SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

# Etiopathogenesis of stapes fixations

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The Examination takes place at the Library of the Ophthalmology Clinic Medical and Health Science Center, University of Debrecen,
26th October 2012. 11:00

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The Ph.D. Defense takes place at the Lecture Hall of the 1st Department of Medicine, Institute for Internal Medicine, Medical and Health Science Center, University of Debrecen,
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## BACKGROUND AND PURPOSES

The etiopathogenesis of stapes fixations is different, one of them still remained unclear. The etiopathogenetic background of otosclerosis is still controversial. Otosclerosis is a bone remodelling disorder of the human otic capsule that leads to progressive and sensorineural heranig loss as a consequence of stapes footplate fixation and cochlear bone resorption with endosteal involvement.

Pathological bone remodeling is characterized by increased osteoclast activation and intensive osteolysis in the otosclerotic foci. Lesions of otosclerosis are exclusively localized only in the bony parts of the otic capsule: footplate of the stapes, and pericochlear- and perilabyrinthine regions. The mechanical properties of the movements of the stapes footplate are modified, leading to consequent conductive hearing loss. In the white population, the prevalence of clinical otosclerosis is 0.3–0.4% in the general population and 9–12% for those suffering from conductive hearing loss. The main etiological factor of otosclerosis is the persistent measles virus infection of the otic capsule. Theoretically, the continuous presence of antigens derived from measles virus stimulates the cellular immune response, eventually leading to inflammatory bone remodeling and consequent sensorineural hearing loss. Earlier studies have supposed the potential role of measles virus infection in the pathogenesis of otosclerosis. The presence of measles virus genome in otosclerotic stapes footplates was demonstrated by reverse transcriptase polymerase chain reaction (RT-PCR). Virus-like particles have been recognized in the

osteoclasts and osteoblasts of otosclerotic foci by electronmicroscopy. The measles virus, being a member of the Paramyxovirus family, penetrates into human cells in three different ways. The most effective infections are carried out via the SLAM (signalling lymphocyte activating protein, CD150) receptor; less effective infections are mediated via the CD46 receptor (membrane cofactor protein, MCP). Measles infections and viral transmission of human cell lines without expression of any known measles virus receptors have been recently demonstrated. These infections were described as having the lowest efficacy. The undescribed measles virus receptor-like molecule has been named as Receptor X. Immunohistochemical studies have shown very low expression levels of SLAM proteins on the cells of the human otic capsule, in contrast to the intensive expression of measles virus receptor CD46. These observations have supposed that the cellular penetration of the measles virus is mainly associated with the expression of CD46 in the human otic capsule. CD46 protein has 14 well-described variants, which are alternatively spliced from the transcripted mRNA of the CD46 gene. CD46 isoforms have been detected on the surface of all nucleated human cells in various expression levels and patterns. However, specific functions have not been attributed to isoform co-expression yet.

Grade I otosclerosis is featured by thickened and distorted stapes footplate with irregular, woven pattern of cement lines. The focus of otosclerosis is basophilic, hypervascularized, and filled with numerous multinucleated osteoclasts, hypercellular fibrous stroma,

and plump, distorted osteoblasts. The otosclerotic lesion shows the ”Swiss cheese” pattern due to the wide pseudovascular spaces, which are Howship-type osteolytic lacunae. Grade II otosclerosis is quite similar, except that typical osteoclast-like, multinuclear cells are missing. The mosaic structure of cement lines and the marked basophilia are retained. Grade III otosclerosis is represented by predominantly eosinophilic, woven bone containing some lamellar structure. Osteoclasts and osteoblasts are vanished; vascular spaces are eventually obliterated. End-stage or Grade IV otosclerosis means a remodeled lamellar bone structure with hypocellularity and avascularization. The compact bone shows intense eosinophilic staining. In some cases, there may be representation of all 4 stages, and the wide pseudovascular spaces seem to be acellular. In early stages of otosclerosis, tumor necrosis factor (TNF-α) is suspected to be released from the foci. Tumor necrosis factor-α could flow into the perilymph and can interfere with the electromotility of outer hair cells, resulting in sensorineural hearing loss (SNHL). Because TNF-α is produced in the otosclerotic bone, the putative source of SNHL in otosclerosis might be the TNF-α release. Increased expression of TNF-α has been demonstrated in active otosclerosis, which may lead to extensive osteoclast activation and bone resorption. Tumor necrosis factor-α is a proinflammatory cytokine that plays a role in the osteolytic process and in the differentiation of bone marrow-derived mononuclear cells ostecytes to osteoclasts or stromal cells to osteoblasts. Tumor necrosis factor-α is produced by activated monocytes, macrophages, B cells, T cells, and osteoclasts, and it is

an important paracrine mediator of the intercellular communication between osteoclasts and osteoblasts. Decreased expression of osteoprotegerin (OPG), also called TNFRSF11b (TNF-α Super Family Member 11b) has also been reported in active otosclerosis. Osteoprotegerin blocks the osteoclast formation and osteolysis and induces the apoptosis of activated osteoclasts. The main function of OPG is to regulate normal bone turnover with balanced osteoclast and osteoblast functions. Osteoprotegerin acts as a decoy receptor: it blocks the interaction of RANK (receptor activator of nuclear factor κB) with its ligand RANKL and thus inhibits osteoclast development and activation. Tumor necrosis factor-α has 2 main types of receptors. Type I TNF-α receptor (TNFRI, member of TNF superfamily I) is generally expressed by all nucleated human cells and has greater broader spectrum of biologic influence effectiveness than TNFRII. Type II TNF-α receptor (TNFRII, member of TNF superfamily II) is expressed by lymphocytes and antigen presenting cells and also by the osteoclasts and resting embryonic cells. Increased expression of TNFRII is a potent indicator of acute inflammatory reaction because it plays an important role in the recruitment of immune cells, activation of osteoclasts, and production of inflammatory cytokines (interleukin IL- 1, IL-6, transforming growth factor-β). After binding of TNF, Type I TNF-α receptors form a homotrimer structure activating the silencer of death domains, which binds the TNFR-associated death domain, allowing 3 different ways of signal transduction. The first and most important way is the activation of nuclear factor-κB (nuclear factor-

κ-lightchain-enhancer of activated B cells) system. Activated heterodimers of nuclear factor-κB being nuclear transcription factors stimulate the transcription of several antiapoptotic and other genes coding inflammatory proteins providing cell survival and proliferation. The second way is the activation of mitogen-activated protein kinases (MAPK) system. This signaling process, which is associated with the activation and phosphorylation of several nuclear transcription factors (c-Jun N-terminal kinases, p38-MAPK, extracellular signal-regulated kinases), c-Jun N-terminal kinases, p38-MAPK, and extracellular signal-regulated kinases transcription factors, which stimulate the expression of c-Fos, c-Jun, c-Myc, and activating transcription factor 2 proteins, leading to intense cell proliferation and survival. The third way of TNFRI-associated signalization is the death domain-mediated and caspase-associated induction of apoptosis. Tumor necrosis factor receptor-associated death domains of TNFRI bind the Fas-associating death domain containing protein, which recruit the cysteine protein caspase 8 complexes. After reaching the critical concentration, cysteine protein caspase 8 is activated by autoproteolysis, and the arising caspase 8 stimulates the effector caspases, leading to apoptotic cell death.

Apoptosis is a special way of cell death, which is functionally and morphologically different from necrosis. In general, apoptosis is characterized by nuclear chromatin condensation, cytoplasmic shrinking, dilated endoplasmic reticulum and blabbing blebbing of the cellular membrane. Mitochondria remain morphologically unchanged. The 2 principal pathways of apoptosis

are 1; the Bcl-2 inhibitable or intrinsic pathway induced by various forms of stress-like intracellular damage, developmental cues, and external stimuli; and 2; the caspase 8/10 dependent or extrinsic pathway initiated by the engagement of death receptors. The caspase 8/10 dependent or extrinsic pathway is a death receptor-mediated mechanism that results in the activation of caspase 8 and caspase 10. Activation of death receptors such as Fas/CD95, TNF-α receptor (TNFR) I, and TRAIL (TNF-related apoptosis inducing ligand) receptor is promoted by the TNF family of ligands, including Fas ligand, TNF-α, lymphotoxin-α (TNF-β), lymphotoxin-β, CD40 ligand, TNF-α superfamily member 14, receptor activator of NF-κ b ligand, and TNF-α superfamily member 13b. These ligands are released as a cytotoxic response to viral infections or as part of the cellular immunity responses during the stimulation or survival of CD8+ T lymphocytes (cytotoxic T lymphocyte [CTL]) and natural killer (NK) cells. It was assumed that inflammatory bone remodeling disorder in otosclerosis might be characterized by a disturbed balance of apoptosis inhibitor (hCIAP1/2) and inducer (granzyme-β) proteins due to increased expression of TNF-α. Cellular inhibitor of apoptosis 1 (hCIAP1, baculoviral inhibitor of apoptosis repeat 2) and 2 (hCIAP2, baculoviral inhibitor of apoptosis repeat 3) are members of a family of proteins that inhibits apoptosis by binding to TNF receptor-associated factors (TRAF1, TRAF2) and probably by interfering with activation of interleukin-1 converting enzyme proteases. hCIAP1 inhibits apoptosis induced by serum deprivation of menadione, a potent inducer of free radicals. In contrast to

hCIAP1, hCIAP2 does not affect apoptosis induced by menadione exposure. Granzyme-β (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1) is a product of CTL and NK cells. CD8+ T lymphocytes and NK cells share the remarkable ability to recognize specific infected target cells. They are thought to protect their host by inducing apoptosis of infected cells, bearing on their surface „nonself" antigens, usually peptides or proteins resulting from viral infections. Granzyme-β plays a crucial role in the rapid induction of target cell apoptosis by CTL in cell-mediated immune response.

To review our current knowledge of the backgroung of otosclerosis including bone-remodelling disorders, persistent measles virus infection, autoimmunity, inflammation, genetic, hormonal and enviromental factors and to discuss our aims for the experimental work:

1. Detection of measles virus genome from otosclerotic tissues, and identification of the unique CD46 (measles virus receptor) expression pattern of the human otic capsule.

2. To study the variable and unique TNFRI/I expression pattern of the human otic capsule.

3. To study the expression levels of apoptosis inducer (Granzyme-β) and inhibitor (hCIAP1/2) proteins which play important role to the

regulation of disturbed balance beetween cell survival and apoptosis in otosclerosis.

## MATERIALS AND METHODS

According to our aims three experiments were started, the experimental work based on the examination of surgically removed (stapedectomy) ankylotic stapes footplates:

*1.* A total of 51 (n=51; males n=17; females n=34; otosclerotic n=21; nonotosclerotic n=30) surgically removed ankylotic stapes footplates were analyzed by histopatological and molecular biological methods respectively. Nucleic acids were extracted. Measles virus sequences were detected by nucleoprotein RNA-specific reverse transcriptase polymerase chain reaction (RT-PCR). Alteratively spliced RNA of CD46 isoforms was amplified by RT-PCR; cDNA amplimers were separated by poly-acrylamide gel electrophoresis and were purified from the gel. Complementary DNA of CD46 isoforms was restricted by endonuclease enzymes having CD46-specific recognition sites. Anti-measles IgG serum levels were measured by ELISA.

2. Otosclerotic and non-otosclerotic ankylotic stapes footplates (n=80; males n=29; females n=51, otosclerotic n=40; nonotosclerotic n=40) were histologically analyzed: conventional haematoxylin-eosin staining, and tumor necrosis factor-α receptor I and II (TNFRI/II) –specific immunofluorescent assay was performed.

3. Ankylotic stapes footplates (n=40; males n=17; females n=23; otosclerotic n=27; nonotosclerotic n=9; negative control n=4) were histologically analyzed by conventional haematoxylin-eosin staining, and hCIAP1/2 (inhibitors of apoptosis) and Granzyme-β (apoptosis inducer) specific immunofluorescet assays were performed.

**RESULTS**

*1. Detection of measles virus genome and restriction analysis of CD46 variants:*

The presence of viral RNA was associated exclusively with the histopathological diagnosis of otosclerosis; the stapes specimens with negative measles virus belonged to nonotosclerotic stapes fixations. All specimens (n=51) were characterized by the consecutive expression of five CD46 variants (c, d, e, f and one shorter unidentified isoform). Histologically confirmed ostosclerotic specimens (n=21) were characterized by increased expression levels of variant "f" and the unknown isoform. Anti-measles IgG levels were significantly lower in the sera of patients with otosclerosis (median = 6.9 IU/ml) in contrast to the virus negative, nonotosclerotic stapes fixations (median = 142 IU/ml).

*2. TNFRI/II polymorphism:*

Active otosclerosis (Grades I-II; n=24) was featured by increased expression of TNFRII and moderate expression of TNFRI; inactive cases (Grades III-IV; n=16) were characterized by permanent expression of TNFRI; however, TNFRII-specific immunoreaction was absent. Nonotosclerotic stapes specimens showed a negligible TNFR expression. Tumor necrosis factor receptor expression pattern showed a strong correlation with the histologic activity of otosclerosis (Yates-corrected $\chi^2$ test; $p < 0.001$).

*3. Apoptosis inducer and inhibitor proteins:*

Active otosclerosis (n=19) was featured by robust expression of apoptosis inhibitor proteins hCIAP1/2 and negligible expression of Granzyme-β. Inactive cases of otosclerosis (n=8) were characterized by inverse reaction: Granzyme-β was highly expressed; however, hCIAP1/2 specific immunoreactions were absent. Nonotosclerotic and normal stapes specimens showed no considerable little Granzyme-β expression and moderate hCIAP1/2-specific immunoreactions. Expression pattern of apoptosis-associated proteins showed strong correlation with the histologic diagnosis and activity of otosclerosis (Yates-corrected $\chi^2$ test, $p < 0.001$).

## DISCUSSION

Our results confirmed the presence of RNA of the measles virus in the histologically diagnosed otosclerotic stapes footplate specimens. This feature was absolutely independent from the histologic grade of otosclerotic bone remodeling. The failure to detect RNA of the measles virus in the stapes footplates was associated with histologically nonotosclerotic stapes fixation. Ankylotic stapes footplates with negative measles virus belong to degenerative disorders with non-otosclerotic histopathology. Chronic and persistent measles virus replication in the human otic capsule has been identified as one of the main etiological factors of the pathogenesis of otosclerosis. The continuous presence of antigens derived from the measles virus might result in a permanent stimulation of the cellular immune response, leading to a constant inflammatory reaction and cellular damage in the concerned bone tissue; however, defective measles virus is unable to directly destroy the tissue. Immune stimuli mediated by antigen-activated CD3 and CD46 molecules are essential factors in differentiation and activation of regulator T-helper 1 cells. These regulator cells play an important role in the elimination of autoreactive cytotoxic, CD8+ T cells. Inactivation or insufficient differentiation of this regulator T cell population may decrease or deactivate the natural self-tolerance, leading to the appearance of different autoimmune diseases. The unknown shorter CD46 splicing variant is presumably one of the

newly described otosclerosis-associated isoforms. The presence of these otosclerosis-specific CD46 variants on the cells of the human otic capsule probably decreases the measles activated CD3 and CD46 co-stimulation in the differentiation of regulator T-helper 1 cells. These events are supposed to lead to the development of an autoimmune reaction against the otic capsule, which might result in consequent sensorineural hearing loss. Restriction analysis of CD46 splicing variants provided. interesting information about the CD46 isoform co-expression pattern of otosclerotic- and non-otosclerotic stapes footplates. The consistent co-expression pattern of the same five CD46 isoforms, with various and histology-specific expression levels characterized otosclerotic- and non-otosclerotic specimens, respectively. Variants “c”, “d”, “e”, “f” and one more unknown shorter isoform were detected in each specimen. Unlike non-otosclerotic stapes fixation, relatively increased expression levels of variant “f” and the unidentified variant characterized otosclerosis. Exon 13 was missing from the mRNA of variant “f” due to alternative splicing. This exon encodes the main part of the cytoplasmic domain of the CD46 receptor. This domain is responsible for the intracellular phosphorylase-mediated signalization after receptor activation. Lack of exon 13 may produce modified or pathological intracellular signalization. Changes of intracellular signal transduction may determine the susceptibility for persistent measles virus infection.

Present observations provide additional information for the inflammatory pathogenesis of otosclerosis and for the molecular

background of the transition between different histopathologic stages. Overexpression of TNFRI and TNFRII in the early stages of otosclerosis induces an inflammatory osteolytic cascade. Several inflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, transforming growth factor-β) and bone-specific proteins (osteoprotegerin, bone morphogenetic protein, dyastrophic dysplasia sulfate transporter) may play a secondary promoting role in this process. The endpoint of the increased bone turnover is apoptotic cell death with calcification of the osteoid substance: burnout otosclerosis. As to return to previous and current results, different etiopathogenesis of otosclerosis and nonotosclerotic stapes fixations should be distinguished. Otosclerotic bone remodeling disorder shows organotropism to the otic capsule. Foci of otosclerosis are limited to the temporal bone, and no lesions have been found outside the ear. Enchondral ossification develops in the otic capsule and the stapes footplate, and it is completed after 1 year. Once calcified, the otic capsule exhibits no significant remodeling. Interestingly, there is very low-grade remodeling in these sites compared with other parts of the skeleton. Bone turnover is almost completely absent within the bone adjacent to the perilymphatic space. Osteoblastic and osteoclastic activity, normally associated with bone turnover, is rarely, if ever, seen in the adult otic capsule. This otic capsule is formed by 3 bone layers such as the endosteal layer next to the perilymphatic space, the interosseal globules (globuli inerossei), which are embryonic cartilage remnants, and the periosteal layer. The interosseal globules may be the sites of the earliest otosclerotic

foci. The stapes footplate consists of 2 layers of the otic capsule because in this anatomic structure, the endosteal layer is absolutely absent. The hyaline cartilage layer of the vestibular surface of the stapes footplate belongs to the middle layer of the otic capsule and can be assumed as an embryonic remnant. Osteoclasts of otosclerotic bone lesions are featured by undifferentiated embryonic phenotype (expression of CD51/61 antigen), in contrast with those observed in nonotosclerotic stapes fixations. Osteoclasts showing uncommon CD51/61 antigen expression may derive from the resting embryonic cells of globuli interossei, which cannot be identified in the otosclerotic bone. This cellular transformation could explain the absence of these structures observed in manifest otosclerosis. The chondrocyte-like cells forming globuli interossei have a quite slow metabolic activity and persist throughout life without considerable morphologic changes. However, these cells should be considered as pluripotent embryonic remnants, which could be reactivated and transformed into osteoclasts due to inflammatory response induced by measles virus infection. The current observations regarding TNFR expression in different stages of otosclerosis and in hyaline cartilage layer of each ankylotic stapes footplates may suggest the confirmation of these results.

Current investigations are parallel with the previously reported disorders in the molecular interaction of the osteoclast-TNF-α-RANK axis. Increased expression of hCIAP1 and hCIAP2 apoptosis inhibitor proteins could be the molecular response to intense TNF-α release mediated by NK cells and osteoclasts in early

stages of otosclerosis. Tumor necrosis factor-α acts through its decoy receptors (TNFRI and TNFRII), activates the TNFR associated factors (TRAF1 and TRAF2), and induces apoptosis due to activation of variable death domains. Inhibitors of apoptosis do not interact with TNF-α or TNFR but associate with TRAF1 and TRAF2. hCIAP1 and hCIAP2 can directly bind to TNFR-activated caspase 3 and caspase 7 and inhibit their proteolytic activities. Overexpression of apoptosis inhibitors result in increased cell survival, proliferation, and extended os-teoclast activation. As to previous results, average life span of an active otosclerotic focus is approximately 5 to 7 years. During this period, TNF-α and the consecutive hCIAP response run down and result in decreased vascularization and moderate activity of osteoclasts. The amount of the osteoid substance increases, and osteolytic lacunae and pseudovascular spaces are eventually obliterated. Activated NK cells and CD8+ cytotoxic T lymphocytes show further accumulation in the perivascular spaces of the otosclerotic focus with decreasing activity. This stage is the histologic „healing" of otosclerosis; however, on the molecular level, a severe cellular destruction can be considered due to granzyme-β and perforin release from immune cells. The molecular cascade of immune-mediated apoptosis starts, whereas increasing osteoprotegerin production leads to further calcification. The woven and concentric structure of cement lines turns into lamellar pattern with marked thickening. The end point of the increased bone turnover is an apoptotic cell death with calcification and avascularization of the osteoid substance: burnout

otosclerosis. However, further in vitro examinations and tissue culturing will be necessary to confirm these observations in the future.

To date, surgery has become the principal therapeutic tool to improve hearing loss in otosclerosis. However, based on the autoimmune-inflammatory characteristics and the involvement of bone metabolism in the pathogenesis of the disease, pharmacotherapy that includes antiosteoporotic, as well as immunosuppressive, antiinflammatory agents may also be considered at least in the early, active phases of otosclerosis. Current observations may establish the central role of TNF-α and its receptors in the pathologic inflammatory bone remodeling in otosclerosis. Because proinflammatory cytokines, including TNF-α, is abundantly produced in the otosclerotic bone, topical or systemic application of anti-TNF biologics may be a therapeutic option in inflammatory active stages of otosclerosis with SNHL. To date, there has been 1 report regarding the effect of local perfusion of infliximab on autoimmune SNHL. In this study, 9 patients, who could not be tapered off corticosteroids or had relapse after the discontinuation of corticosteroids, were treated for 4 weeks with a weekly infusion of infliximab. Hearing tresholds improved in most patients, and corticosteroids could be tapered off after the administration of TNF blocker. Altogether, 7 of 9 patients responded to infliximab therapy. Short-term recombinant OPG (OPG-Fc) treatment could also have a powerful potent antiosteolytic effect, principally in early stages of otosclerosis. There is a potential use of disrupting RANK-mediated

osteolysis and to preserve normal bone remodeling in otosclerosis with inflammatory background. Regarding the modulation of bone metabolism, bisphosphonates are potent strong inhibitors of bone morphogenetic protein synthesis. There has been some clinical evidence suggesting the efficacy of bisphosphonate treatment in early active stages of otosclerosis. For example, *Brookler* and *Tanyeri* demonstrated efficacy of etidronate in the treatment of SNHL associated with otosclerosis. As to our current knowledge regarding the pathogenesis of otosclerosis, anti-TNF-α biologics may have the most specific and powerful effect in the inhibition of otosclerotic bone remodeling disorder.

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## List of publications related to the dissertation

1. **Csomor, P.**, Sziklai, I., Liktor, B., Z. Szabó, L., Pytel, J., Jóri, J., Karosi, T.: Otosclerosis: Disturbed balance between cell survival and apoptosis.
   *Otol. Neurotol. 31* (6), 867-874, 2010.
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2. **Csomor, P.**, Sziklai, I., Karosi, T.: TNF-[alpha] receptor expression correlates with histologic activity of otosclerosis.
   *Otol. Neurotol. 30* (8), 1131-1137, 2009.
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3. **Csomor, P.**, Szalmás, A., Kónya, J., Sziklai, I., Karosi, T.: Restriction analysis of otosclerosis-associated CD46 splicing variants.
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4. **Csomor, P.**, Liktor, B., Liktor, B., Szekanecz, Z., Sziklai, I., Karosi, T.: Expression of bone morphogenetic protein 2, 4, 5, and 7 correlates with histological activity of otosclerotic foci.
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6. **Csomor, P.**, Liktor, B., Liktor, B., Sziklai, I., Karosi, T.: No evidence for disturbed COL1A1 and A2 expression in otosclerosis.
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IF:1.214 (2010)

7. **Csomor, P.**, Sziklai, I., Karosi, T.: Controversies in RELN/reelin expression in otosclerosis.
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8. Toth, L., **Csomor, P.**, Sziklai, I., Karosi, T.: Biofilm detection in chronic rhinosinusitis by combined application of hematoxylin-eosin and gram staining.
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9. **Csomor P.**, Szalmás A., Kónya J., Karosi T., Sziklai I.: Az otosclerosisra jellemző CD46 variánsok molekuláris biológiai jellemzése.
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13. **Csomor P.**, Karosi T., Pytel J., Jóri J., Z. Szabó L., Liktor B., Sziklai I.: A TNF-alfa receptor expresszió összefügg az otosclerosis szövettani aktivitásával.
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*Otol. Neurotol. 30* (8), 1058-1066, 2009.
DOI: http://dx.doi.org/10.1097/MAO.0b013e31819fe802
IF:1.435

17. Karosi T., Tóth Á., **Csomor P.**, Sziklai I.: Differenciáldiagnosztikai nehézséget okozó, retrochoanális orrpolyp: Esetismertetés.
*Fül-Orr-Gégegyógy. 55* (4), 164-168, 2009.

18. Karosi, T., Szalmás, A., **Csomor, P.**, Kónya, J., Petkó, M., Sziklai, I.: Disease-associated novel CD46 splicing variants and pathologic bone remodeling in otosclerosis.
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DOI: http://dx.doi.org/10.1097/MLG.0b013e31817c133d
IF:1.877

**Total IF: 16.131**

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The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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