Are the studies validated on RANTES/CCL5 in bone marrow defects in the jaw?

15 scientific publications by Dr.Dr (PhD-UCN). J. Lechner in abstracts and free PDF downloads.

Several publications by Dr. Lechner and co-authors W. Mayer and Dr. V. von Baehr have been accepted by international medical journals on the topic of "**Dental interference fields and systemic diseases**". Consistent theme of this publication series is research of silent chronic **fatty degenerative inflammation of the jaw bone** (**FDOK**, also called "maxillary osteitis",
"NICO"), where the key pathogenetic element is the chemokine RANTES/CCL5 in up to 60-fold overexpression. RANTES/CCL5 is implicated in many systemic diseases - rheumatoid arthritis, breast cancer, Hashimoto's disease, melanoma, multiple sclerosis, ALS, etc. Our first laboratory detection of this inflammatory messenger in the jawbone is the contradiction-free proof of a holistic-systemic signaling effect from the jawbone with modern immunological methods. Since these articles have been peer reviewed by several experts and included in the PubMed or ScienceDirect (Elsevier) medical library for their academic rigor, these articles are to be considered accepted science and natural science undisputed part of medical progress.

The listing is chronological; always indicated is the link to the corresponding journal, followed by the link in PubMed.

1. June 2010: **European Journal of Integrative Medicine** *"Immune messengers in Neuralgia Inducing Cavitational Osteonecrosis (NICO) in jawbone and systemic interference".* http://dx.doi.org/10.1016/j.eujim.2010.03.004

Kostenpflichtiger Download in ScienceDirect (Elsevier) unter:
http://www.sciencedirect.com/science/article/pii/S1876382010000260

Focus and conclusion: pilot study of 6 cases revealing RANTES and FGF-2 out of 27 cytokines studied as singularly extremely overexpressed inflammatory messengers in chronic fatty degenerative altered jawbone (FDOK/"NICO"/jaw ostitis).

2. April 2013: **International Journal of General Medicine: Lechner J, von Baehr V.** *"RANTES and fibroblast growth factor 2 in jawbone cavitations triggers for systemic disease"*

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Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23637551

Focus and conclusion: RANTES and FGF-2 in FDOK as promoters of many immunological and neurodegenerative systemic diseases (rheumatoid arthritis, tumors, Hashimoto's, MS/ALS) when extremely overexpressed in the jawbone.

3. May 2014: **Journal of Breast Cancer: Basic and Clinical Research:** Lechner J, von Baehr V. "*Hyperactivated Signaling Pathways of Chemokine RANTES/CCL5 in Osteopathies of Jawbone in Breast Cancer Patients – Case Report and Research"*.

Free Download: http://journals.sagepub.com/doi/pdf/10.4137/BCBCR.S15119

Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/24899812

"Article Metrics" at the bottom of the journal website shows number of retrievals and their global distribution:

Over 2,000 views(?) by April 2021.

Focus and conclusion: Case description: Extremely overexpressed RANTES in a FDOK sample from a breast cancer patient with metastasis of the tumor to the jawbone. Can RANTES be a contributory cause of breast cancer development and metastasis? (English). Surgical removal of FDOK may decrease RANTES expression and be used to treat inflammatory systemic disease.

4. August 2014: **Clinical, Cosmetic and Investigational Dentistry: "***Validation of dental X-ray by cytokine RANTES – comparison of X-ray findings with cytokine overexpression in jawbone".*

Free Download: http://www.dovepress.com/articles.php?article_id=18049.

Over 12,888 views by July 2021.

Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/25170282

Focus and conclusion: Fatty degeneration of the jaw (FDOK) as a source of RANTES cannot be detected with conventional radiographs/OPGs. Complementary ultrasound measurement of bone density (transalveolar ultrasound TAU) should be used to diagnose FDOK.

5. May 2015: **EPMA Journal** (European Association for Predictive, Preventive and Personalized Medicine): Lechner J, von Baehr V. *"Chemokine RANTES/CCL5 as an unknown link between wound healing in the jawbone and systemic disease: is prediction andtailored treatments in the horizon?"*.2015, 6:10. doi:10.1186/s13167-015-0032-4

Free Download: https://doi.org/10.1186/s13167-015-0032-4

Over 2,800 views by July 2021.

Link in PubMed: https://pubmed.ncbi.nlm.nih.gov/25987906/

Focus and conclusion: areas of incompletely healed surgical and extraction wounds in the jaw in the form of

Areas of incompletely healed surgical and extraction wounds in the jaw in the form of fatty degenerative osteolysis of the jaw (=FDOK) represent a little-known inflammatory phenomenon, since **the cell response is not bacterial or viral, but is triggered by persistent metabolic derailments**. Carriers of these abacterial and aviral cell responses are cytokines (FGF-2 and MCP-1) and primarily the chemokine RANTES. The systemic inflammatory effects of chronic RANTES overexpression in areas of impaired wound healing in the jaws have been pointed out by the authors in previous publications.

6. June 2015: Lechner J, von Baehr V. **Evidence-Based Complementary and Alternative Medicine** *"Peripheral Neuropathic Facial/Trigeminal Pain and RANTES/CCL5 in Jawbone Cavitation"*, Vol. 2015, Article ID 582520, 9 pages, 2015. doi:10.1155/2015/582520

Free Download: http://www.hindawi.com/journals/ecam/2015/582520/

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Table of Contents of Volume 2015: http://www.hindawi.com/journals/ecam/contents/

Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/25987906

Focus and conclusion: Atypical facial pain and trigeminal neuralgia (ATG/TrN) are common causes of suicide. Opioid receptors play an important role in pain transmission in both peripheral and CNS neurons, but are inhibited by RANTES/CCL5, which amplifies pain signals. Since we demonstrated the extreme overexpression of RANTES in fatty degenerative osteolysis of the jawbone (FDOK) in previous studies (see w.w.o.), it is obvious to mitigate a reduction of RANTES signaling in ATG/TrN by surgically clearing the FDOK areas. In ATG/TrN, the triggering FDOK areas are also called "NICO" in the literature. In 15 patient cases, the study proves RANTES overexpression and remediation therapeutic success of pain reduction.

7. July 2017: **Journal of BIOLOGICAL REGULATORS:** J Lechner [1], K Huesker [2], V VonBaehr [3].“ *The impact of RANTES from jawbone on Chronic Fatigue Syndrome”.*

Abstract www.biolifesas.org/contentsJBRHA.htm **JBRHA 31, No. 2, April - June 2017**

Link in PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=Lechner+J+CFS

Focus and conclusion: Does chronic inflammation in the jawbone contribute to the development of chronic fatigue syndrome (CFS)? Fatty degenerative osteonecrosis of the jawbone (FDOK) may contribute to CFS by inducing inflammatory mediators. To clarify neurological interactions, samples from 21 CFS patients were analyzed from retromolar wisdom teeth. Each of the retromolar maxillary samples showed FDOK with high expressions of RANTES/CCL5 (R/C). The FDOK cohort showed a 30-fold mean overexpression of R/C compared to healthy controls. Since R/C has been discussed in the literature as contributing to inflammatory diseases, we hypothesize that FDOK may hyperactivate signaling pathways in areas of incomplete wound healing in the jawbone and represent a previously unknown cause for the development of CFS.

8. October 2017: Lechner J, von Baehr V. **Clinical, Cosmetic and Investigational Dentistry: “**Aseptic-avascular osteonecrosis: local “silent inflammation” in the jawbone and RANTES/CCL5 overexpression.” 2017:9 99-109.

Free Download: https://www.dovepress.com/articles.php?article_id=35541.

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Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/29184447

Focus and conclusion: In ICD-10, the disease name is: "Idiopathic aseptic bone necrosis" in combination with "avascular bone necrosis" also in the maxillary bone (KK). The literature speaks abbreviated of "aseptic ischemic osteonecrosis in the KK/jawbone" (AIOJ). To elucidate clinical details on this, abnormal osteolytic samples of KK are examined in a collective of 24 patients with different systemic immunological diseases in four steps: preoperative dental radiography and postoperative histology, PCR-DNA- bacterial analysis and RANTES/CCL5 expression. The comparison shows that **neither radiography nor histology, clear evidence of inflammatory processes and the PCR examination give no indication of a microbial load in the jaw samples**. However, a consistent overexpression of the chemokine RANTES/CCL5 in the AIOJ specimens is striking. This work substantiates the aseptic existence of inflammation in the KK, clinically proceeding as "silent inflammation". The difficult-to-interpret term in ICD-10 (AIOJ) is substantiated with clinical content and its cytokine expression explains the immunological-systemic effect in the studied patient collective.

9. April 2018: **International Journal of General Medicine:** *" The vitamin D receptor and the etiology of RANTES/CCL-expressive fatty-degenerative osteolysis of the jawbone: An interface between osteoimmunology and bone metabolism"*.
Doi https://doi.org/10.2147/IJGM.S152873

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Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/29731660

Focus and conclusion: Recent research on vitamin D shows that our understanding of the factors that lead to chronic inflammation should be overhauled. One of the key mechanisms by which microbes succeed in immunosuppression, could be the suppression of one of the body's most prevalent nuclear receptors, the vitamin D receptor (VDR). Autoimmune diseases could thereby correlate with a deactivated VDR (VDR-deac) if the receptor cannot transcribe antimicrobial agents. Excess 1,25-dihydroxylvitamin D is not broken down into 25-hydroxyvitamin D, so that high 1,25D levels are counterbalanced by low 25D levels. Because

1,25-dihydroxylvitamin D promotes osteoclast activity, causing osteoporosis, fatty degenerative osteolysis of the jaw (FDOK), which we have described, may also be related to VDR-deac. VD turnover, immune system, and quality of bone loss and formation in the jaw are interrelated factors that may be amplified in chronic inflammatory processes. This work examines in patients with FDOK and diagnosed with immunological systemic diseases (ISD) **the connection of immunology and bone metabolism**. It establishes a link between fatty degenerative osteolysis of the jawbone (FDOK), its RANTES/CCL5 overexpression and a VDR-deac. **Clinical data demonstrate the interaction of a VDR-deac with proinflammatory RANTES/CCL5 overexpression in patients.**

10. June 2018: **EPMA Journal/Springer:** Lechner, J., Noumbissi, S. von Baehr, V. "*Titanium implants and silent inflammation in jawbone – a critical interplay of dissolvedtitanium particles and cytokines TNF-a and RANTES/CCL5 on overall health?*" EPMA Journal (2018). https://doi.org/10.1007/s13167-018-0138-6

Free PDF Download : http://link.springer.com/article/10.1007/s13167-018-0138-6

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Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/30174768

Titanium implants and silent inflammation in the jawbone - a critical association of dissolved titanium particles and the cytokines TNF-a and RANTES / CCL5 with systemic health?

Background and introduction: It is a well-known fact that titanium particles originating from dental titanium implants (DTI) diffuse into the surrounding bone.

Although titanium (TI) is considered a compatible implant material, there is growing concern that the dissolved titanium particles trigger inflammatory reactions around the implant.

Specifically, the inflammatory cytokine tumor necrosis factor alpha (TNF-α) is expressed in the adjacent bone. The transition from TNF-α-induced local inflammation after DTI insertion to a chronic stage of "silent inflammation in the jawbone" could be a neglected cause of unexplained disease.

Material and methods: The signaling pathways involved in the induction of cytokine release were analyzed by multiplex analysis. We analyzed samples of jawbone (KK) for seven cytokines in two groups: Samples from 14 patients were analyzed in areas of DTI for particle-

mediated release of cytokines. Each of the tissue samples adjacent to a DTI showed clinically fatty degenerative and osteonecrotic medullary changes (FDOK) in the KK. Samples from 19 patients were from healthy KK. In five cases, we measured the concentration of dissolved Ti particles spectrometrically.

Results: All DTI-FDOK samples showed RANTES / CCL5 (R / C) as the only extremely overexpressed cytokine. The DTI-FDOK cohort showed a 30-fold mean overexpression of R / C compared with a control cohort of 19 healthy KK samples. The concentration of dissolved Ti particles in DTI-FDOK was 30-fold higher than an estimated maximum of 1,000 µg / kg.

Discussion: Since R / C is discussed in the literature as a possible cause of inflammatory diseases, the work presented here investigates whether DTI can trigger the development of chronic inflammation in the jawbone in the presence of an impaired healing process. Such changes in areas of the KK may become hyperactivated signaling pathways of TNF-a induced R / C overexpression and unrecognized sources of silent inflammation. This may contribute to disease patterns such as rheumatoid arthritis, multiple sclerosis and other systemic inflammatory diseases, which is discussed in detail in scientific publications.

Conlusion: From a systemic perspective, we recommend that more attention be paid to cytokine overexpression caused by dissolved Ti particles from DTI in medicine and dentistry. This may contribute to the further development of personalized strategies in preventive medicine.

11. November 2018: Lechner J, Rudi T, von Baehr V. **Clinical, Cosmetic and Investigational Dentistry: "***Osteoimmunology of Tumor Necrosis Factor-alpha, Interleukin 6, and RANTES/CCL5: A Review of Known and Poorly Understood Inflammatory Patterns in Osteonecrosis*

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Background: Immune and bone systems are closely linked via cytokine cell communication. This interdisciplinary field of research is called osteoimmunology and covers inflammatory and osteoresorptive diseases with primary expression of tumor necrosis factor-alpha (TNF-a) and interleukin 6 (Il-6).

Question: Are there bone resorptive processes whose chronic inflammatory states are not associated with expression of TNF-a and Il-6, but with expression of other cytokines?

Material und methods: Umfangreiche Literaturrecherche in PubMed central.

Discussion: Although in all diseases with bone resorption cytokines TNF-a and IL-6 are in the foreground of the inflammatory-destructive process, an exception is found in the literature: Fatty degenerative osteporosis/osteolysis in the jawbone (FDOK) shows morphologically massive bone softening, although TNF-a and IL-6 are below the levels of healthy jawbone. In contrast, up to 35-fold overexpression of the chemokine RANTES/CCL5 (R/C) is striking in all FDOK areas studied in the literature so far.

Conclusion: FDOK appears to represent a cytokine and inflammatory pattern with osteolysis unique in the body. R/C can be defined as the dominant carrier of a "Maxillo-mandibular osteoimunology".

12. August 2019: Lechner J, Schulz T, von Baehr V. **EPMA Journal/Springer:** *"Immunohistological staining of unknown chemokine RANTES/CCL5 expression in jawbone marrow defects – osteoimmunology and disruption of bone remodeling in clinical case studies targeting on predictive preventive personalized medicine".* EPMA Journal, (2019), 1-14. DOI 10.1007/s13167-019-00182-1

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Immunohistochemical staining of unknown chemokine RANTES/CCL5 expression in maxillary medullary defects - Osteoimmunology and bone remodeling disorders in clinical case studies, from the perspective of predictive preventive and personalized medicine.

Fat-degenerative osteonecrosis in maxillary bone marrow (FDOJ) can be identified as a poorly understood source of RANTES/CCL5 (R/C) overexpression. R/C also interferes with bone metabolism, leading to osteolysis in FDOJ areas. Many dental procedures (extraction, surgery, implants) require functional repair mechanisms that can be disrupted by R/C overexpression. Immunochemical staining is needed to elucidate how R/C expression of adipocytes in FDOJ causes disruption of osteogenesis and effects on medullary stem cells. We examined tissue samples from 449 patients with FDOJ to determine the level of chemokine R/C using Luminex® analysis. In six clinical case studies of FDOJ, we compare Hounsfield bone density, histological findings, R/C expression, and immunohistochemical

staining. R/C is overexpressed by up to 30-fold in the 449 FDOJ- cases compared with healthy jawbone samples. The six clinical cases consistently show severely reduced bone density (i.e., osteolysis), but vary in the degree of agreement between the other three parameters. R/C from FDOJ sources may be involved in multiple immune responses and may be considered an important pathogenetic pathway for increased adipogenesis and for lack of osteogenesis. Adipocytes act pathogenically via R/C expression in local FDOJ and systemically on the immune system.

Focus and conclusion: R/C can be considered an important trigger for possible pathological developments in the fate of hematopoietic stem cells. FDOJ is not a rigidly uniform process but reflects changing developmental stages. The absence of correlating findings should not be interpreted as a misdiagnosis. It seems appropriate to continue research in the field of "maxillo-mandibular osteoimmunology" and focus on R/C overexpression in FDOJ areas.

13. April 2021: Lechner J, Schulz T, Lejeune B, von Baehr V. Jawbone Cavitation Expressed RANTES/CCL5: Case Studies Linking Silent Inflammation in the Jawbone with Epistemology of Breast Cancer. *Breast Cancer (Dove Med Press)*. 2021; 13: 225-240; https://doi.org/10.2147/BCTT.S295488

Link on journal: https://www.dovepress.com/articles.php?article_id=63767.

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Link to paper on PubMed: https://pubmed.ncbi.nlm.nih.gov/33859496/

Background: The role of signaling pathways as part of cell-cell communication within tumor progression is considered a crucial process. The chemokine RANTES (regulated upon activation, normally T-cell expressed and secreted), also known as chemokine C-C motif ligand 5 (CCL5) (R/C), is a protein that has been the focus of cancer research due to its association with aggressive tumor development.

Purpose: Studies of fat degenerative osteonecrosis in the jawbone (FDOK) show a striking overexpression of R/C in these areas. Here, we seek to elucidate a possible link between R/C in the jawbone and breast cancer (BM) and compare these findings by immunohistochemical staining.

Methods: 39 FDOJ samples from 39 female BK patients and samples from 19 healthy controls were analyzed for R/C expression by bead-based Luminex® analysis. R/C levels of 5 BK patients were measured in serum before and after FDOJ surgery. Bone density, histology, R/C expression and immunohistochemistry were analyzed in 4 clinical case studies. R/C

staining of two FDOK-BK patients were compared with immunohistochemical staining of BK cell preparations.
Results: High overexpression of R/C was detected in all FDOK samples. Serum R/C levels were statistically downregulated after FDOK surgery (p=0.0241). Discussion: R/C-induced "silent inflammation" in BM is frequently discussed in scientific papers, as well as the triggering of various signaling pathways by R/C, which may be a key point in the development of BM.
Conclusion: The authors hypothesize that FDOK may serve as a trigger of BM progression through R/C overexpression and thus encourage clinicians throughout the dental and medical community to clarify the presence of FDOK in BM cases.

14. April 2021: Lechner J, Schmidt M, von Baehr V, Schick F. Undetected Jawbone Marrow Defects as Inflammatory and Degenerative Signaling Pathways: Chemokine RANTES/CCL5 as a Possible Link Between the Jawbone and Systemic Interactions? *J Inflamm Res*. 2021; 14: 1603-1612; https://doi.org/10.2147/JIR.S307635

Link on journal: https://www.dovepress.com/articles.php?article_id=64152

Link to PubMed: https://pubmed.ncbi.nlm.nih.gov/33911892/

Background: Cytokines, especially chemokines, are of increasing interest in immunology. This study characterizes the little-known phenomenon of “bone marrow defects of the jawbone” (BMDJ) with known overexpression of the chemokine RANTES/CCL5 (R/C).

Purpose: Our investigation clarifies why BMDJ and the intensity of local R/C overexpression are challenging to detect, as examined in patients with seven different systemic immunological diseases. Specifically, we investigate whether R/C overexpression is specific to certain disease groups or if it represents a type of signal disruption found in all systemic immunological diseases.
Patients und Methods: In a total of 301 patients, BMDJ was surgically repaired during clinical practice to reduce “silent inflammation” associated with the presence of jaw-related pathologies. In each case of BMDJ, bone density was measured preoperatively (in Hounsfield units [HU]), while R/C expression was measured postoperatively. Each of the 301 patients suffered from allergies, atypical facial and trigeminal pain, or were diagnosed with neurodegenerative diseases, tumors, rheumatism, chronic fatigue syndrome, or parasympathetic disorders.
Results: In all BMDJ cases, strongly negative HU values indicated decreased bone density or osteolysis. Consistently, all cases of BMDJ showed elevated R/C expression. These findings were consistently observed in every disease group.

Discussion: BMDJ was confirmed in all patients, as verified by the HU measurements and laboratory results related to R/C expression. The hypothesis that a specific subset of the seven disease groups could be distinguished either based on the increased presence of BMDJ and by the overexpression of R/C could not be confirmed. A brief literature review confirms the importance of R/C in the etiology of each of the seven disease groups.

Conclusion: In this research, the crucial role played by BMDJ and the chemokine R/C in inflammatory and immune diseases is discussed for seven groups of patients. Each specific immune disease can be influenced or propelled by BMDJ-derived R/C inflammatory signaling pathways.

Over 1,210 views by July 2021.

15. July 2021: Lechner J, von Baehr V, Schick F. RANTES/CCL5 Signaling from JawboneCavitations to Epistemology of Multiple Sclerosis – Research and Case Studies. *Degener Neurol Neuromuscul Dis*. 2021; 11: 41-50. https://doi.org/10.2147/DNND.S315321.

Link to paper in journal: https://www.dovepress.com/articles.php?article_id=66565

Link to paper on PubMed: https://pubmed.ncbi.nlm.nih.gov/34262389/

Background: The role played by signaling pathways in the cell–cell communication associated with multiple sclerosis (MS) progression has become a critical area in research. Chemokine RANTES (regulated upon activation, normal T-cell expressed and secreted), also named chemokine C-C motif ligand 5 (CCL5; R/C), is a protein that has been investigated in neuroinflammatory research due to its link to MS development.

Purpose: Research on bone marrow defects in the jawbone (BMDJ), which morphologically presents as fatty-degenerative osteonecrosis of the jawbone (FDOJ), presents overexpression of R/C signaling in affected areas. Here, we try to elucidate the potential link between jawbone-derived R/C and MS.

Methods: Seventeen BMDJ/FDOJ samples extracted from 17 MS patients, as well as samples from 19 healthy controls, were analyzed for R/C expression using bead-based Luminex® analysis. The serum R/C levels from 10 MS patients were examined. Further, bone density, histology, and R/C expression were analyzed in two clinical case studies.

Results: High R/C overexpression was found in all BMDJ/FDOJ samples obtained from the MS group. Serum R/C levels were also upregulated in the MS group. R/C serum levels in the MS cohort were higher than in the healthy controls. In contrast, the histology of BMDJ/FDOJ

samples showed no inflammatory cells.

Discussion: R/C-induced “silent inflammation” in MS is widely discussed in the scientific literature, along with R/C triggering of inflammation in the central nervous system, which might be key in the development of MS.

Conclusion: The authors suspect that BMDJ/FDOJ may serve as a trigger of MS progression via R/C overexpression. As such, the dental and medical communities should be made aware of BMDJ/FDOJ in cases of MS.

Keywords: chemokine RANTES/CCL5, multiple sclerosis, bone marrow defects in the jawbone, osteonecrosis of the jawbone, hyperactivated signaling pathways

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