



Chemokine RANTES/CCL5 from Jawbone Cavitations

- Hidden Interface to Many
Systemic-Immunological Diseases

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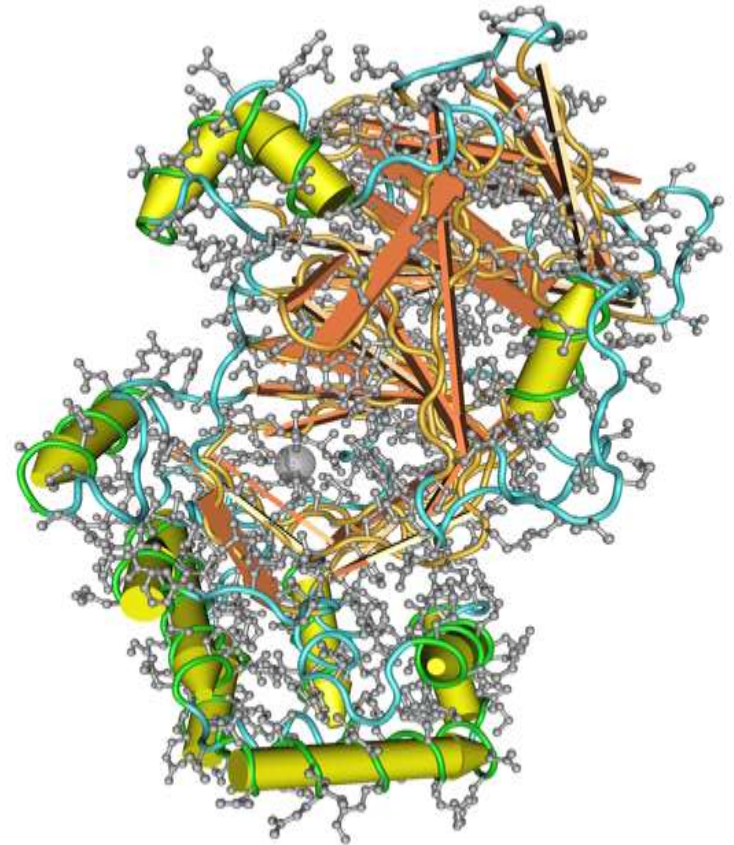


What is RANTES?

**Proinflammatory
Chemokine CCL-5/**

RANTES:

regulated on activation,
normal T cell expressed
and secreted



Why is RANTES/CCL5 of interest for dentist?

The critical interplay of
jawbone cavitations/bone marrow defects
and RANTES/CCL5 overexpression
in jawbone areas

Jawbone cavitations

without typical signs of acute inflammation

filled with **fatty-degenerated adipocytes**

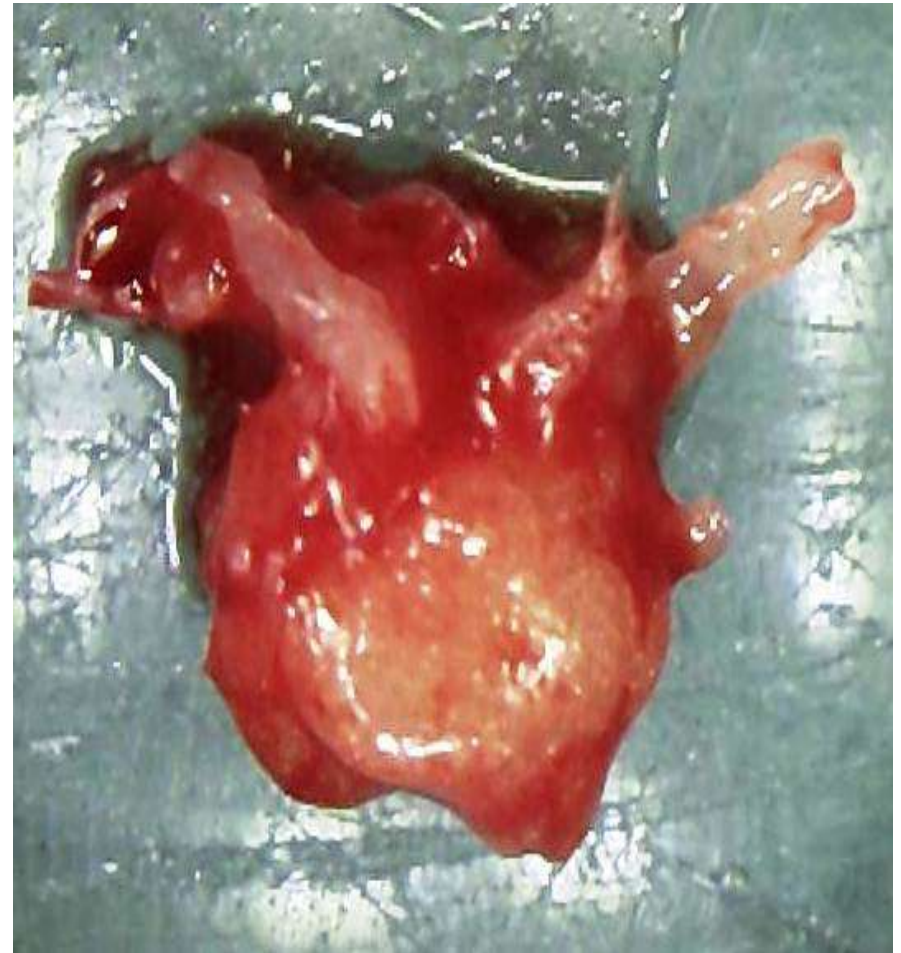
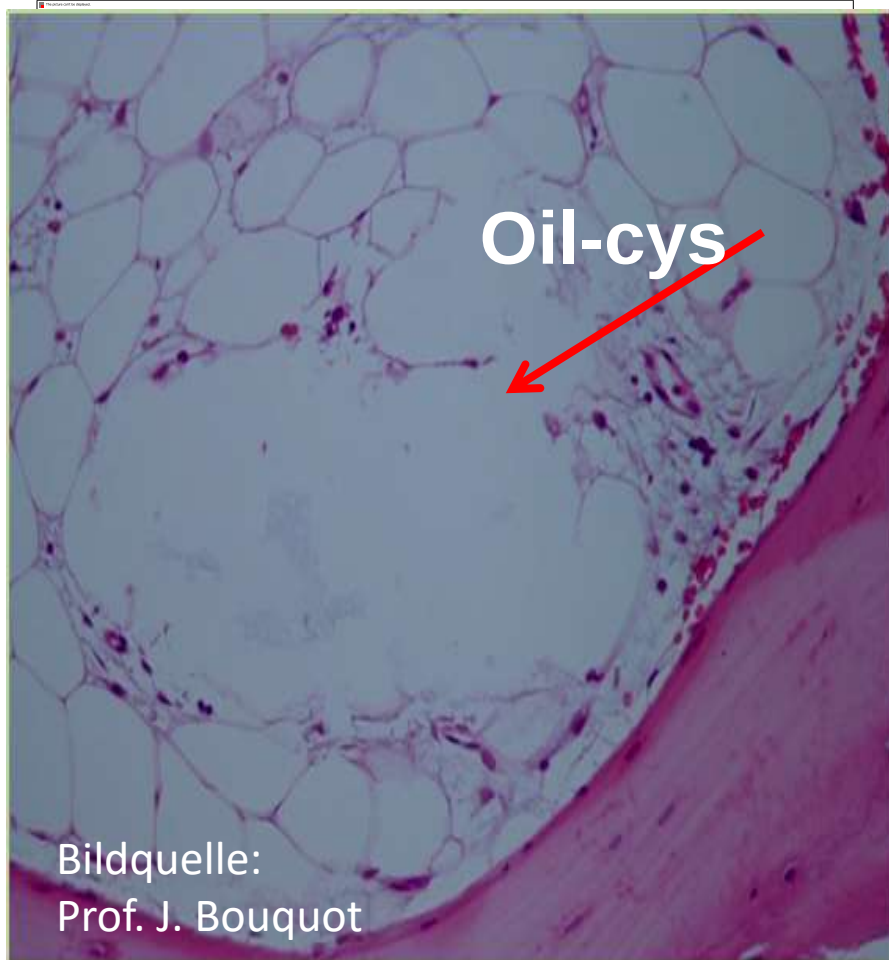
fatty degenerated osteolysis
of jawbone - FDOJ

in cases of facial/trigeminal
pain is also called “NICO”
(Bouquot: Neuralgia inducing
cavitation osteonecrosis)



1:12

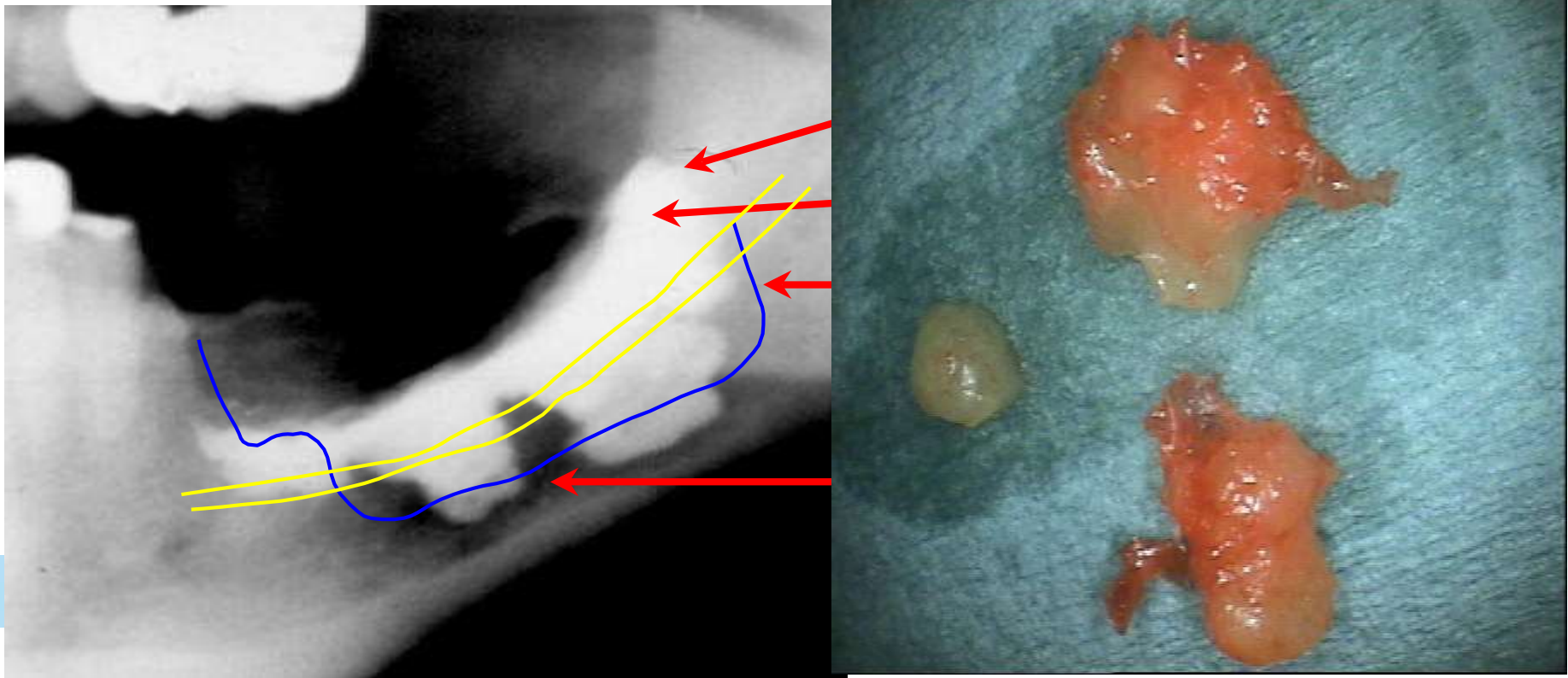
The object of our interest: Morphology and extent of a Fatty-degenerative osteolysis/osteonecrosis of jawbone (**FDOJ**)

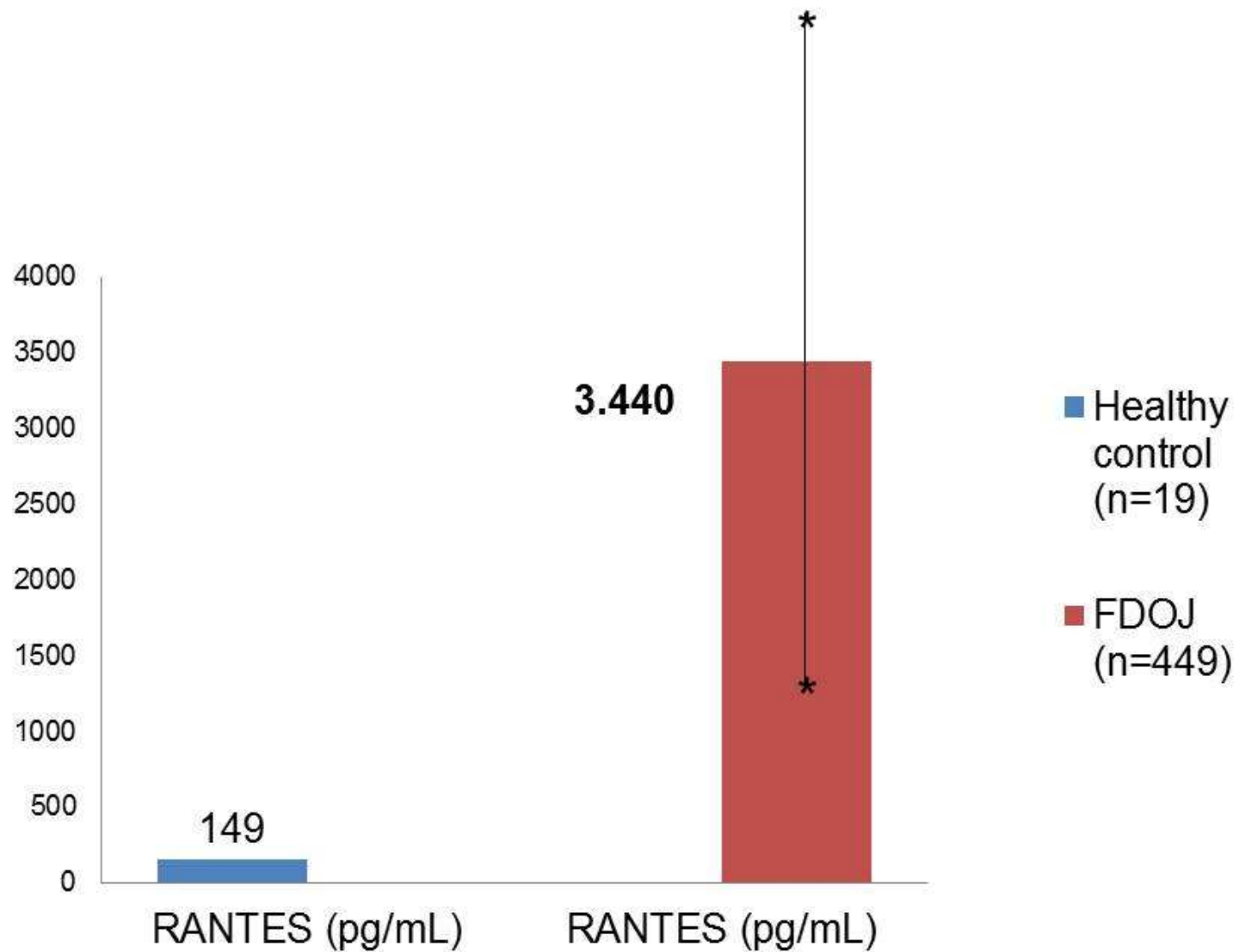


The guiding question of the presented research was:

Does FDOJ contain inflammatory immune messengers?

Can immune messengers-Cytokines in FDOJ possibly be related to silent inflammation and to systemic diseases?



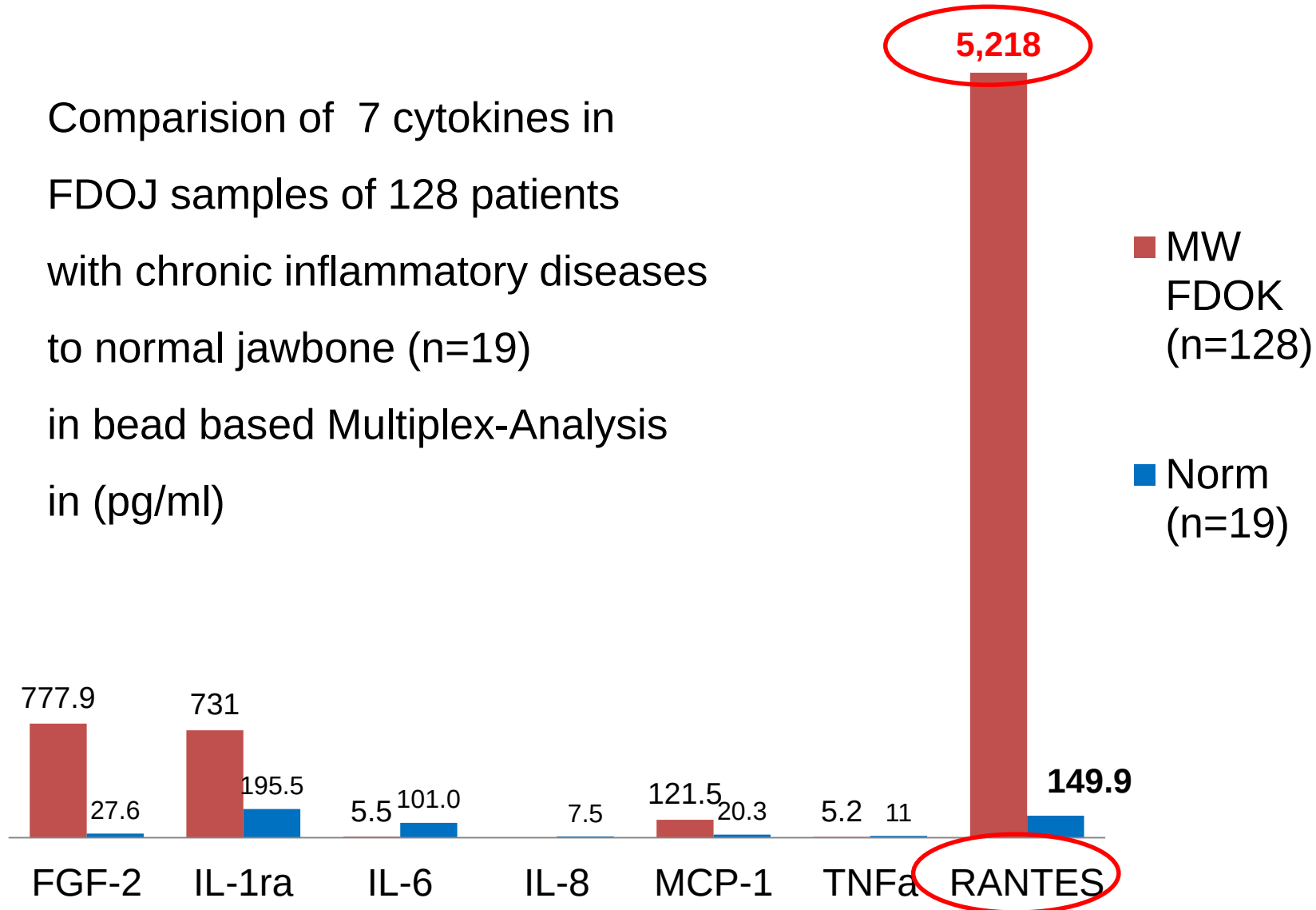


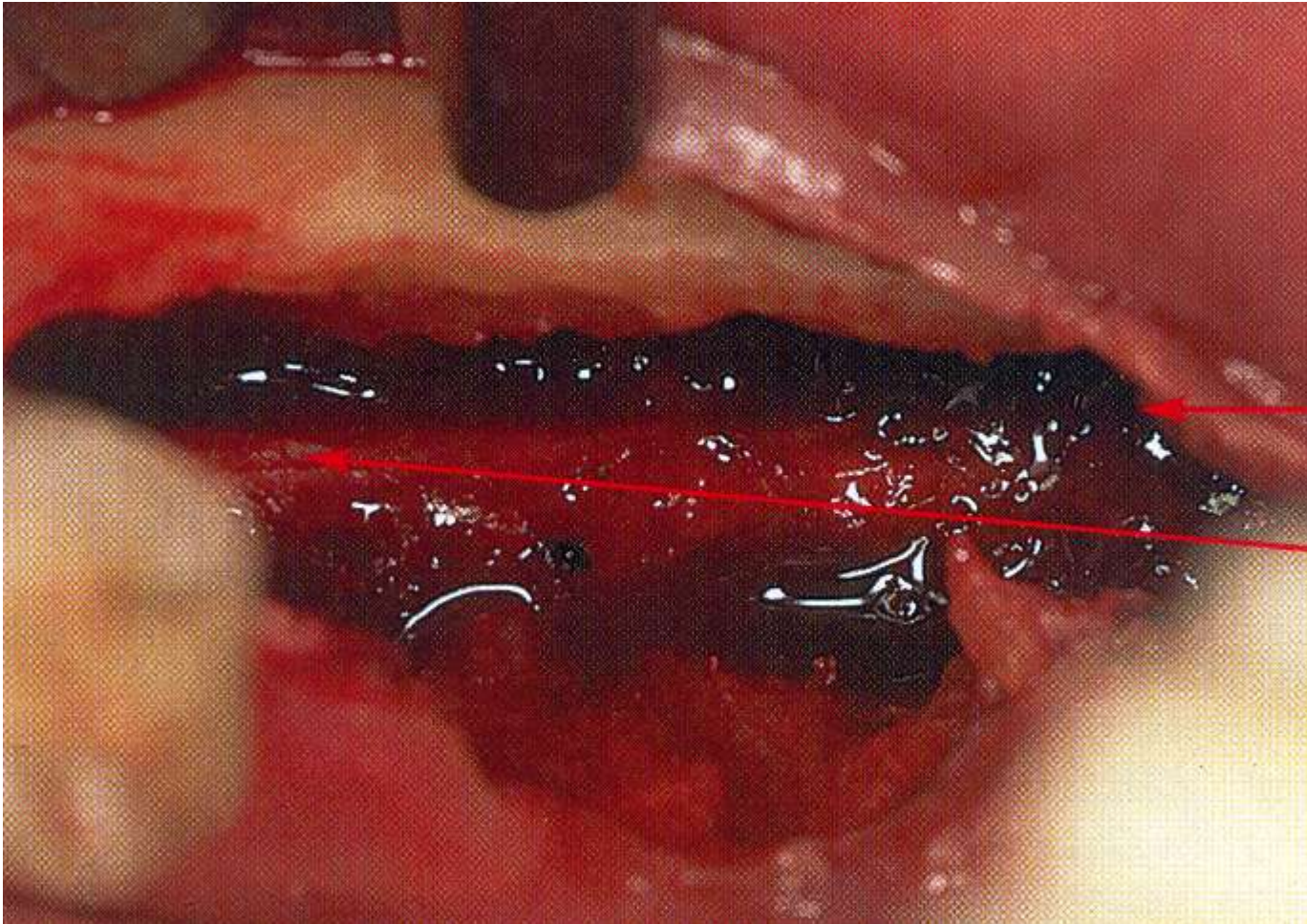
"Elephant
in the room"



Is the local RANTES/CCL5 overexpression in
jawbone marrow defects of interest for general health?

Comparison of 7 cytokines in
FDOJ samples of 128 patients
with chronic inflammatory diseases
to normal jawbone (n=19)
in bead based Multiplex-Analysis
in (pg/ml)





Manibular Nerve

Characteristics of RANTES

RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted),
CCL-5 = [chemotactic cytokine](#) = [chemokine](#).

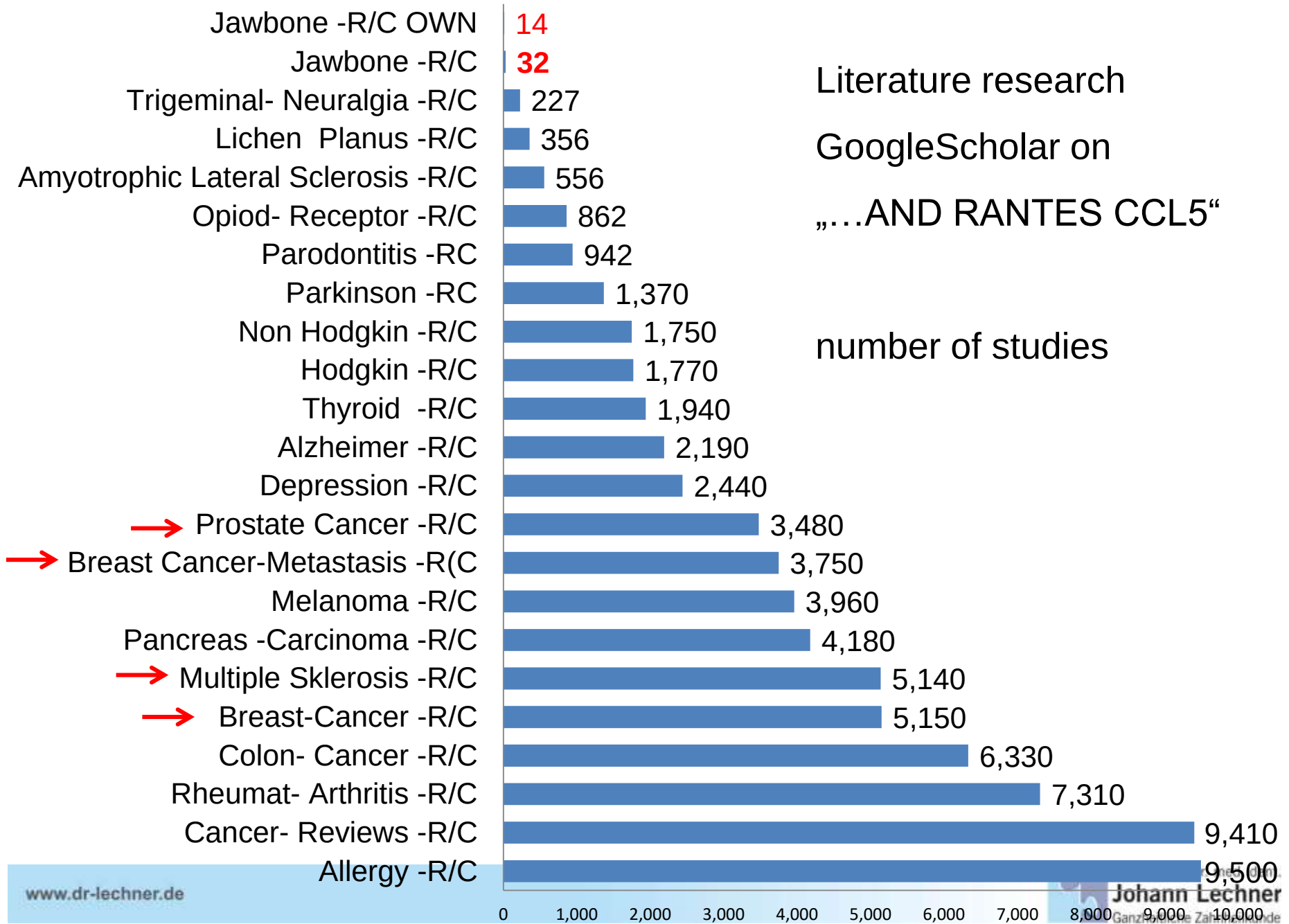
RANTES can have detrimental effects via the recruitment of immune cells that **enhance inflammatory processes such as arthritis, atopic dermatitis, nephritis, colitis, and other disorders** (Appay, V., S. L. Rowland-Jones. 2001. RANTES: a versatile and controversial chemokine. Trends Immunol. 22: 83-87)

RANTES targets the central nervous system and is **able to cause multiple sclerosis and Parkinson's disease**. In targeting mast cells, **RANTES causes allergies, alopecia (marked by hair loss), and thyroid disorders**.
(Rossi, D., A. Zlotnik. 2000. The biology of chemokines and their receptors. Annu. Rev. Immunol. 18: 217-242)

Why is RANTES/CCL5 interesting
for general health?

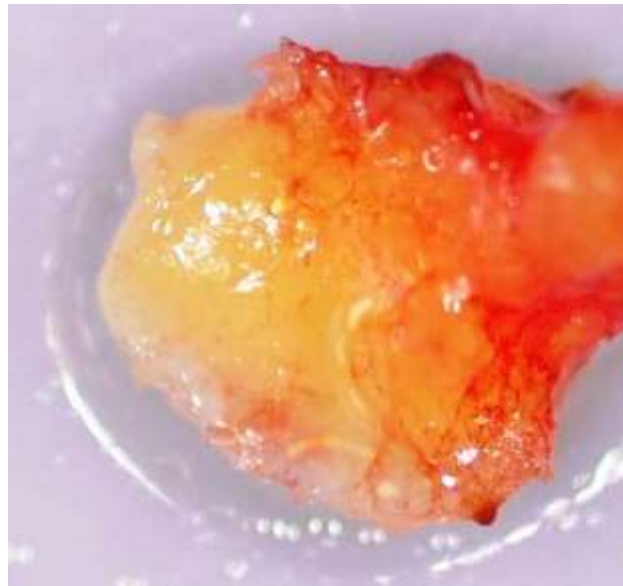
A simple answer is a literature research
in GoogleScholar on

„*DISEAS* AND RANTES CCL5“



Bead-based processing (Luminex®):

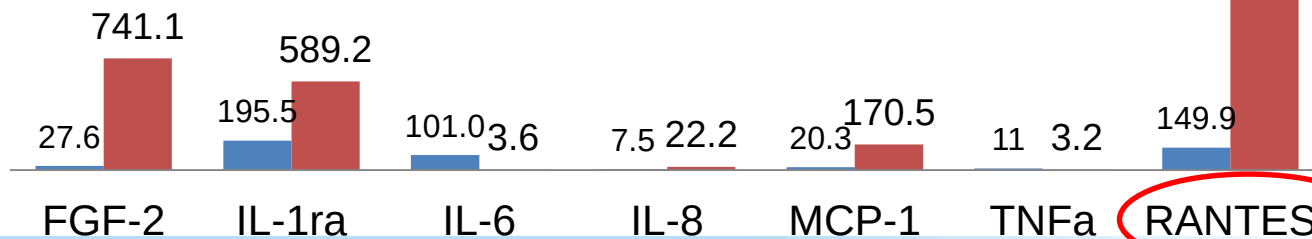
7 cytokines in FDOJ (pg/ml) in **BC patients** (n=23) compared to normal jawbone (n=19) (pg/ml)



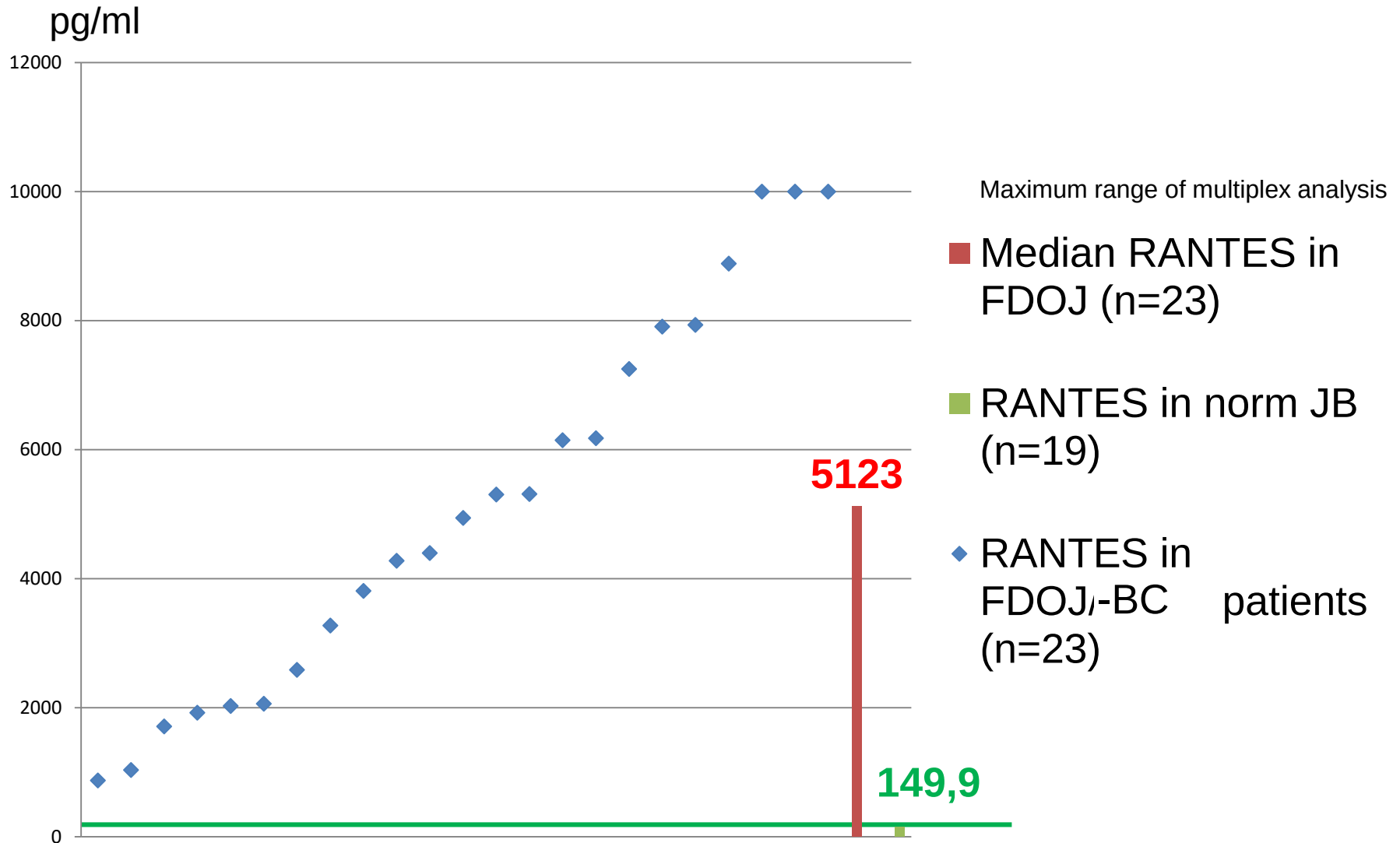
5.123

■ Norm
jawbone
(n=19)

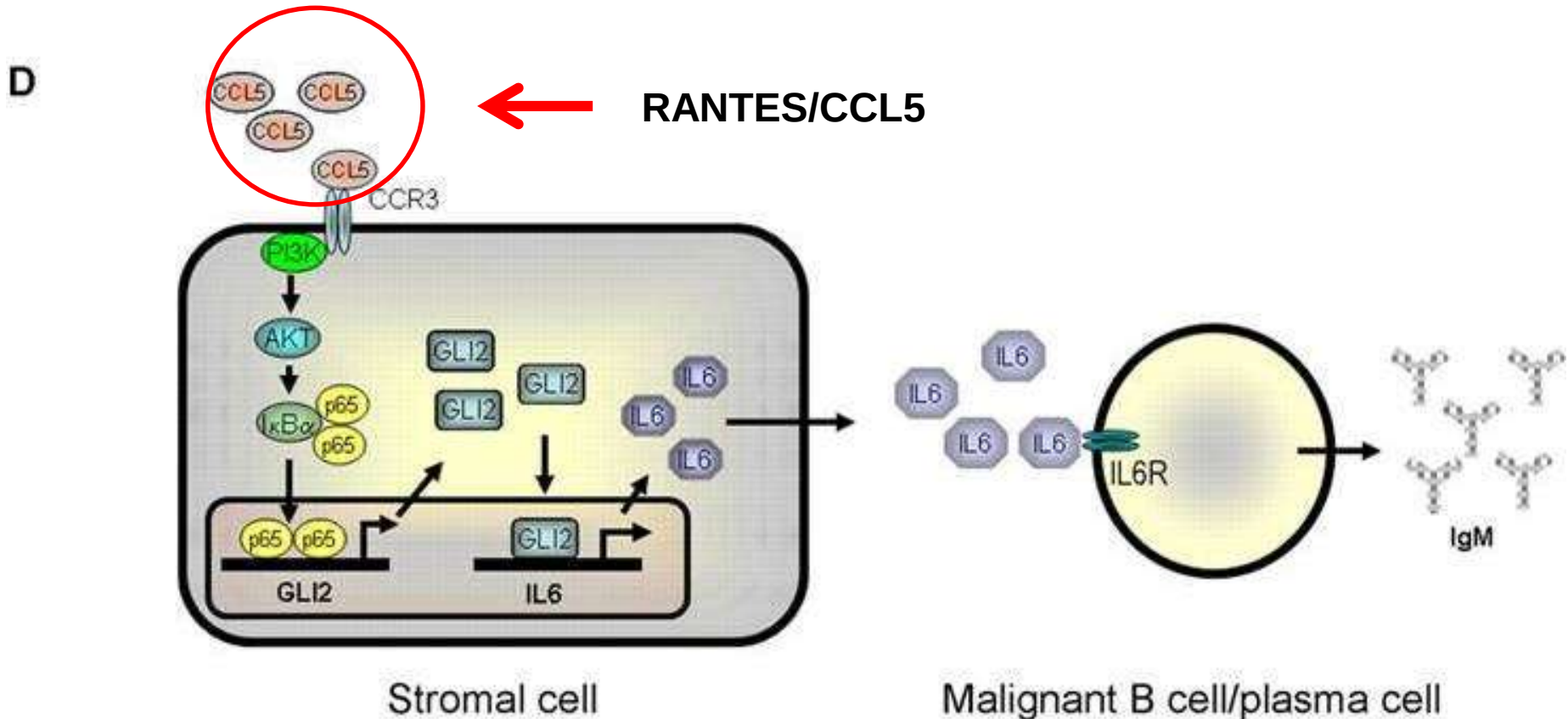
■ FDOJ of
BC
patients
(n=23)



Distribution of RANTES (pg/ml) in FDOJ of **BC patients** (n=23)



RANTES/CCL5 mediates cytokine cross-talk in the tumor microenvironment



Sherine F. Elswa et al. J. Biol. Chem. 2011;286:21524-21534

RANTES and its role in breast cancer

RANTES has been associated as well with the **induction or promotion of cancer** (e.g., prostate and breast).

Soria, G., A. Ben-Baruch. 2008. The inflammatory chemokines CCL2 and CCL5 in breast cancer. Cancer Lett. 267: 271-285

....development of breast cancer is the potential ability of RANTES, to act directly on the tumor cells and **to promote progression of the tumor.**

Niwa, Y. et al. Correlation of Tissue and Plasma RANTES Levels with Disease Course in Patients with Breast or Cervical Cancer. ClinCancer Res February 2001 7; 285.

“.. analysis of RANTES expression demonstrates that **expression of RANTES in breast tumor cells is elevated significantly...**

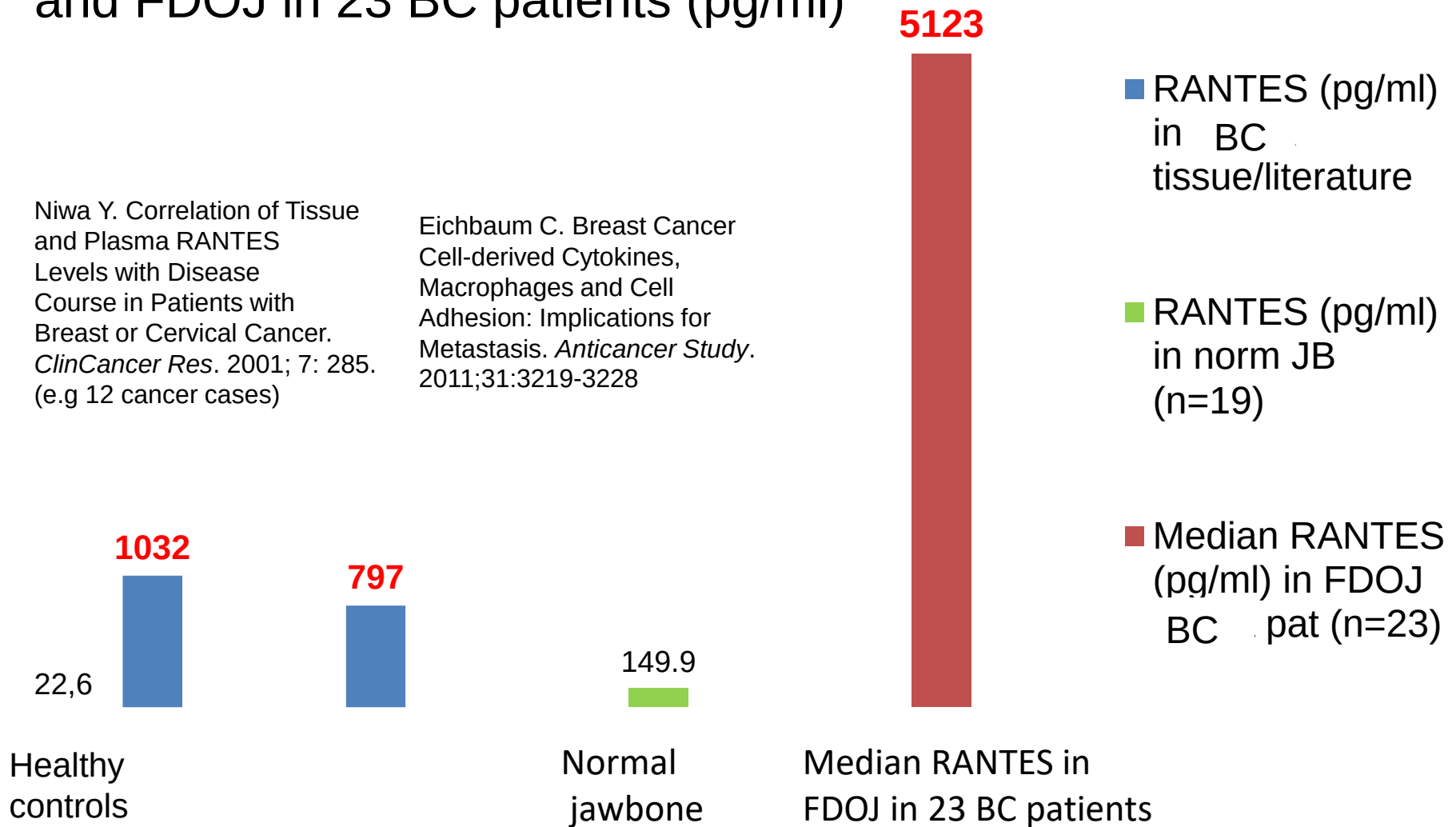
breast tumor cell-derived **RANTES may promote breast cancer progression.**“

Azenshtein E. et al The CC chemokine RANTES in breast carcinoma progression: regulation of expression and potential mechanisms of promalignant activity. Cancer Res. 2002 Feb 15;62(4):1093-102.).

Comparison of RANTES in **BC tissue** to normal jawbone and FDOJ in 23 BC patients (pg/ml)

Niwa Y. Correlation of Tissue and Plasma RANTES Levels with Disease Course in Patients with Breast or Cervical Cancer. *ClinCancer Res.* 2001; 7: 285. (e.g 12 cancer cases)

Eichbaum C. Breast Cancer Cell-derived Cytokines, Macrophages and Cell Adhesion: Implications for Metastasis. *Anticancer Study.* 2011;31:3219-3228

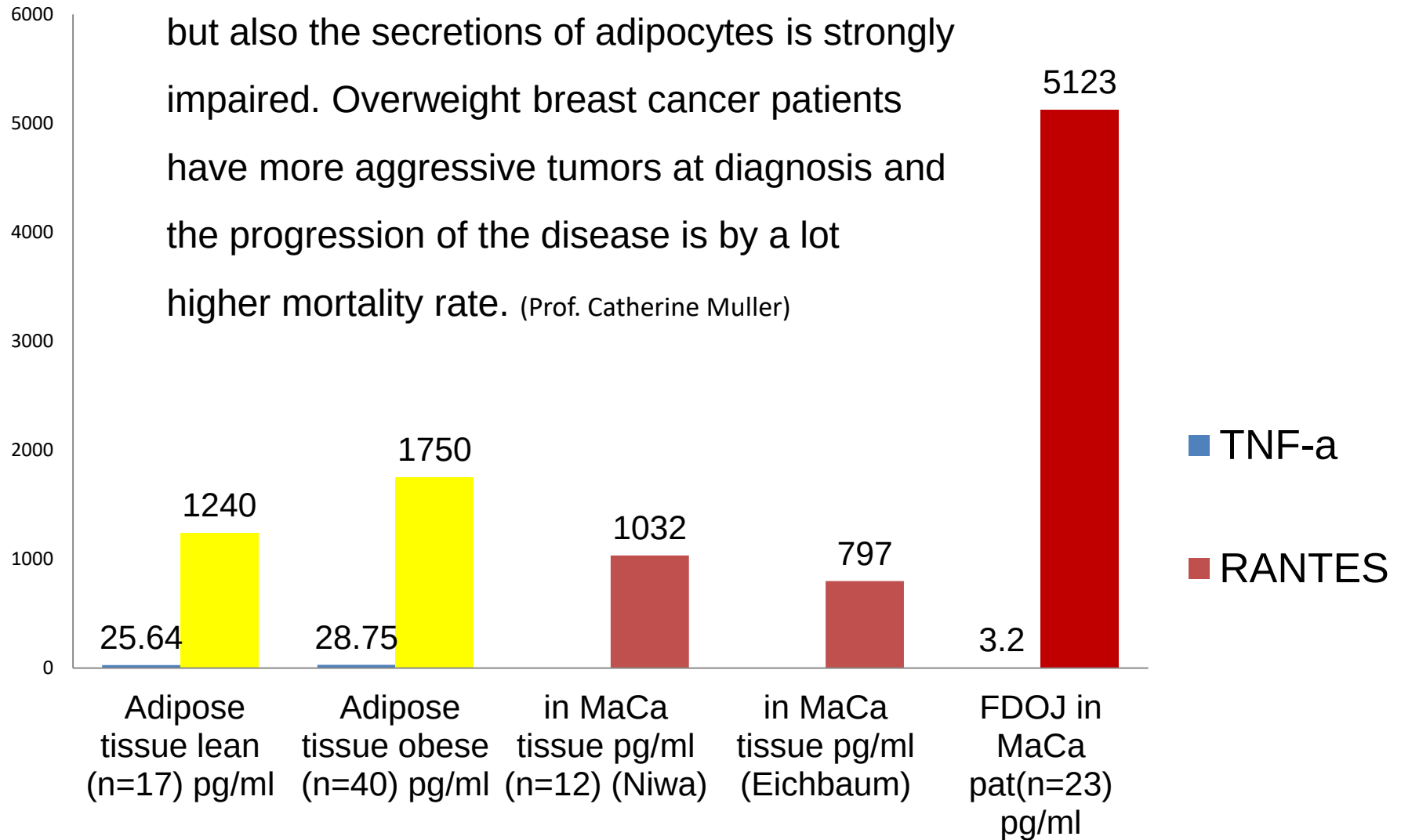


Healthy controls

Normal jawbone

Median RANTES in FDOJ in 23 BC patients

Obesity is not just about size and number,
but also the secretions of adipocytes is strongly
impaired. Overweight breast cancer patients
have more aggressive tumors at diagnosis and
the progression of the disease is by a lot
higher mortality rate. (Prof. Catherine Muller)



RANTES/CCL5 expression in FDOJ in 23 BC cases is

- 35-fold higher than in normal jawbone
- 5-fold higher than in BC tissue

„The body's own stem cells stimulate cancer cells to mutate, to spread and to form tumors in other organs...This enhanced metastatic ability is reversible and is **dependent on CCL5/RANTES signaling...**”

Karnoub AE., et al. Mesenchymal stem cells within tumourstroma promote breast cancer metastasis. Nature, Volume 449, Issue 7162, pp. 557-563 (2007).

7 cytokines in retromolar area with **metastasis of BC** compared to normal jawbone (n=19)

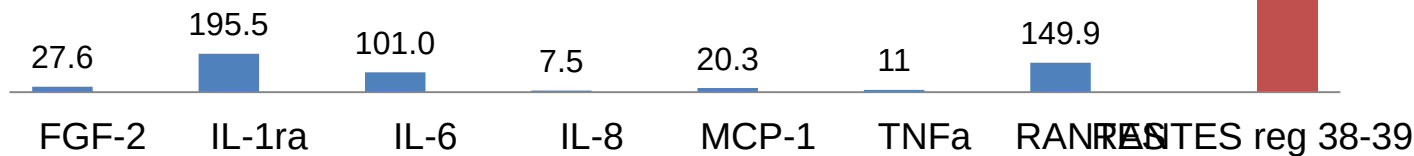
Pathohistology:
„Metastasis of
adenocarcinoma
of breast cancer
in jawbone“

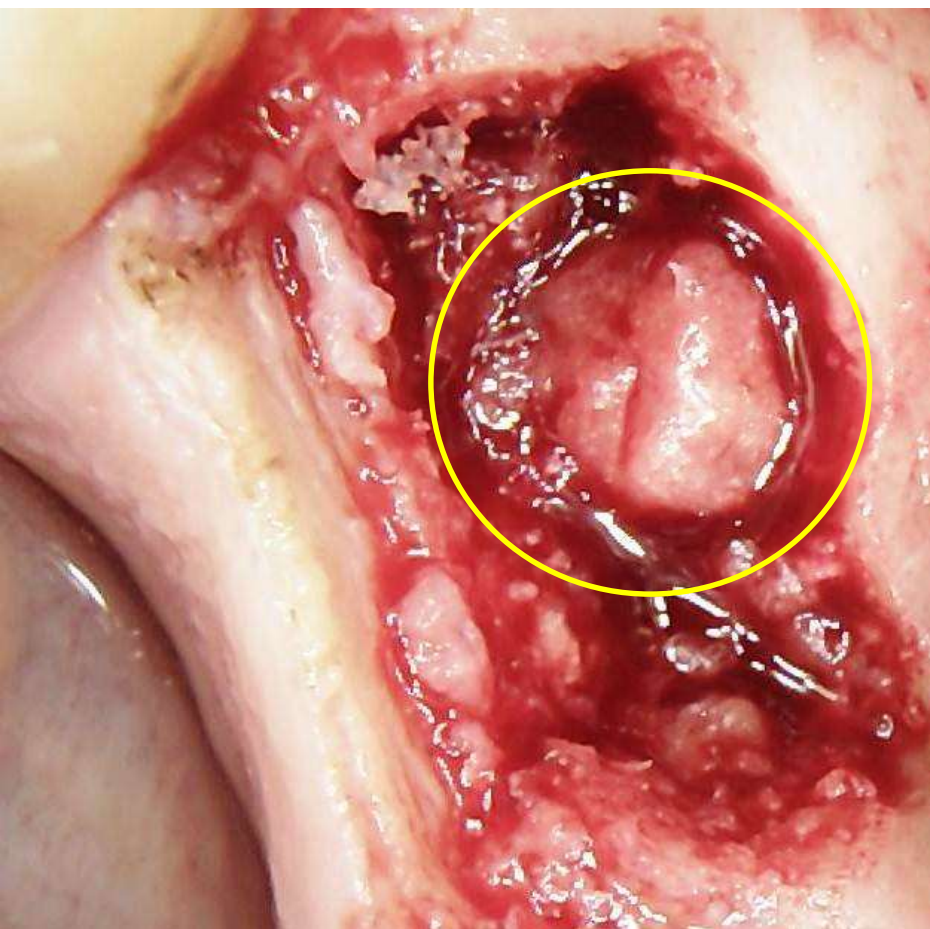


4606

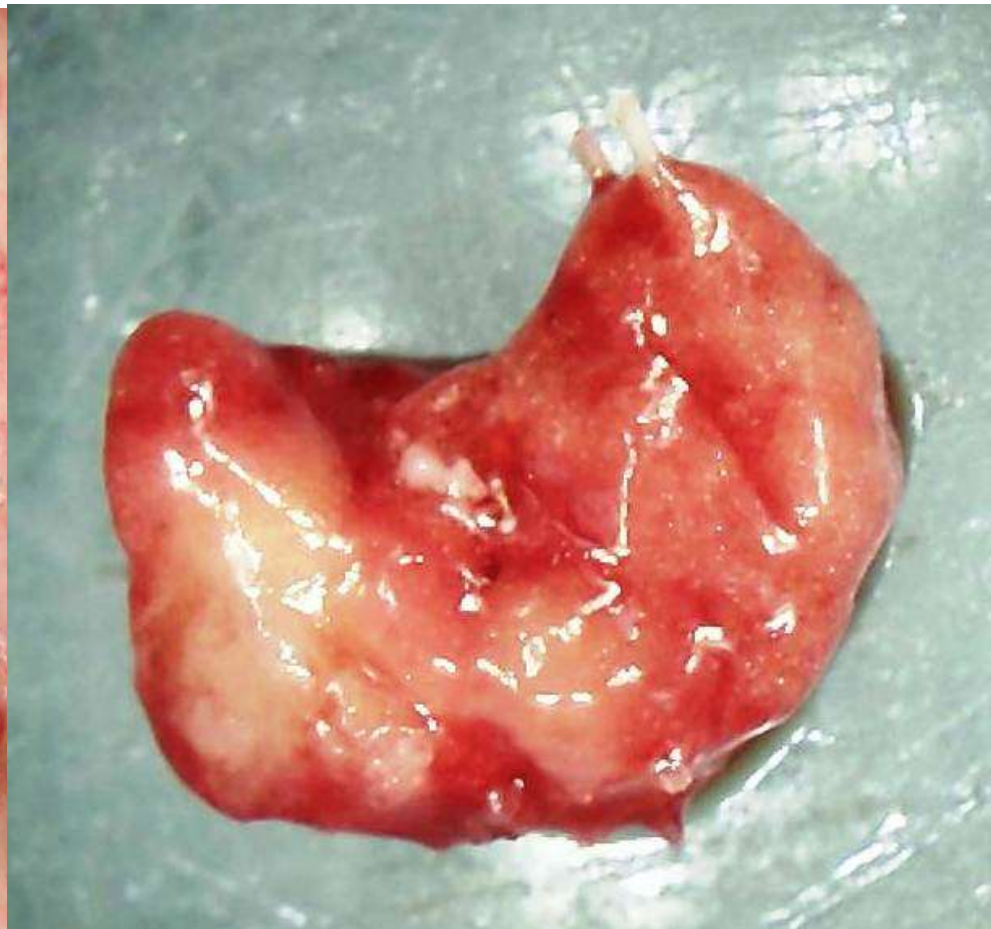
■ = normal
Jawbone

■ = fatty
degenerative
osteonecrosis
of jawbone
(FDOJ)





Left panel: retromolar area after decortication shows fatty bone marrow



Right panel: lump of fatty-degenerated
Osteolysis/osteonecrosis of bone marrow

RANTES/CCL5 and its role in BC metastasis

...RANTES can also **increase the metastatic potential** of cancer cells.

Eissa S.A.L. et al. Importance of Serum IL-18 and RANTES as Markers for Breast Carcinoma Progression, Journal of the Egyptian Nat. CancerInst., Vol. 17, No. 1, March: 51-55, 2005.

...BC cells stimulate secretion of RANTES from mesenchymal stem cells, which then acts on cancer cells to **enhance their motility, invasion and metastasis**.

Karnoub, A et al. Mesenchymal stem cells within tumourstroma promote breast cancer metastasis, Nature, Volume 449, Issue 7162, pp. 557-563 (2007).

...this increased propensity towards metastasis **is reversible and dependent on the RANTES signaling**.

Azenshtein E. et al The CC chemokine RANTES in breast carcinoma progression: regulation of expression and potential mechanisms of promalignant activity. Cancer Res. 2002 Feb 15;62(4):1093-102.).

Immunohistochemic staining of FDOJ

- jawbone marrow defects

The visible prove
of RANTES/CCL5 signaling pathway
connection from jawbone to tumors

We generated a panel of **anti-RANTES monoclonal antibodies** for immunohistologic staining of RANTES expression in jawbone.

Most normal adult tissues contain **few, if any, RANTES positive cells**.

In contrast, RANTES expression dramatically increases in inflammatory sites. In addition, megakaryocytes and some tumours, express high levels of RANTES message and protein.

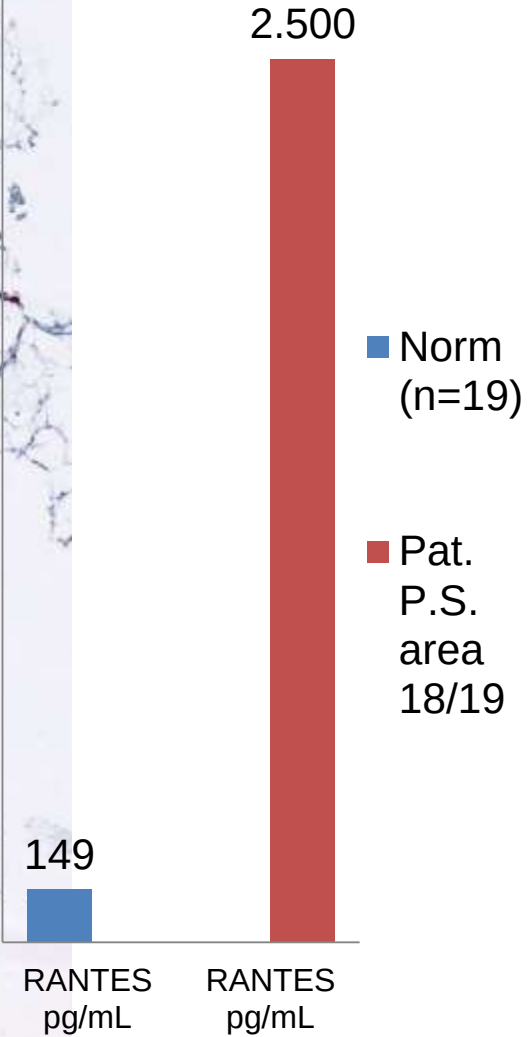
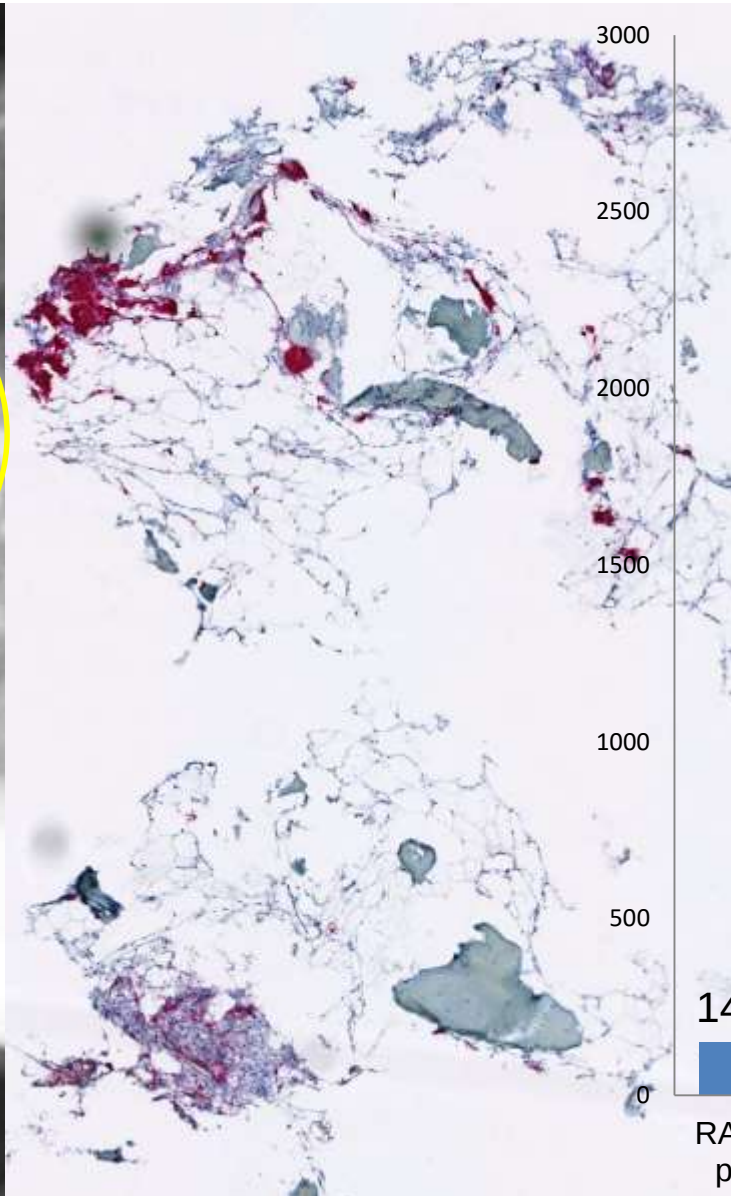
[von Luettichau I](#) et al. **RANTES chemokine expression in diseased and normal human tissues.** [Cytokine](#). 1996 Jan;8(1):89-98.

These results indicate a wider expression of RANTES than previously appreciated and suggest multiple physiologic roles for this soluble factor.

Female, aged 51 years; clinical diagnosis: Breast cancer

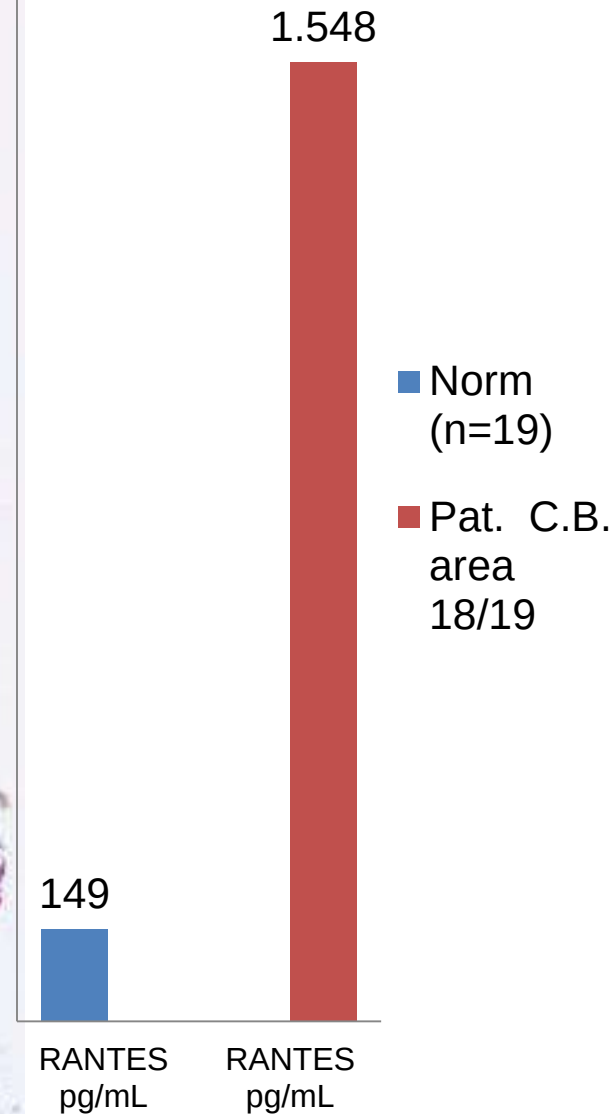
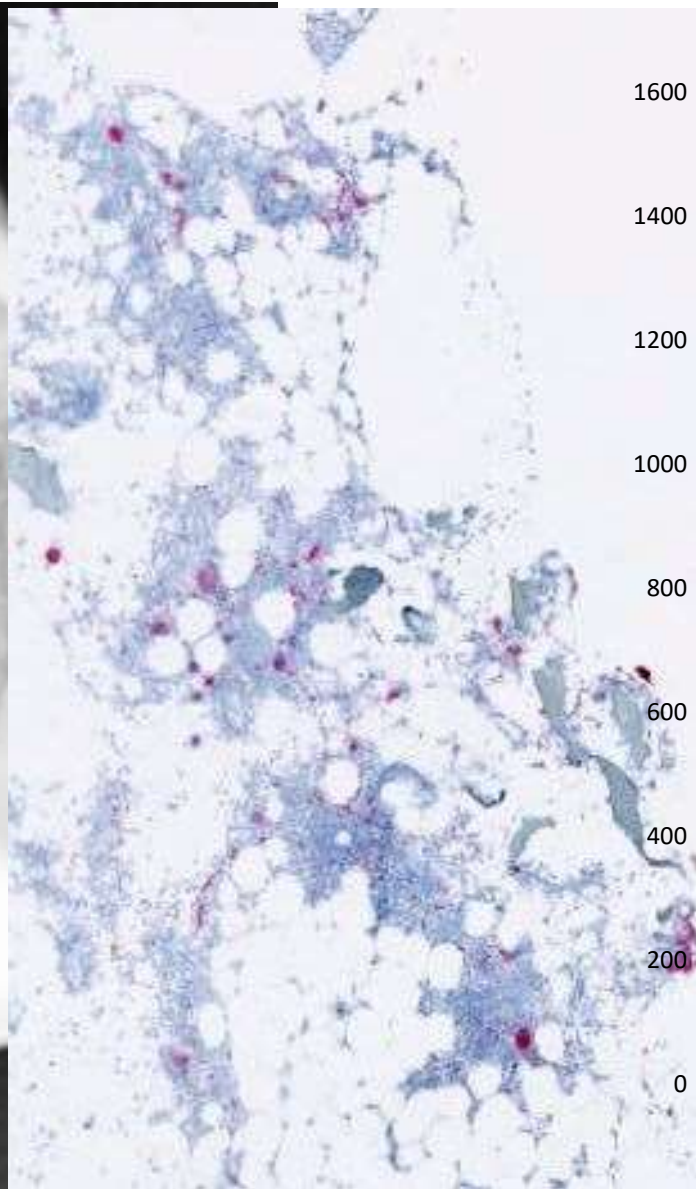


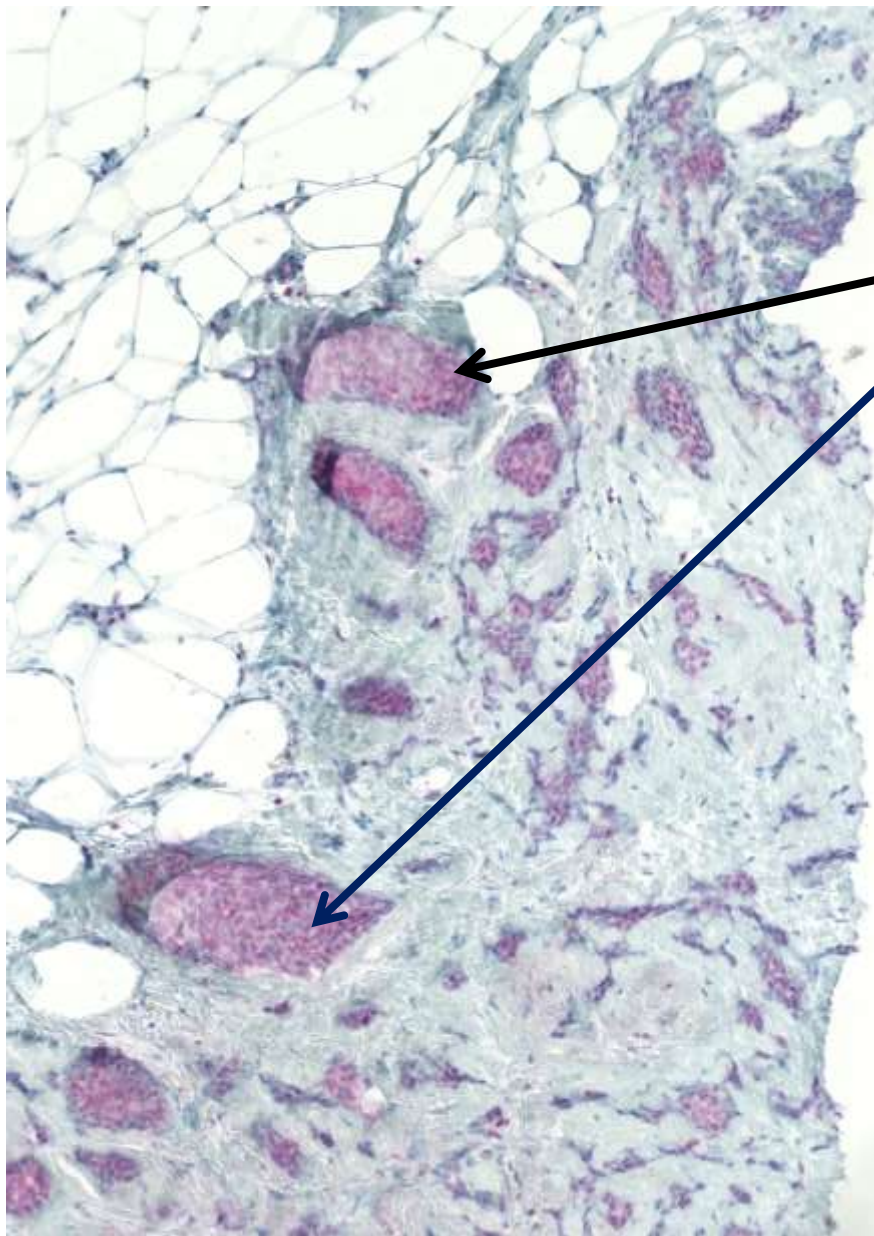
HU: -118





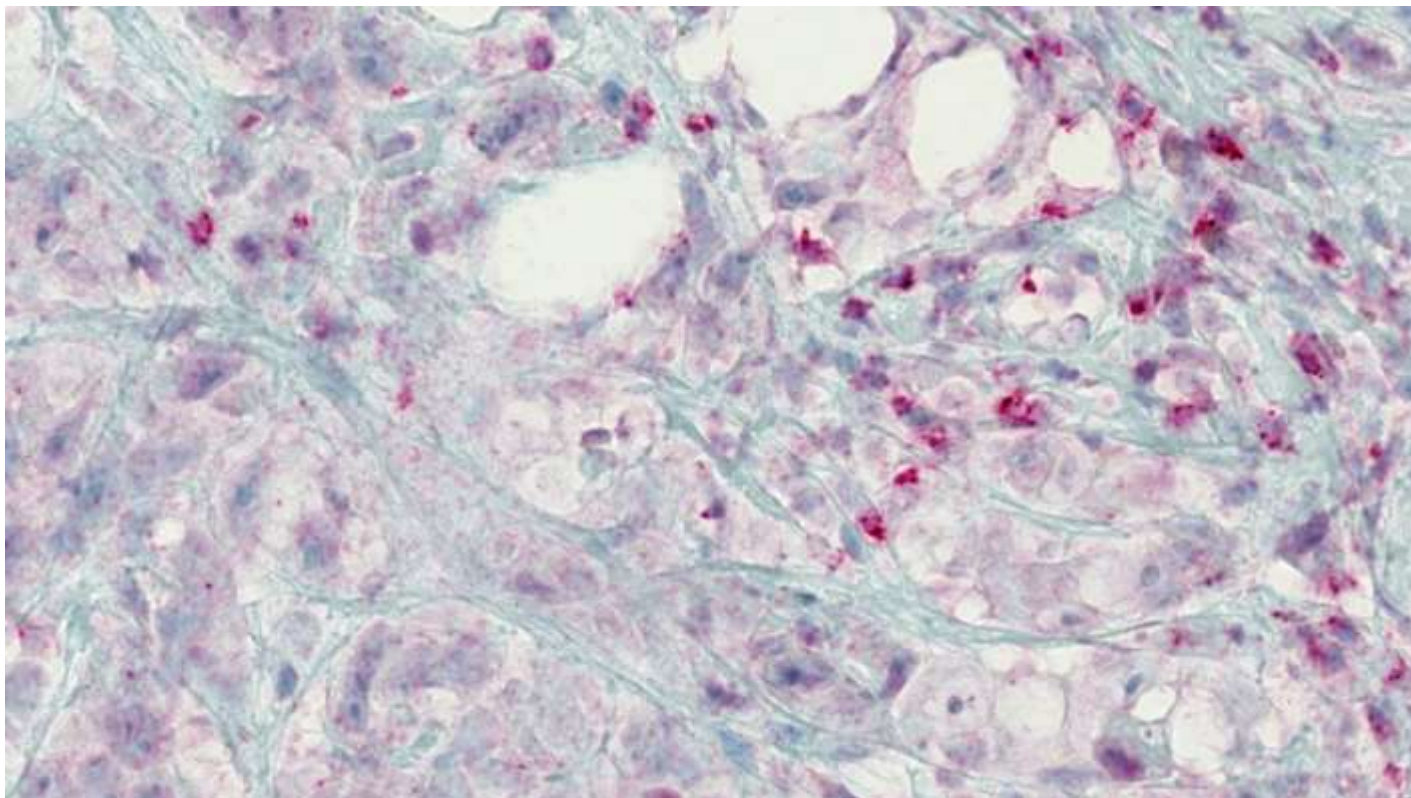
Female, aged 63 years; clinical diagnosis: Breast cancer



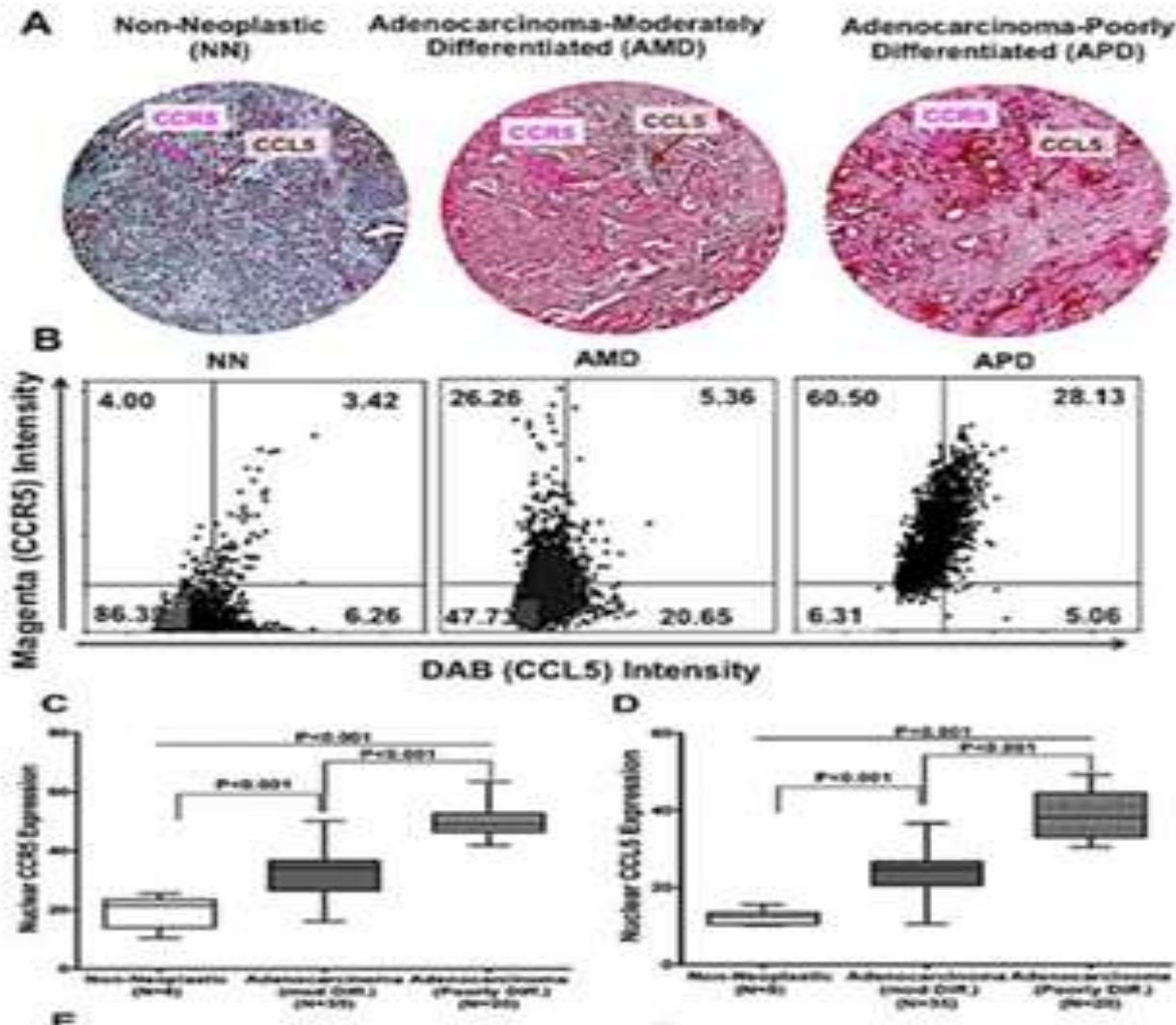


Duct-invasive
breast carcinoma with
RANTES/CCL5-positive tumor
cell nests (arrows).

The staining is not as strong
as in the FDOJ samples.



Breast cancer and associated connective adipose tissue.
There are also distinct RANTES/CCL5-stained cells,
while the breast cancer epithelial tracts show only mild-to-moderate,
non-specific background staining.



CCR5/CCL5 axis interaction promotes migratory and invasiveness of pancreatic cancer cells
[Santosh Kumar Singh](#),
[Manoj K. Mishra](#),
[Isam-Eldin A. Eltoum](#),
[Sejong Bae](#),
[James W. Lillard Jr.](#) &
[Rajesh Singh](#)
Scientific Reports 8,
 Article number: 1323
 (2018)

If chronic inflammation, per se, were a sentinel event in the transformation of a normal cell to a cancer cell, one would expect a high incidence of cancer in patients with chronic arthritis, but that is not evident. **Why?**

The answer is:

RANTES/CCL5

and NOT TNF-a

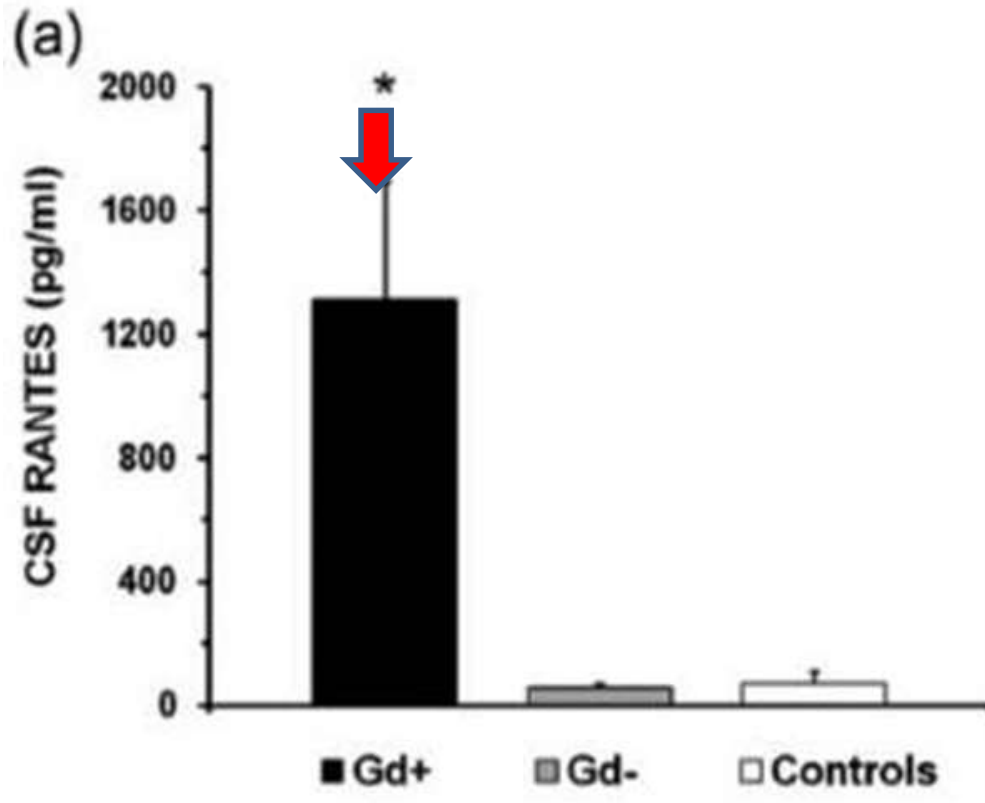
is possibly the signal

for cancer development

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

	TNF-a	IL-6	RANTES
Rheumatoid arthritis	+++	++	+
Osteoporosis	+++	++	-
Obesity	+++		-
Periodontitis	+++	++	+
Peri-implantitis	+++	++	-
Biphosphonate-induced osteonecrosis	++	++	-
Fatty-degenerative osteonecrosis	-	-	+++

RANTES–levels in CerebroSpinalFluid (CSF) of MS-patients

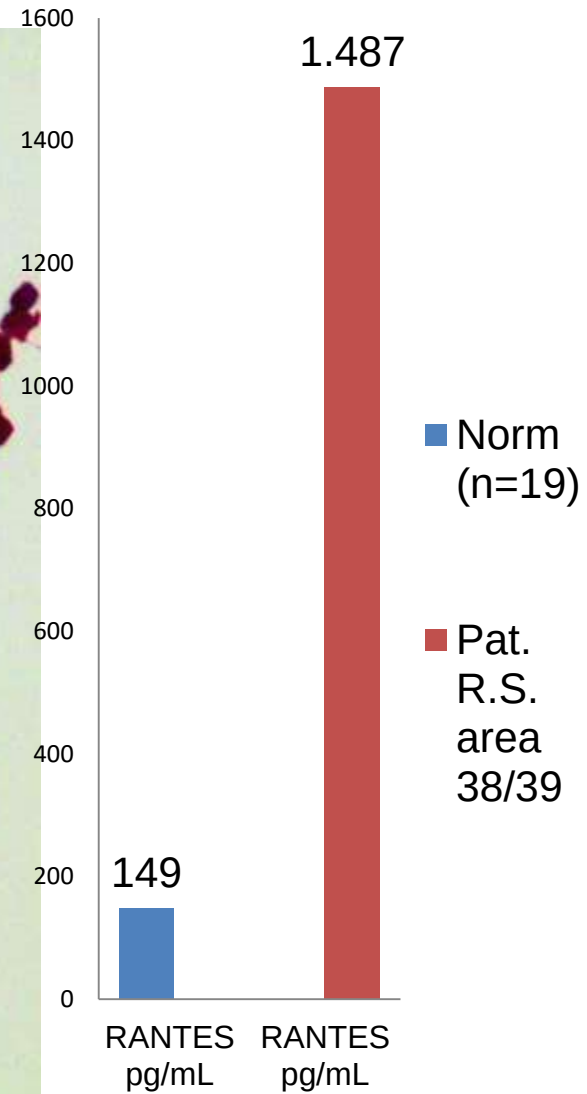
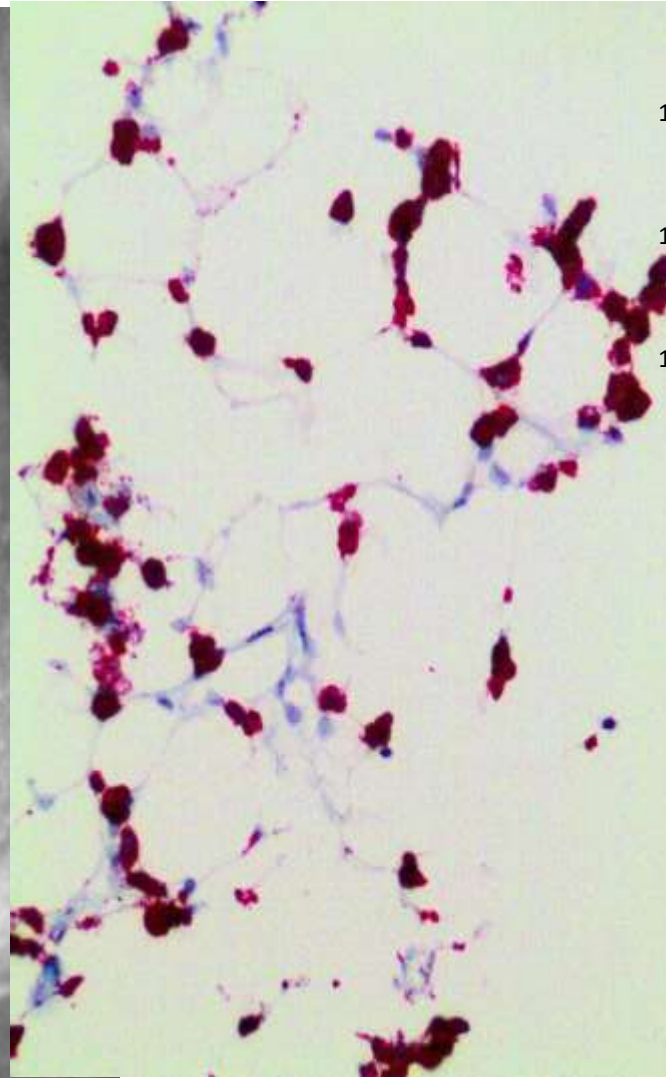
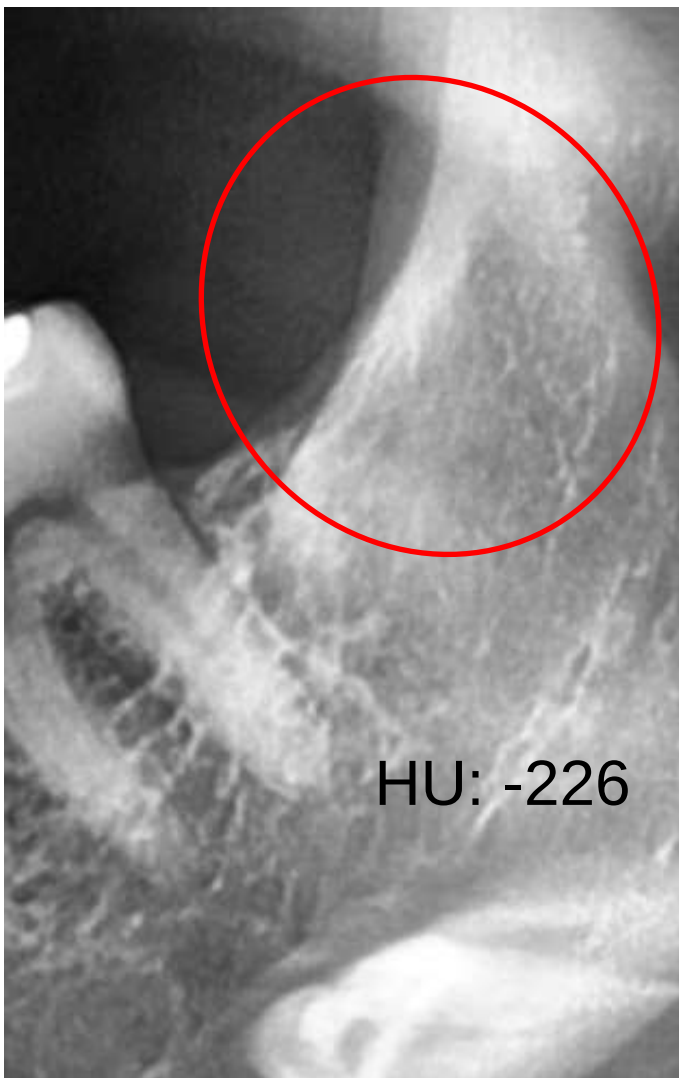


“CSF levels of RANTES were remarkably high only in active MS patients....

RANTES correlates with inflammation and synaptic excitability in MS brains.”

Mori F, et al. [RANTES correlates with inflammatory activity and synaptic excitability in multiple sclerosis](#). Multiple Sclerosis Journal 1–8; DOI: 10.1177/1352458515621796

Female, aged 58 years; clinical diagnosis: ALS



....in order to investigate whether RANTES as index of immune activation is present in ALS patients.

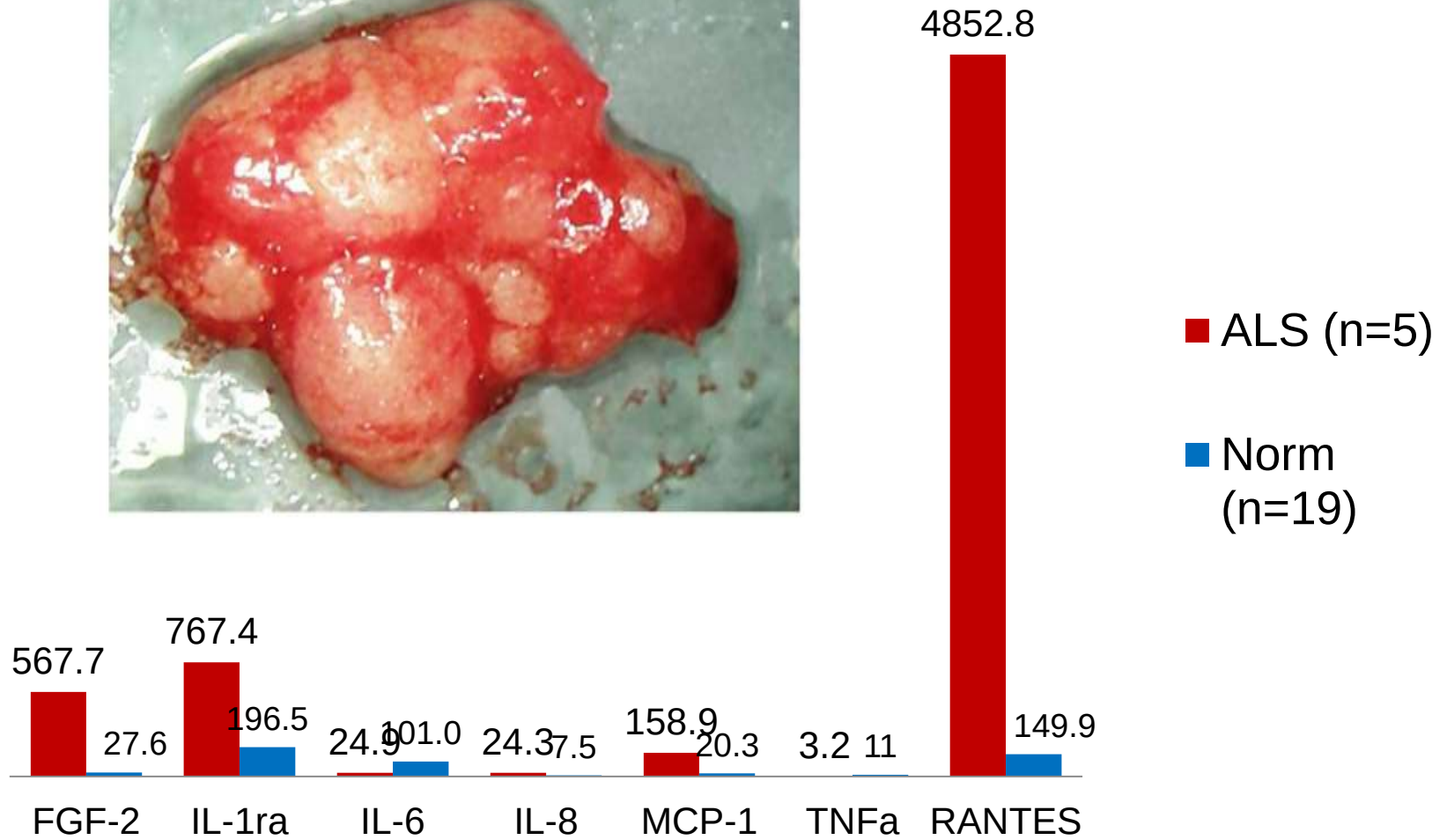
Patients with ALS had higher RANTES levels compared with the NoneIND patients and CTRL subjects in serum.

CSF RANTES levels were also higher compared with the NoneIND patients.

These results may suggest an activated microglia induced recruitment of peripheral inflammatory cells to sites of inflammation in ALS patients.

([Rentzos M](#), et al. RANTES levels are elevated in serum and cerebrospinal fluid in patients with amyotrophic lateral sclerosis. [Amyotroph Lateral Scler.](#) 2007 Oct;8(5):283-7.)

Comparison of 7 cytokines in ALS patients (n=5) in FDOJ and in normal jawbone marrow (n=19) in pg/ml



FDOJ – chronic inflammation in jawbone

- a) FDOJ is characterized by fatty degenerative softening and **osteolysis and osteonecrosis of jawbone**
- b) FDOJ is characterized by **degeneration of adipocytes**, metabolic disturbance and total lack of typical leukocytic inflammation
- c) FDOJ is characterized biochemically by **high levels of proinflammatory RANTES/CCL5** in comparison to normal jawbone.
- d) FDOJ is characterized by **absence of acute cytokines** such as TNF-alpha and IL-6, which explains the painless and cryptic nature of FDOJ.

Data presented support our hypothesis:

- There are hyperactive signaling pathways through RANTES expression in jawbone cavitations
- FDOJ sites promote pathogenesis and metastasis of BC as a **silent inflammation**
- Surgical debridement of FDOJ in jawbone is eliminating RANTES sources



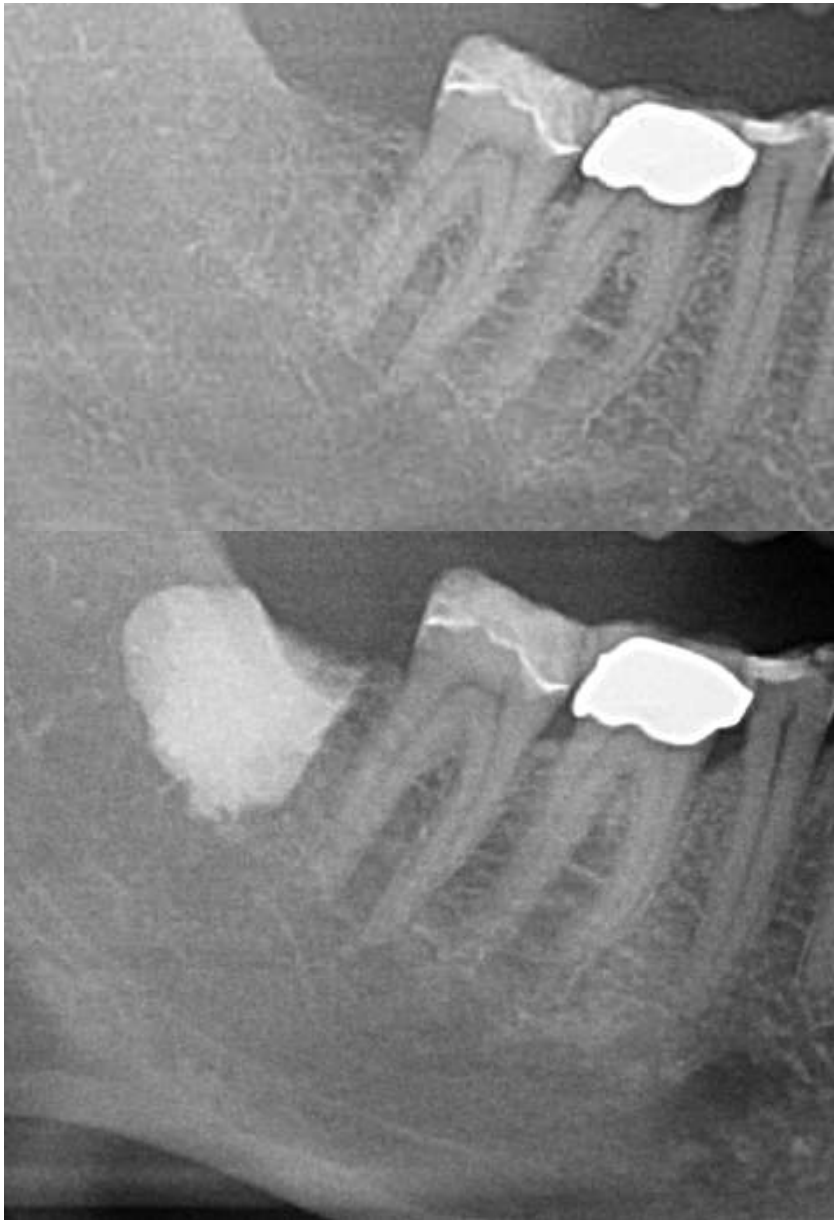
Why is FDOJ neglected in dentistry?



Validation of dental X-ray by cytokine RANTES – comparison of X-ray findings with cytokine overexpression in jawbone

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

FDOJ sample:
Bone marrow of jawbone
changed to fatty-degenerative
osteonecrosis



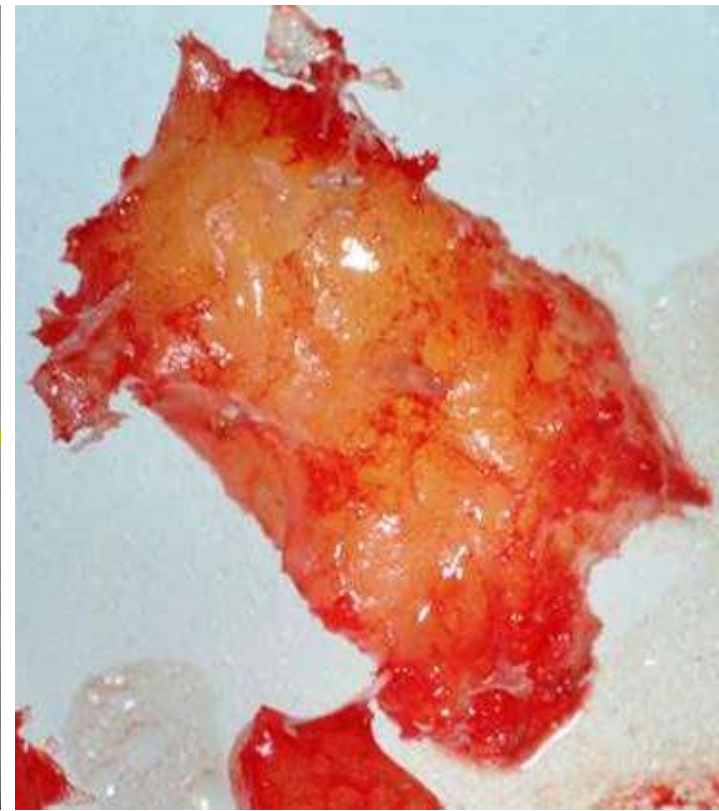
Existence of FDOJ is neglected in dentistry because of diagnostic problems in x-rays



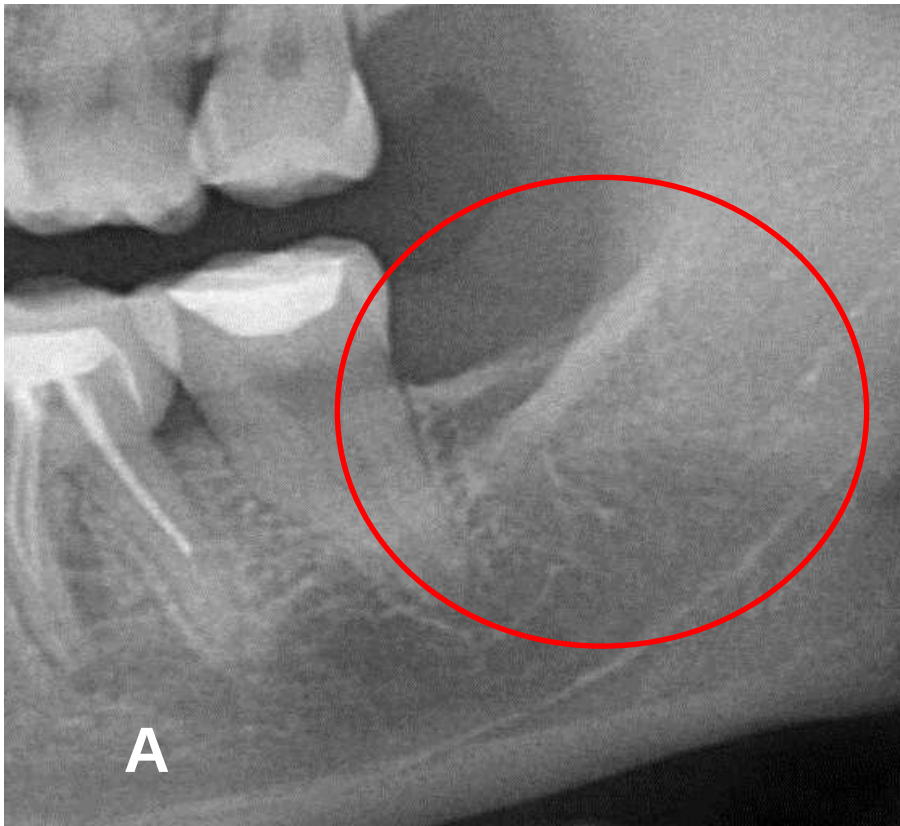
Inconspicuous
retromolar area



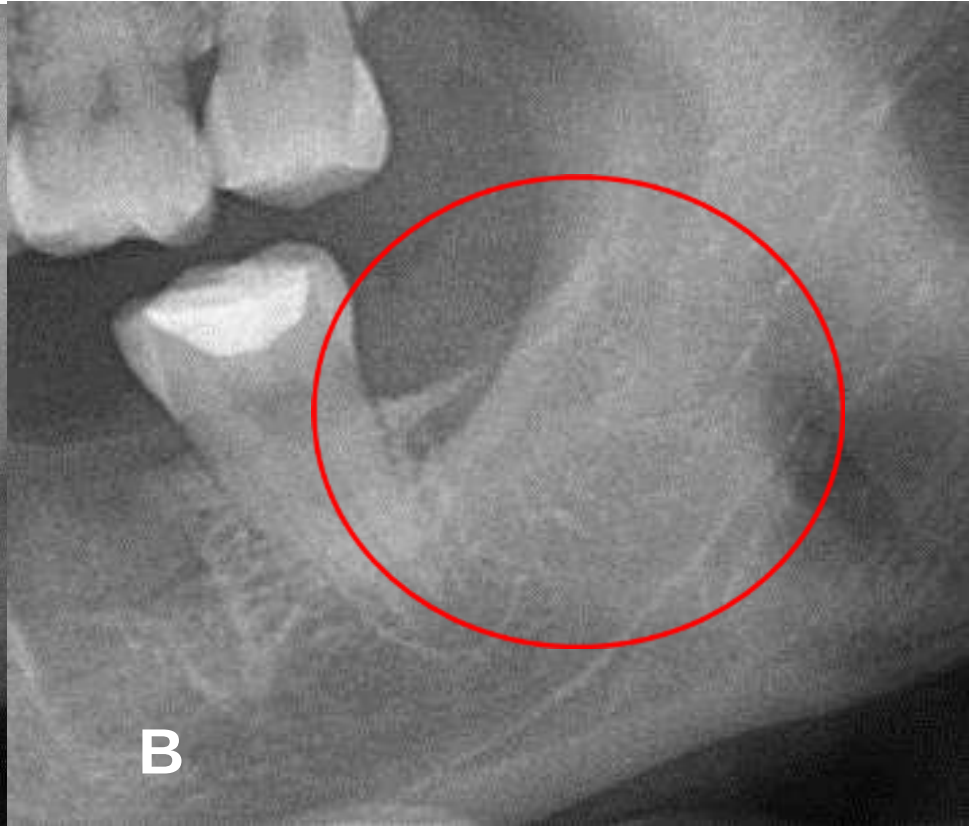
Extent of softened
bone marrow in
retromolar area



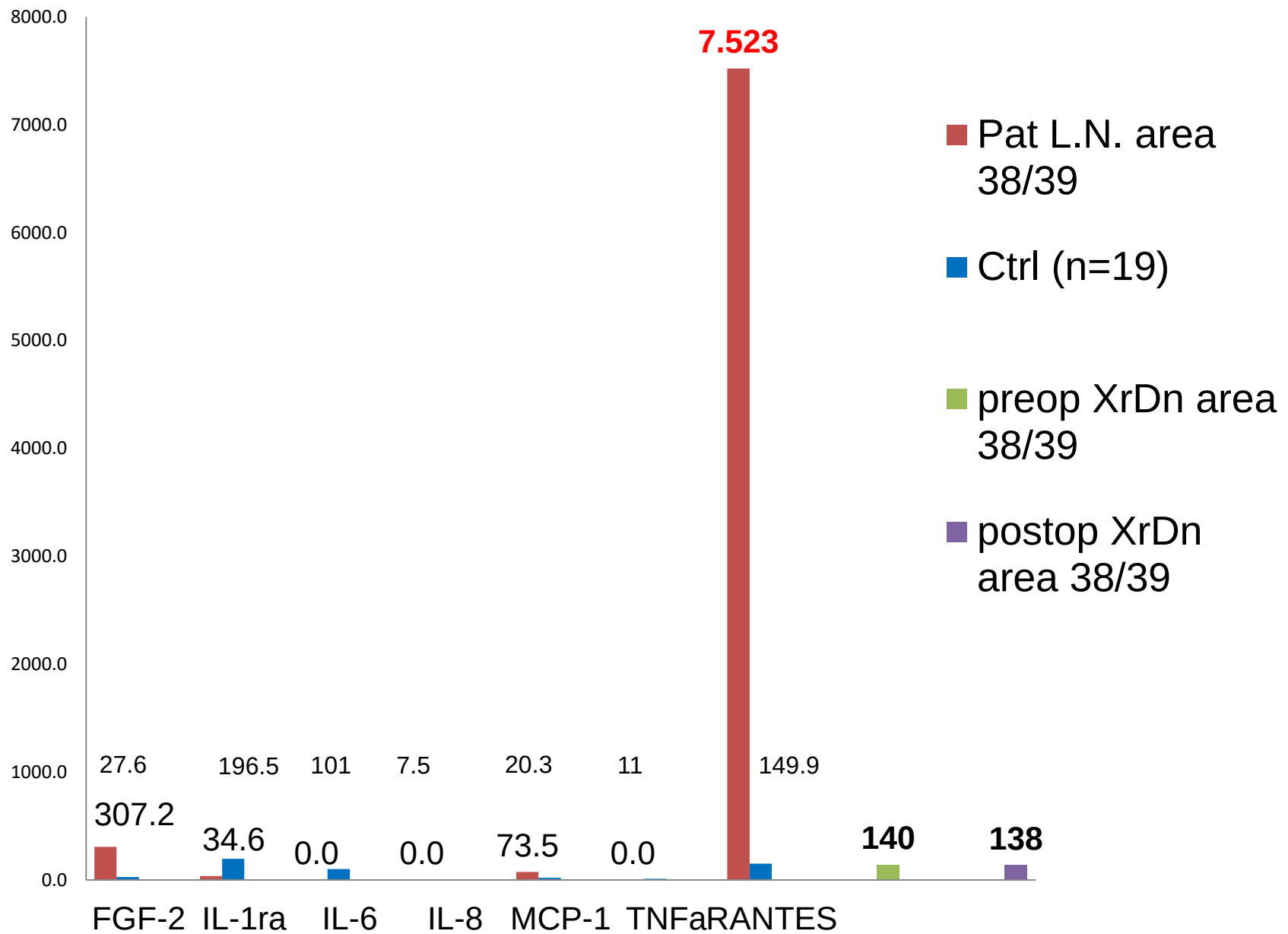
Sample of FDOJ in
retromolar area



X-ray density area 38/39
preop = 140



X-ray density area 38/39
postop = 138



How to detect and locate cavitations in jawbones?

Or: How to find
the source of chronic
overexpression of
RANTES in jawbone ?



Through-Transmission Alveolar Ultrasonography (TAU).

New TAU® generates an ultrasound pulse and passes the pulse through the jawbone.

The pulse is detected and monitored by an ultrasound receiving unit.

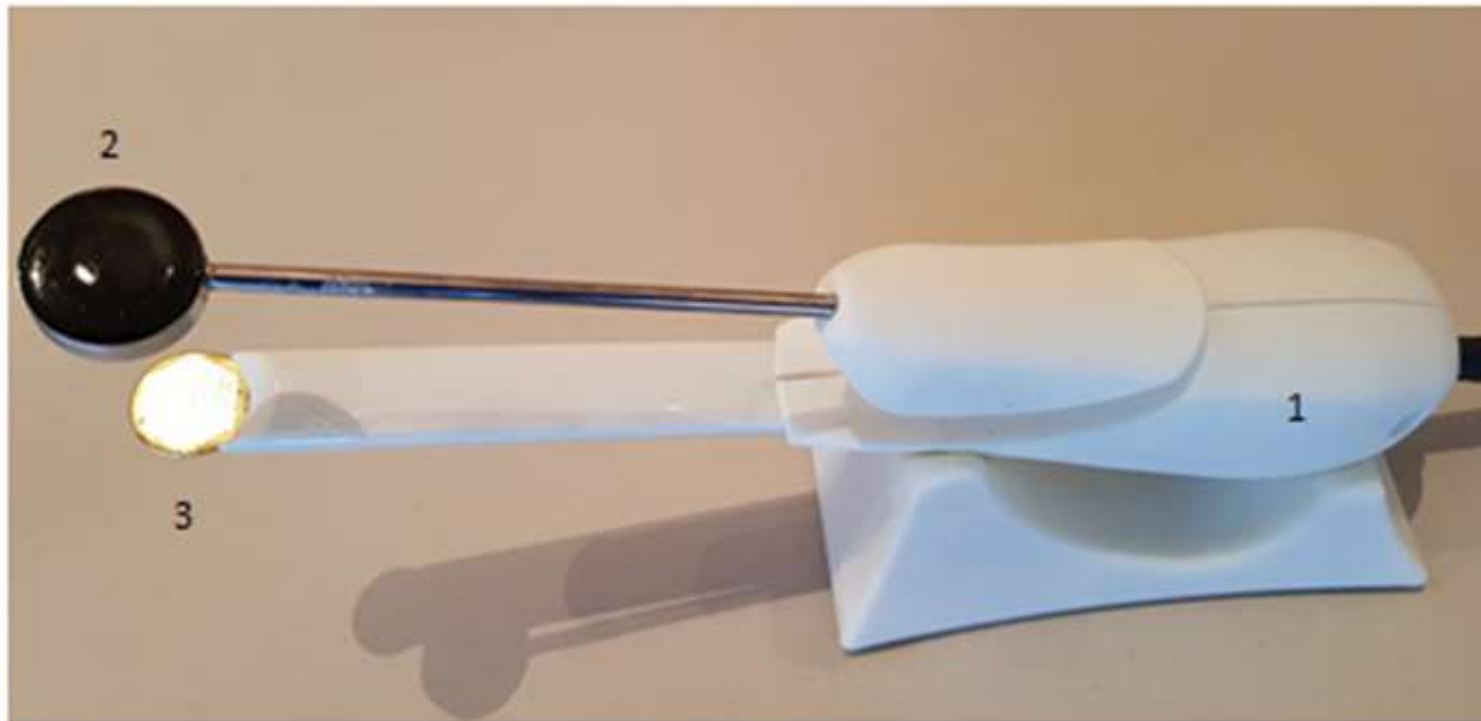
Attenuations of the amplitude of the pulse are indicative for pathological changes in the jawbone.

The results are displayed on a color monitor, showing different colors according to different degrees of attenuation.

CaviTAU®

2= Ultrasound sender 3= Ultrasound receiver/sensor

1= Handpiece with
Ultrasound sender and
-sensor unit





Family Name

Given Name

Date of Birth Scan Date

31.05.2019

DATA VIEWER
APPLICATION

NO LIVE SCANS
POSSIBLE

Tooth # Shot #
27 4

Threas- Con-
hold trast

Data
Received

25.99 mm

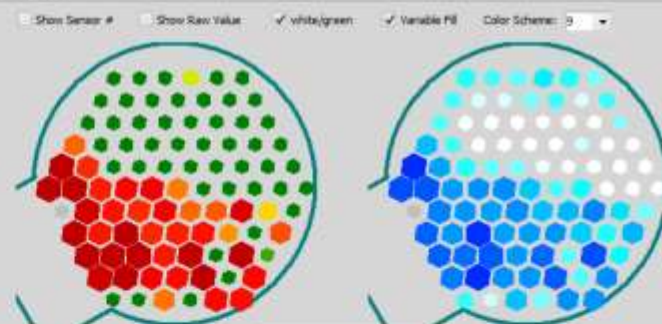
EPG

Praxis 1
Geburtsdag: 29.09.1968
Aufnahmeparameter: 0kV, 0mA, 0ms, 0dGy*cm²

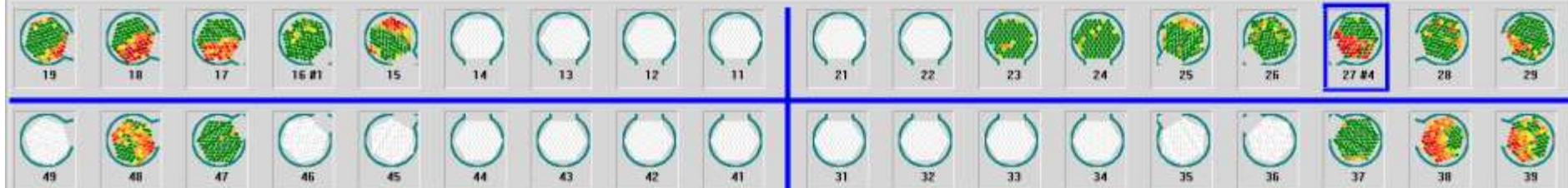
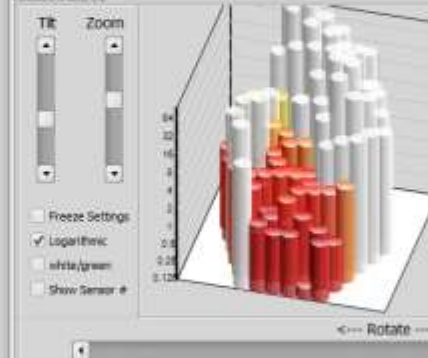
Patient: Emmanuel Ismann
Aufn. Datum: 04.02.2019



SessionField 3D

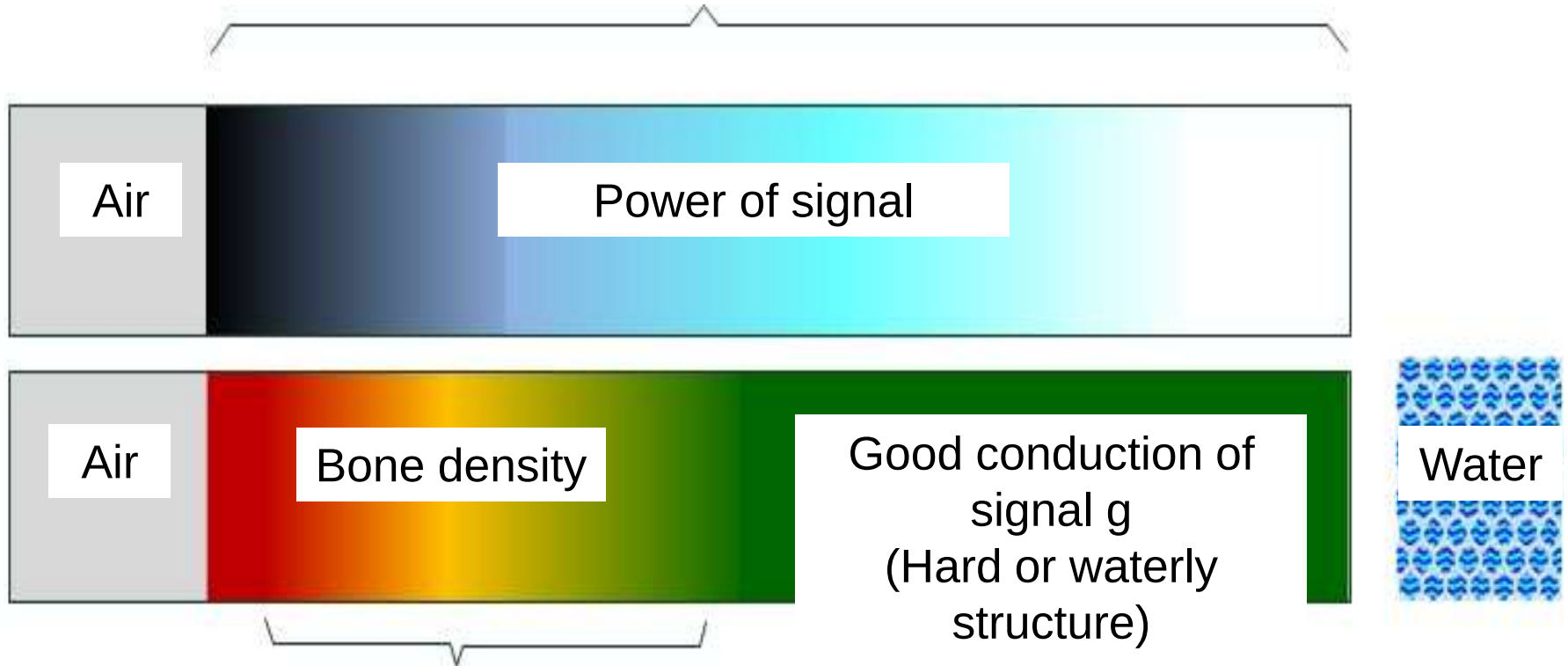


SessionField 3D



CaviTAU® red/green-imaging of bone density

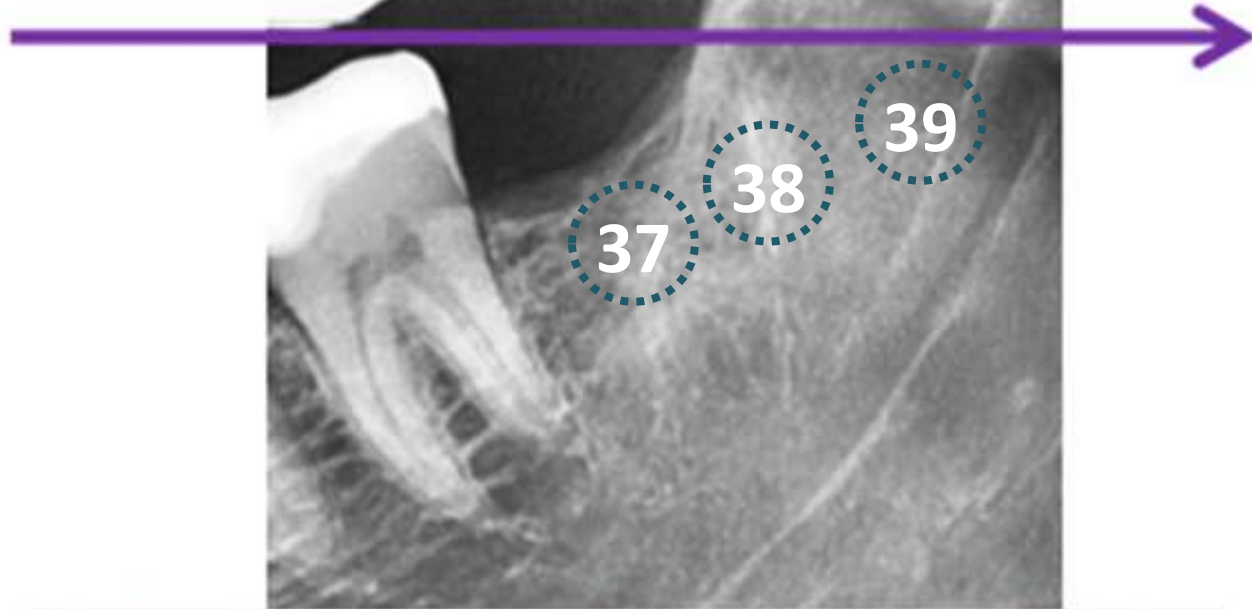
Range of signal for orientation in jawbone



Evaluation range of bone density

Increasing coefficient of density in CaviTAU®

Messung von mesial nach distal, von 37 bis 39



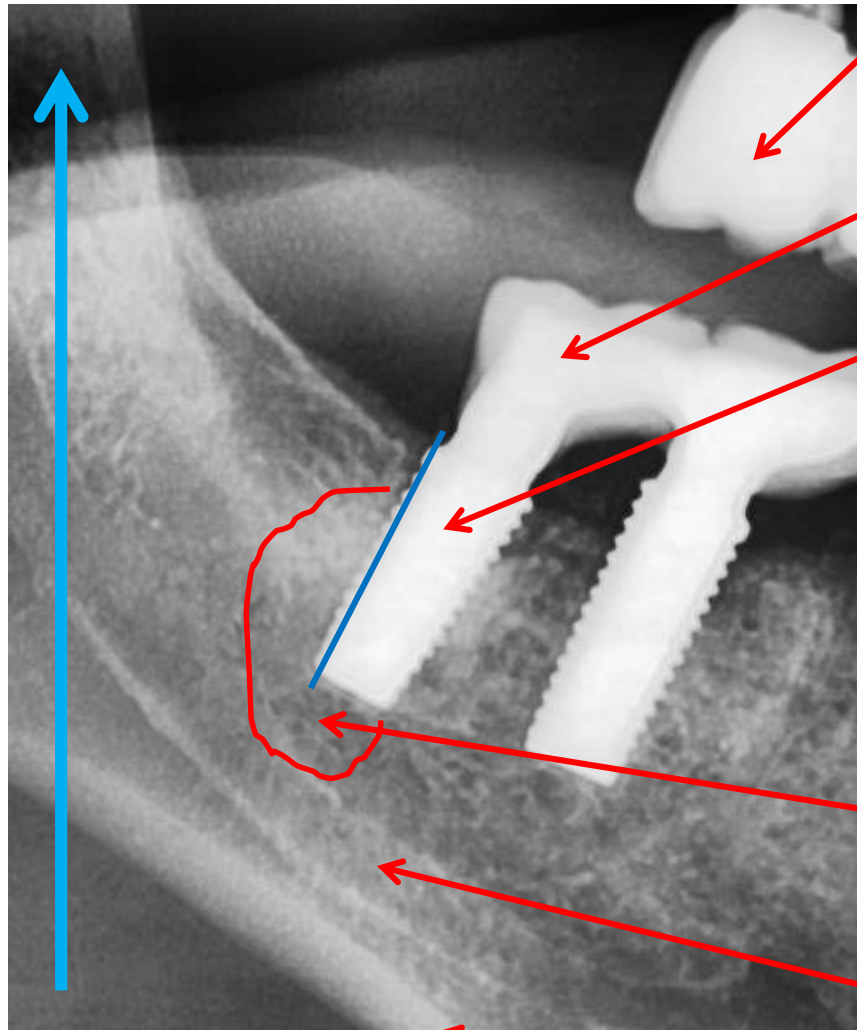
37 #1



38 #1



39 #1



Direction of measuring
(from caudal to cranial)

High
density

Crown

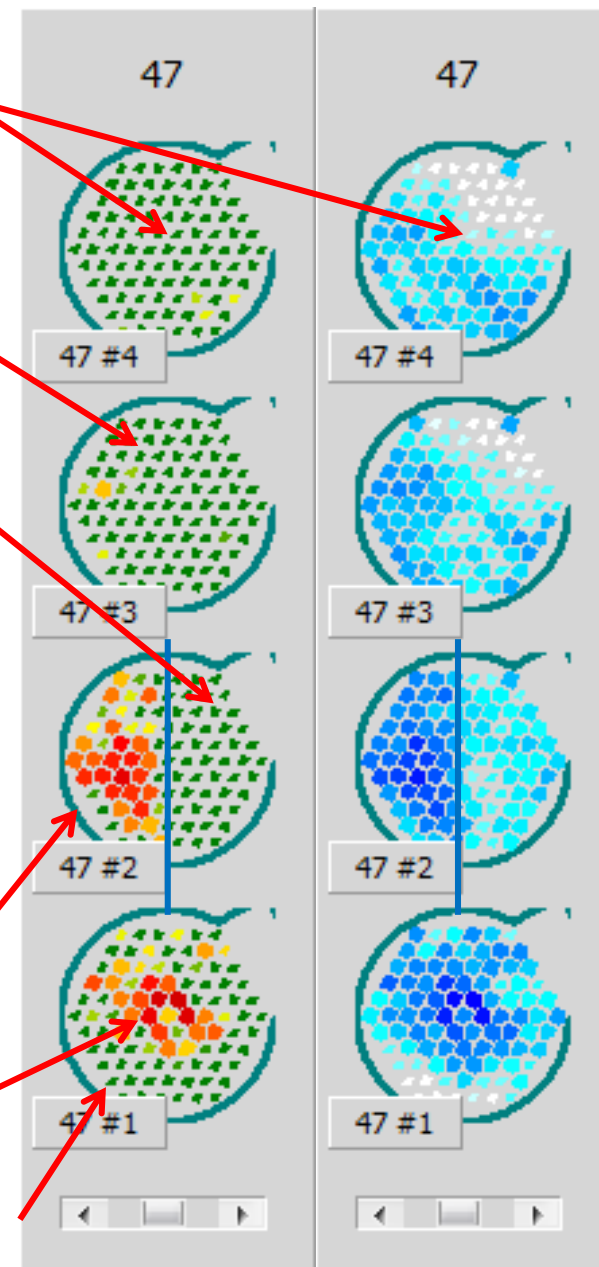
Implant

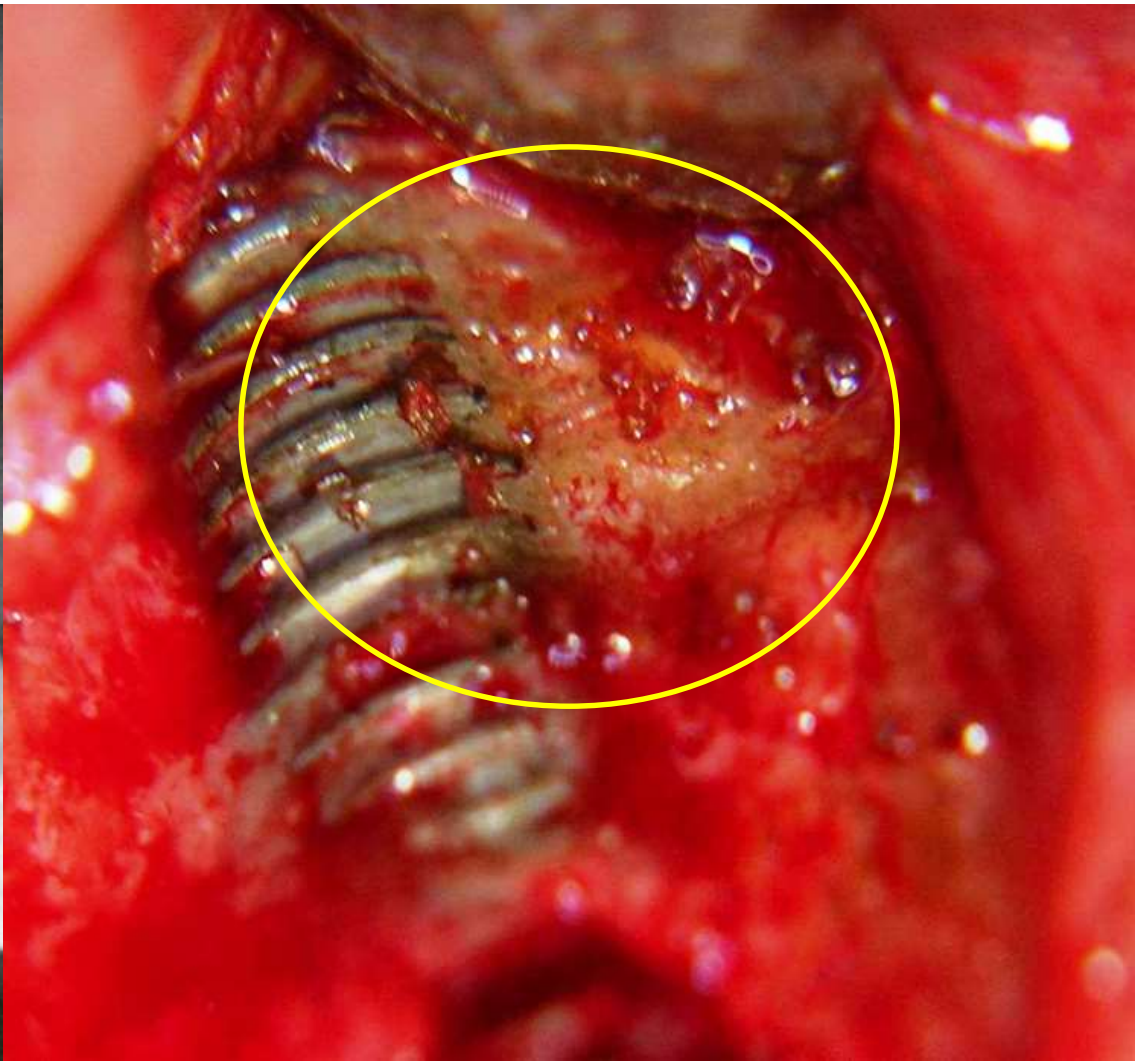
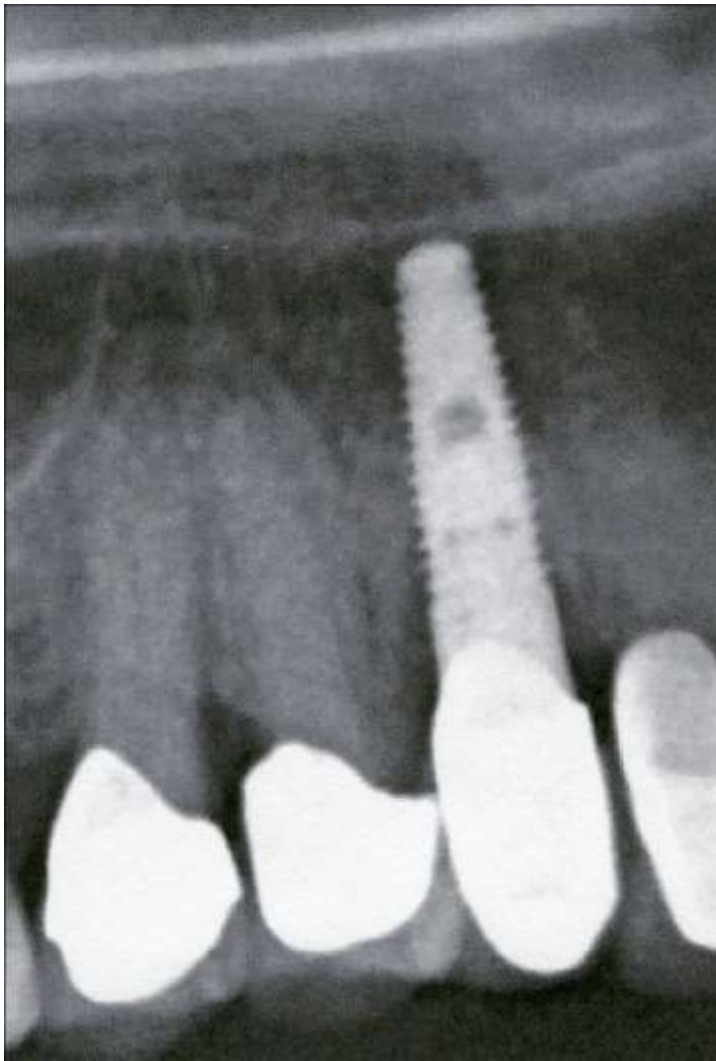
= straight
border line
to the
implant

Diminished
bone density

Nerv canal
less dense

Lower cortical
rim





Lechner J, Noubissi S, von Baehr V. Titanium implants and silent inflammation in jawbone – a critical interplay of dissolved titanium particles and cytokines TNF-a and RANTES/CCL5 on overall health? EPMA Journal (2018). <https://doi.org/10.1007/s13167-018-0138-6>

Take home messages

Collectively our data reveal a hitherto unknown function of **chronic inflammation** in **jawbone** promoting overexpression of chemokine **RANTES/CCL5**

The challenge posed by these discoveries is the need to raise awareness of **jawbone cavitations (FDOJ)** throughout the medical and dental community under the **integrative aspect** of “**silent inflammation**”.



Interest in trans-alveolar ultrasound device?

Please refer to
www.cavitaudio.de/ in English/ Newsletter
and submit with your name and email

*Many thanks for your
highly appreciated attention*