclerosis comes from association analysis revealing a very significant association between the polymorphism in the regulatory Sp1 site in the first intron of the COL1A1 gene and clinical otosclerosis in both familial and sporadic cases [18]. The allele frequencies of this polymorphism in patients with otosclerosis were similar to those reported in patients with osteoporosis. Interestingly, osteoporosis is fourfold more common in women with otosclerosis than in those without otosclerosis [19]. Additional insight into how COL1A1 defects might produce otosclerosis comes from research in a related disorder of skeletal bones, osteogenesis imperfecta. Type I osteogenesis imperfecta, which mostly results from a null expression of the mutant COL1A1 gene, shares many clinical and histopathologic similarities with otosclerosis: about 50% of patients with type I osteogenesis imperfecta develop clinical otosclerosis [20], the histopathological appearance of the affected otic capsule is similar in the two diseases [21,22], and some patients with otosclerosis have blue sclerae, which is a cardinal clinical feature of osteogenesis imperfecta. In addition, there is similar COL1A1 expression in fibroblasts from some patients with clinical otosclerosis and those with type I osteogenesis imperfecta [23].

**Osteoprotegerin–receptor activator of nuclear factor κB–receptor activator of nuclear factor κB ligand system**

At a cellular level, bone remodeling is a continuous process that is ongoing throughout the skeleton, except in the otic capsule. Such remodeling is due to growth, injury, mechanical stress and metabolic requirements. Bone resorption (by osteoclasts) is tightly coupled to bone formation (by osteoblasts) under normal circumstances, so that the amount of bone resorbed is equal to the amount of bone formed. Recent research has established that bone remodeling at a local level is tightly regulated by a delicate balance between three cytokines: osteoprotegerin (OPG), receptor activator of nuclear factor κB (RANK), and RANK ligand (RANKL) [24,25]. Osteoblasts present the cell surface protein ligand RANKL, which binds to its receptor RANK on precursor and immature osteoclasts. The RANKL–RANK interaction results in mature osteoclasts that initiate the process of resorption of bone. OPG is a soluble factor that competes with RANK for the RANKL receptor on osteoblasts, and thereby is a powerful inhibitor of bone remodeling. The ratio of OPG to RANKL is critical in determining the kinetics of local bone remodeling. Overexpression of OPG causes excessive bone formation or osteopetrosis, while lack of OPG results in osteoporosis [26–28]. The OPG–RANK–RANKL system is the final common pathway for regulation of bone metabolism, and various biochemical, hormonal and biomechanical stimuli that influence bone remodeling do so via this pathway. It is likely that diverse etiological factors that trigger otosclerosis affect the OPG–RANK–RANKL system.

A recent study [29**] showed that the normal otic capsule contains very high levels of OPG (by factors of 20 or more than other bones), and that OPG is produced in extremely high concentration within the inner ear, primarily by type I fibrocytes of the spiral ligament, and secreted into the perilymph. Some of this inner ear OPG may contribute to inhibition of otic capsule remodeling by diffusing into the surrounding otic capsule bone via an intricate canalicular system. These findings provide the first molecular insight as to why the otic capsule remodels minimally, if at all.

**OPG** mice exhibit foci of active remodeling within the otic capsule with features that resemble otosclerosis, including recruitment of osteoclasts and osteoblasts, deposition of woven bone, enhanced angiogenesis, hyalinization of the spiral ligament, and progressive and severe hearing loss [30**]. Unlike human otosclerosis, however, **OPG** mice do not develop stapes fixation, and they exhibit diffuse remodeling affecting the ossicular chain and the systemic skeleton. Nevertheless, these mice provide the best available animal model to
date to study abnormal otic capsule remodeling that closely resembles otosclerosis.

**Infection with measles virus**

There is mounting evidence that the measles virus plays an important role in pathogenesis of otosclerosis [31–38]: measles virus-like nucleocapsid structures are present in osteoblasts of otosclerotic lesions [31], measles antigens and measles RNA are found in active otosclerosis [32,37,39,40], elevated levels of IgG specific for measles virus are present in perilymph of patients with otosclerosis [41], and decreased levels of circulating antibodies to measles are found in otosclerosis [42]. Recent evidence indicates that the incidence of otosclerosis has fallen after introduction of the measles vaccine [38]. Moreover, serum levels of antimeasles IgG can be used for serologic diagnosis of ossicular fixation due to otosclerosis, where a combination of decreased antimeasles IgG serum level and conductive hearing loss portends high diagnostic specificity and sensitivity [43*].

Despite compelling evidence that the measles virus contributes to the pathogenesis of otosclerosis, the reason for the sole predilection of the otic capsule remains unknown. Studies on persistent viral infection have shown that the factors that predispose a cell type to persistent infection are complex, and are dependent on molecular and metabolic features other than the presence of viral receptors [44]. The mechanisms by which measles infection results in otosclerosis have not been established.

**The role of the endocrine system**

It is well established that sex steroid hormones are critical regulators of the skeleton [45]. The endocrine system has been implicated in the pathogenesis of otosclerosis because many researchers noted a progression of symptoms or the onset of otosclerosis in 30–60% of women who had at least one pregnancy [1,8,46,47]. Recently, however, authors [48*] found no adverse effect on hearing in otosclerotic women who had children compared with women without children, and no deleterious impact on hearing even with increasing numbers of pregnancies. Current active research on the roles of estrogen in hearing [49] will likely have implications for understanding hearing loss in otosclerosis.

Parathyroid hormone (PTH) has also been implicated in the pathogenesis of otosclerosis because of the major role this hormone plays in the physiology of bone turnover, and the fact that otosclerotic foci are characterized by pathologic bone turnover. An early study found normal levels of calcium, phosphorus and alkaline phosphatase in patients with otosclerosis [50], whereas a more recent study [51] found elevated levels of alkaline phosphatase in patients who had otosclerosis for 3–5 years. Cellular and molecular studies of otosclerotic stapes revealed an abnormal response to PTH, suggesting that altered PTH signaling contributes to the abnormal bone turnover in otosclerosis [52].

**Angiogenesis**

Schwartzte sign, a red blush observed through the tympanic membrane due to hyperemic vessels on the promontory, has long been associated with clinical otosclerosis. Recent measurements of blood flow to the promontory through the tympanic membrane using laser speckle flowgraphy and laser Doppler flowmetry found that patients with otosclerosis and Schwartzte sign exhibited elevated and pulsating blood flow to the promontory [53*]. It is likely that sustained angiogenesis is a key determinant of clinical otosclerosis since quantitative measures of angiogenesis can reliably distinguish between clinical and histological otosclerosis [54*].

**The role of the immune system**

Although autoimmunity has been suggested as a possible cause of otosclerosis, the supporting data are conflicting. Some authors reported elevated levels of antibodies to type II collagen in patients with otosclerosis [55,56], especially in patients with the disease of long duration [57]. Other authors, however, found no difference in otosclerotic patients compared with controls in levels of type II collagen [58]. In animal models, induction of immunity to type II collagen either did [59] or did not [60] lead to otosclerosis-like bone lesions in the otic capsule. Similarly, the evidence for association of otosclerosis with the human leukocyte antigen (HLA) system is equivocal (reviewed by Menger and Tange [7]). Nonetheless, studying interactions between the otic capsule and the immune system may prove to be a fruitful avenue for future research. Recently, osteimmunology has emerged as a new field, combining studies of bone and the immune system [61], based on developmental, mechanistic and functional parallels between these two organ systems. It is likely that studies of the cross-talk between the otic capsule and the immune system will contribute to and benefit from advances in osteimmunology.

**Conclusion**

The otic capsule is unique in that it exhibits very little or no bone remodeling under normal conditions. Ootosclerosis, a disease of the otic capsule with a genetic predisposition that occurs only in humans and is among the most common causes of acquired hearing loss, is histologically characterized by abnormal bone remodeling. Future design of rational treatment strategies for otosclerosis will depend on understanding of molecular mechanisms and cell signaling that inhibit bone remodeling in the normal otic capsule, and initiate bone remodeling in the otosclerotic otic capsule.
The authors used linkage analysis in a large Greek pedigree segregating oto-
sclerosis. The fourth locus of otosclerosis, OTSC4, was linked to the 16q21–23.2 interval,”

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 361).


15. Iliadou V, Van Den Bogaert K, Eleftheriades N, et al. Monogenic nonsyndromic otosclerosis: audiological and linkage analysis in a large Greek pedigree. Int J Pediatr Otorhinolaryngol 2006; 70:631–637. The authors used linkage analysis in a large Greek pedigree segregating otosclerosis as a monogenic autosomal dominant trait, and excluded linkage to four known otosclerosis loci (OTSC1, OTSC2, OTSC3, and OTSC5), as well as to the COL1A1 and COL1A2 genes, indicating that otosclerosis involves at least five different genes.


Lippy WH, Berenholz LP, Schuring AG, Burkey JM. Does pregnancy affect otosclerosis? Laryngoscope 2005; 115:1833–1836. The authors found no adverse effect on hearing in otosclerotic women who had children compared with women without children. Even with increasing numbers of pregnancies, no deleterious impact was noted.


