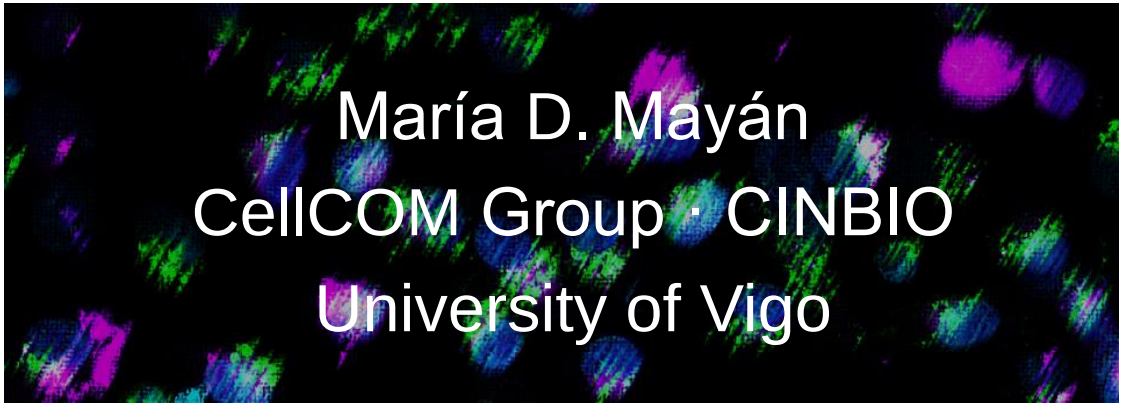
Universidade Vigo

CINBIO

Next-generation therapeutics: Extracellular vesicles as tools and targets



María D. Mayán

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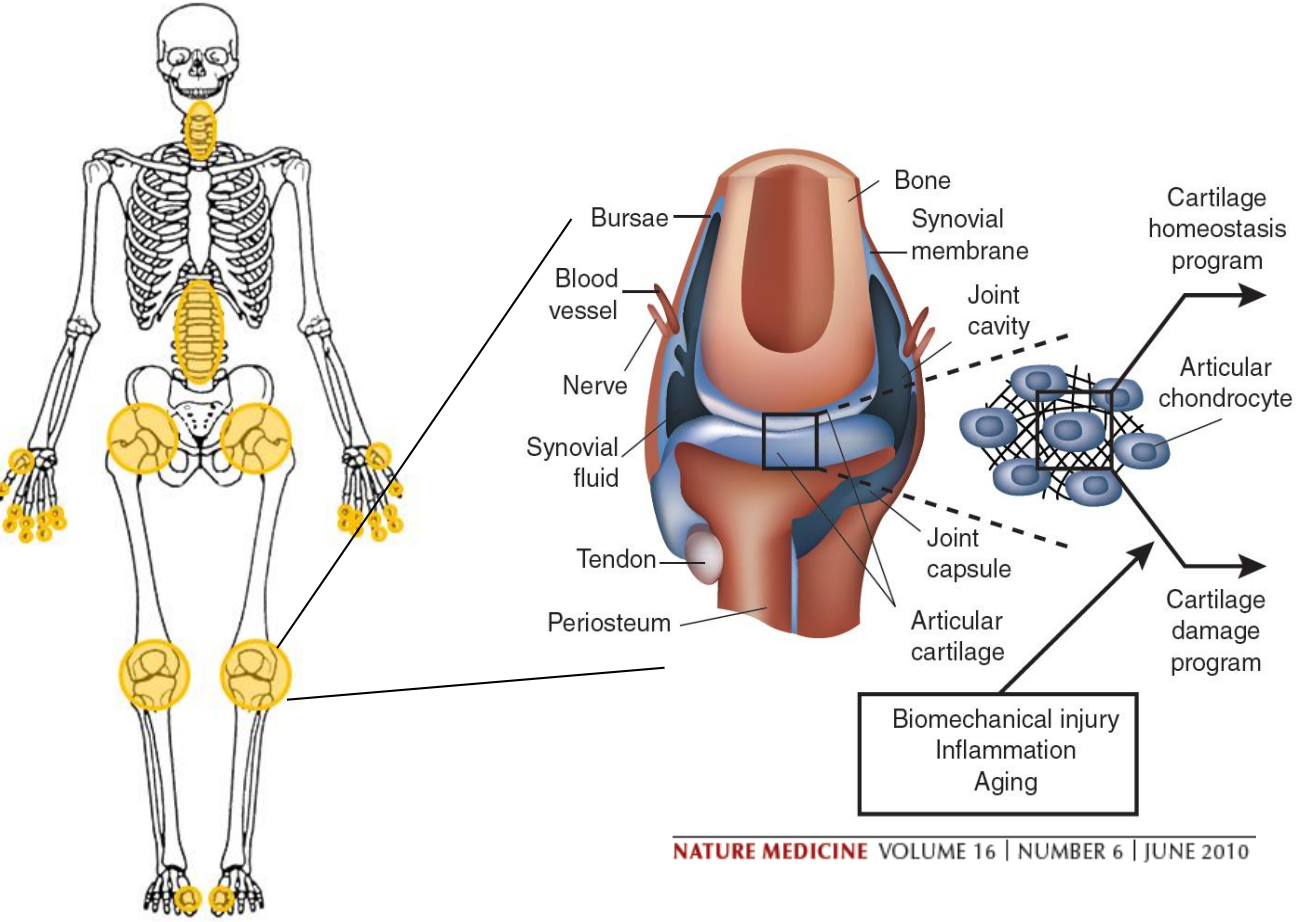
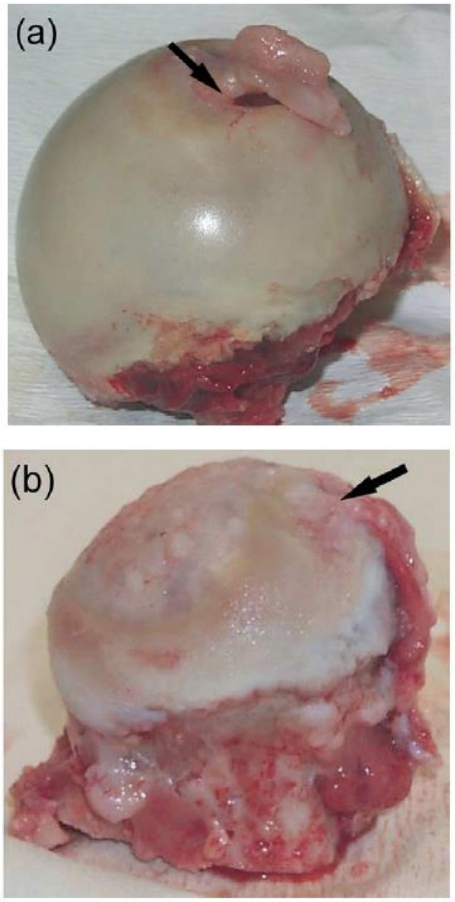
University of Vigo

The progressive loss of articular cartilage is hallmark of Osteoarthritis



en.rheumatologie.usz.ch



Holloway *et al.* Osteoarthritis Cartilage. 2004

Osteoarthritis prevalence is **GROWING**

Affects

240 million

People worldwide

Osteoarthritis limits **LIFE** quality

25% cannot do normal activities

80% are limited with movement

High risk of cardiovascular diseases, diabetes, hypertension & **death**

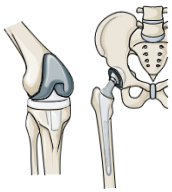
Osteoarthritis has **NO CURE**

Treatment can reduce **PAIN**, but...

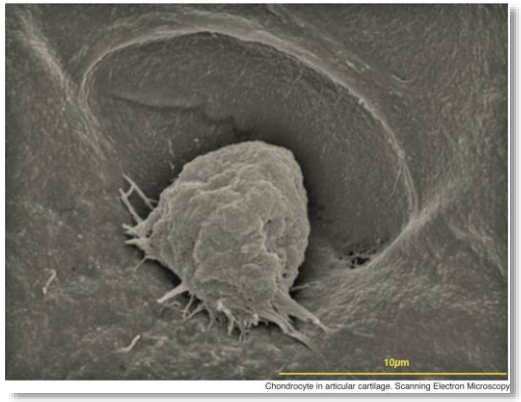
NO approved drugs prevent OA

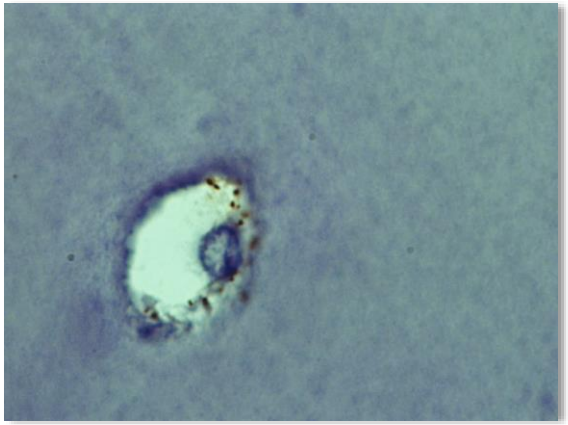
NO approved drugs slow OA progression

Surgery can **REPLACE** but not **RESTORE** the joint

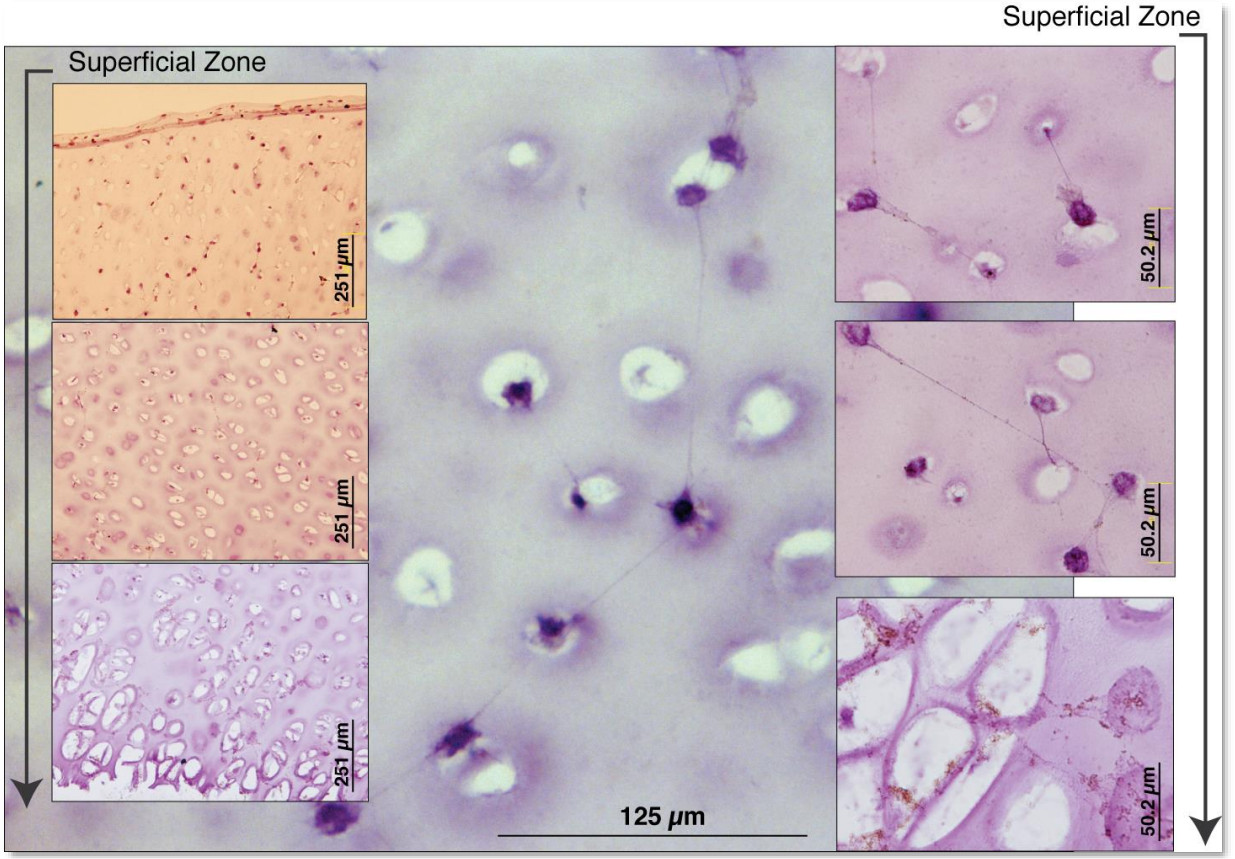


Articular cartilage is composed by chondrocytes and a dense extracellular matrix



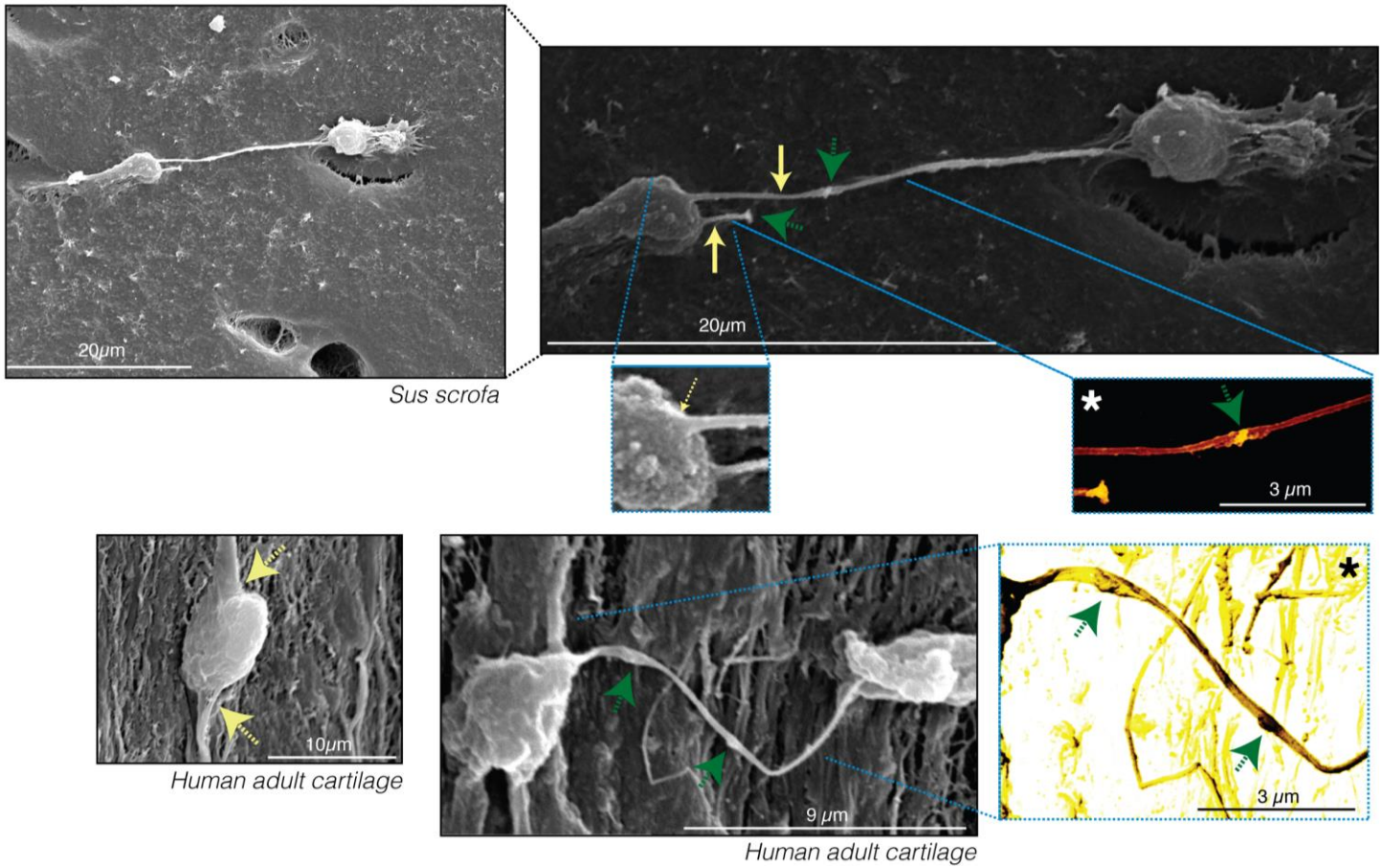


Mayan, M. D. et al. **Ann Rheum Dis**. 2015 doi: 10.1136/annrheumdis-2013-204244



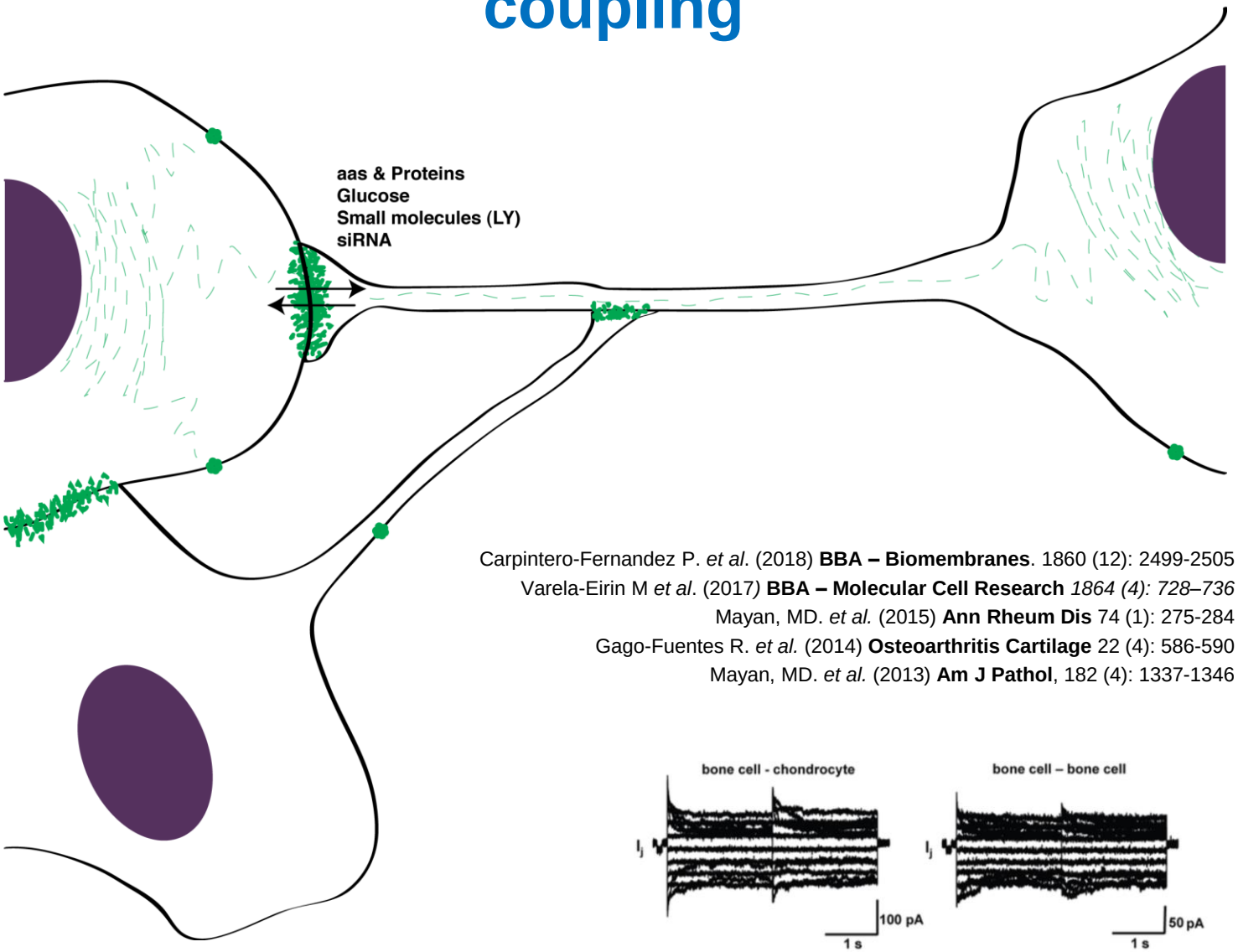
Mayan, M. D. *et al*. **Ann Rheum Dis**. 2015 Jan;74(1):275-84. doi: 10.1136/annrheumdis-2013-204244

Scanning electron microscope to validate the presence of cytoplasmic arms extending from the cell body and connecting with distant cells



Mayan, M. D. *et al*. **Ann Rheum Dis**. 2015 Jan;74(1):275-84. doi: 10.1136/annrheumdis-2013-204244

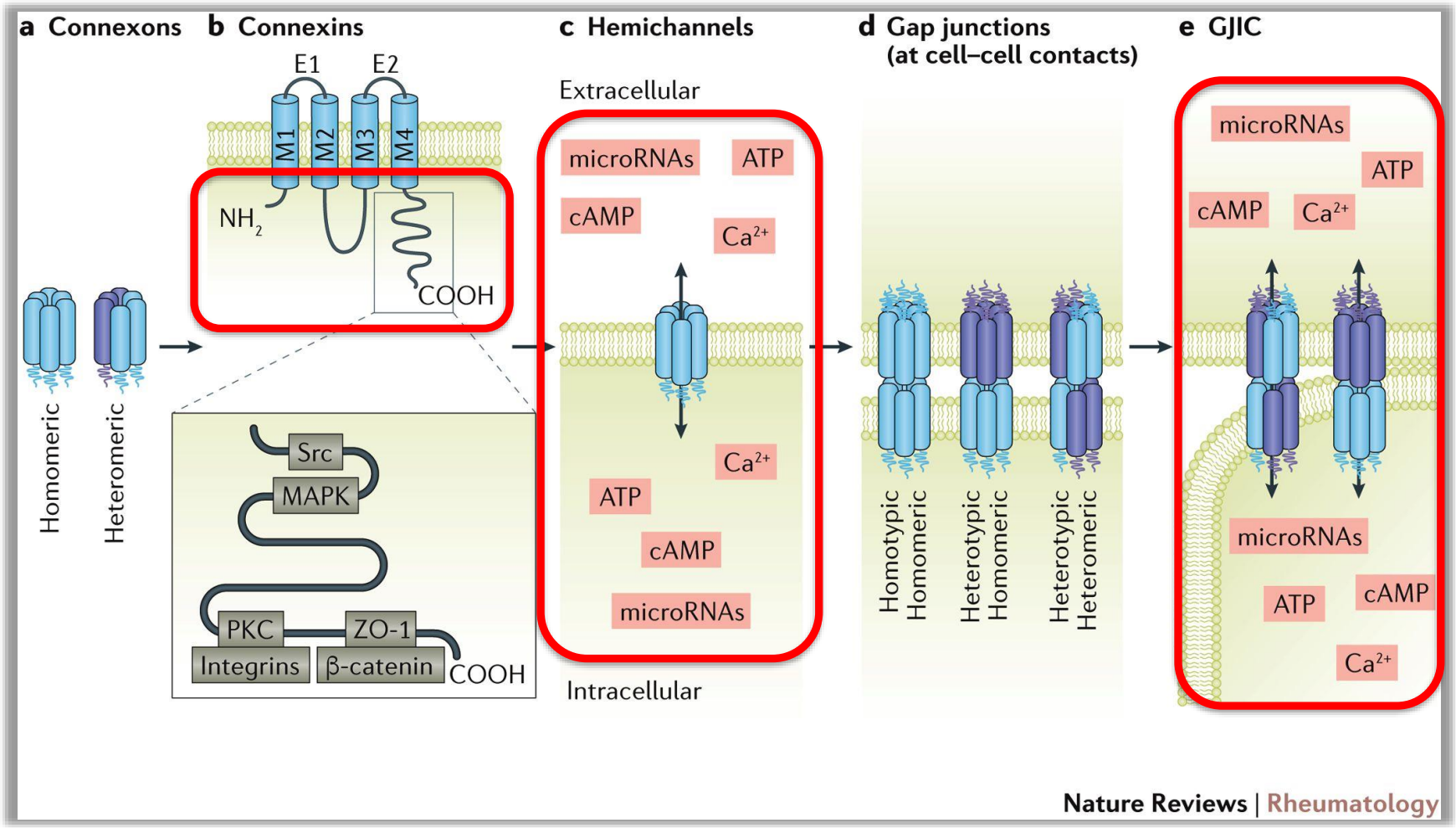
Articular chondrocytes network mediated by gap junction channels: chemical and metabolic coupling



Carpintero-Fernandez P. *et al*. (2018) **BBA – Biomembranes**. 1860 (12): 2499-2505
Varela-Eirin M *et al*. (2017*)* **BBA – Molecular Cell Research** *1864 (4): 728–736*
Mayan, MD. *et al.* (2015) **Ann Rheum Dis** 74 (1): 275-284
Gago-Fuentes R. *et al.* (2014) **Osteoarthritis Cartilage** 22 (4): 586-590
Mayan, MD. *et al.* (2013) **Am J Pathol**, 182 (4): 1337-1346

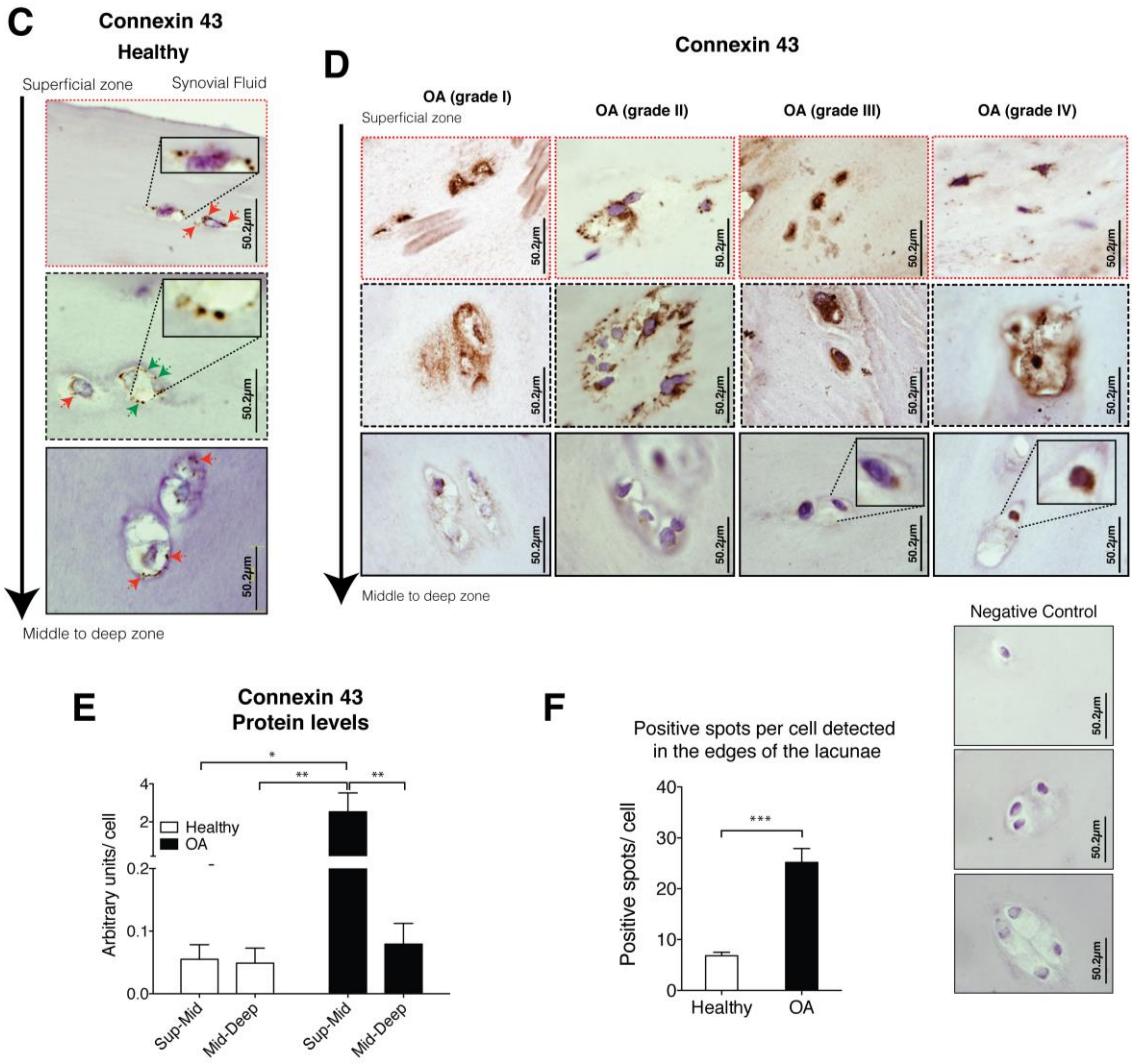
Carpintero-Fernandez P. *et al*. (2018) **BBA – Biomembranes**. 1860 (12): 2499-2505

Connexins: gap junctions, hemichannels and signalling hubs



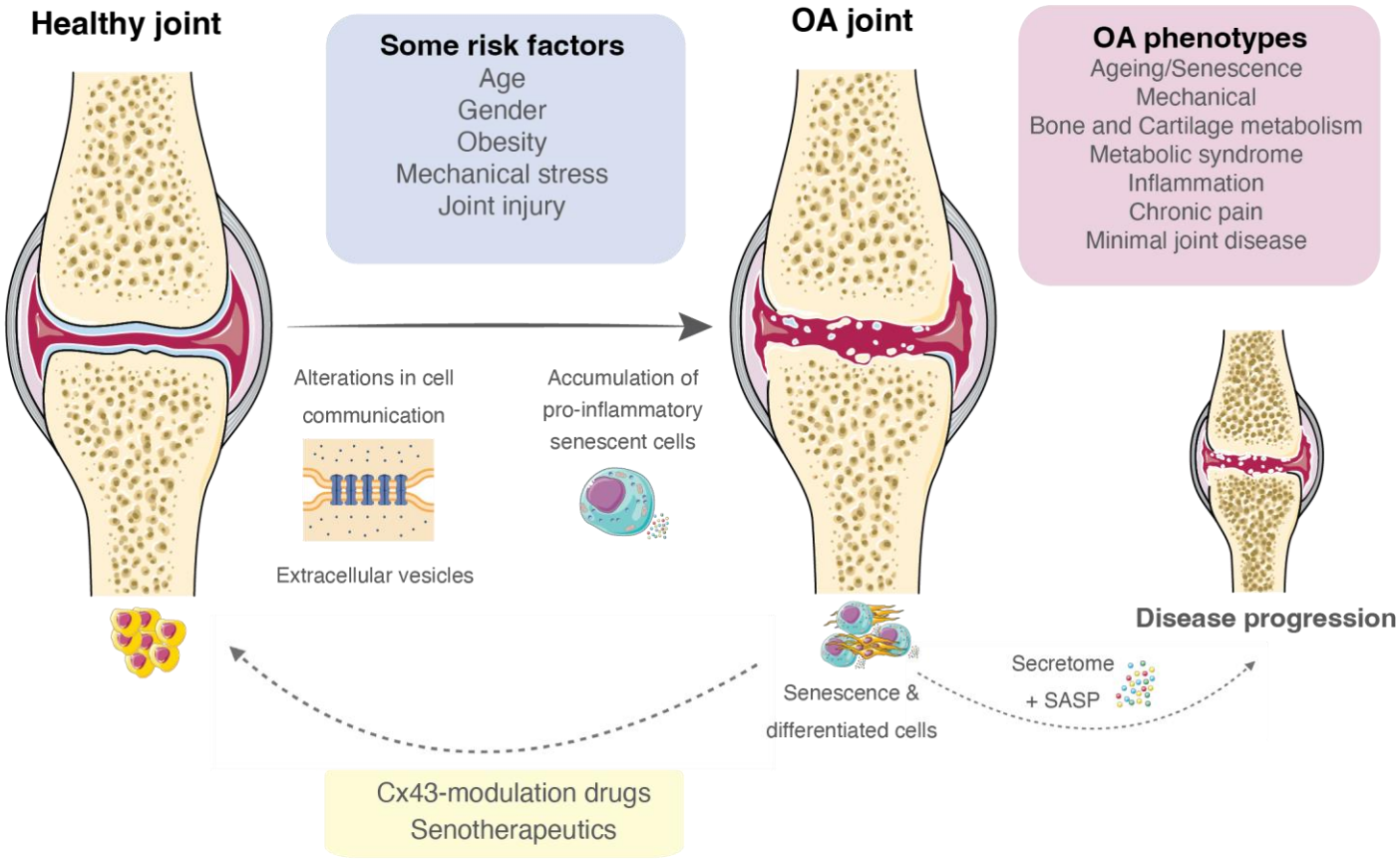
Nature Reviews Rheumatology volume 14, pages42–51(2018)

Overexpression of Cx43 since the early stages of OA (knee and hip) occurs independently of the clinical phenotype



Mayan, M. D. *et al*. **American Journal of Pathology**, 182, 4, 2013. 1337-1346

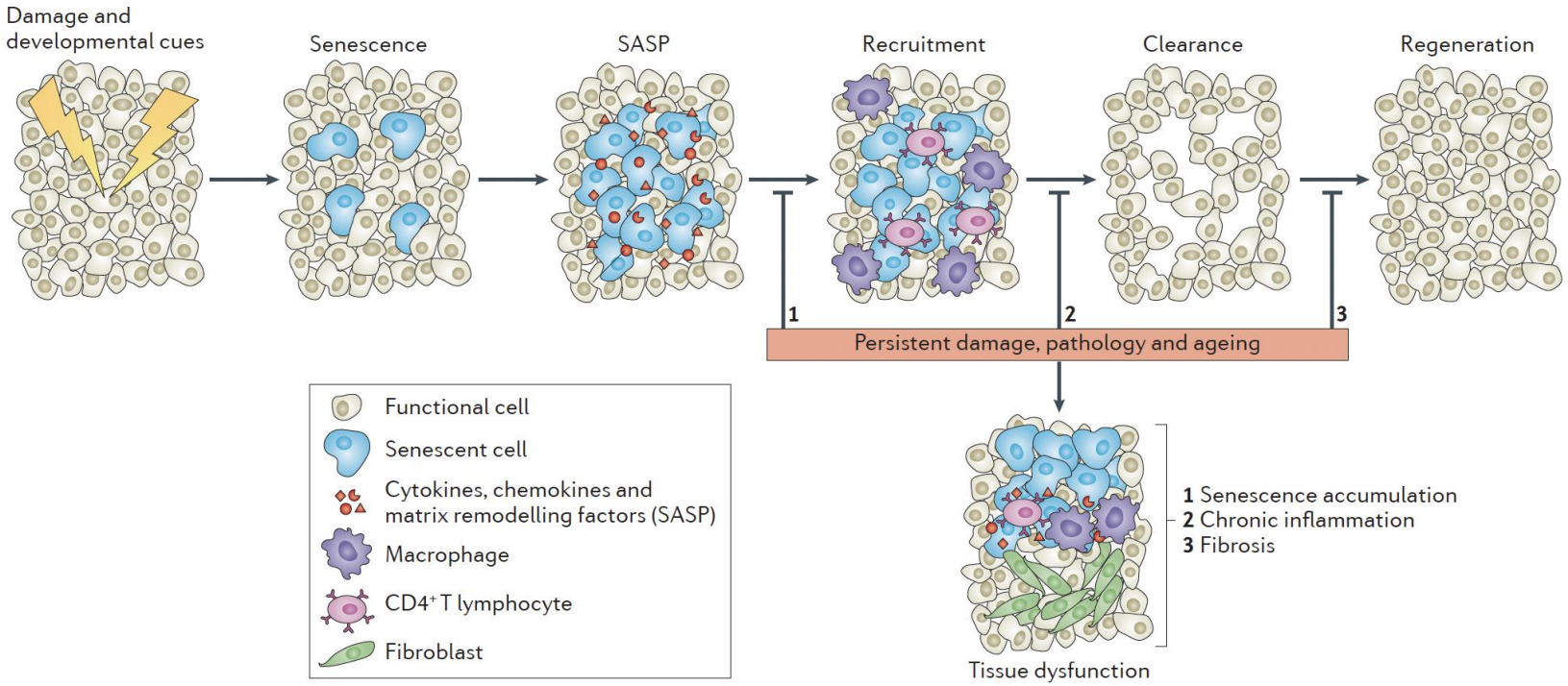
Overactivity of Cx43 interferes with cartilage regeneration in OA: EMT and accumulation of senescent cells



Varela-Eirin M. *et al.*, **Cell Death and Disease**. 2018 Dec 5;9(12):1166

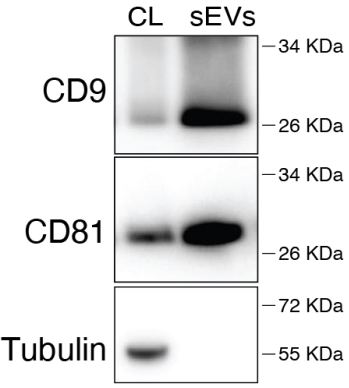
Carpintero-Fernandez et al., February 2022 **Bioelectricity** DOI:10.1089/bioe.2021.0039

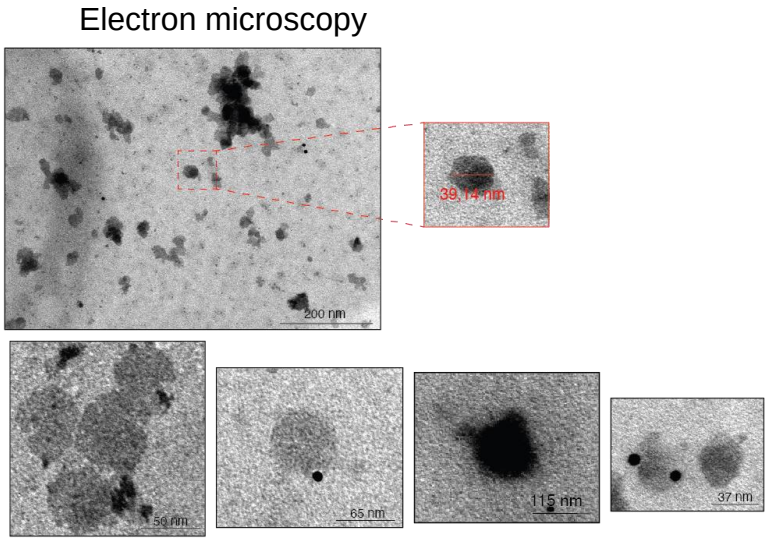
Cellular Senescence in Tissue Repair and Aging

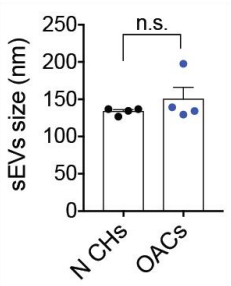


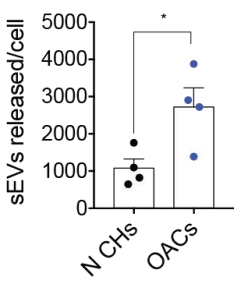
Nature Reviews Molecular Cell Biology **volume 15**, pages482–496 (2014)

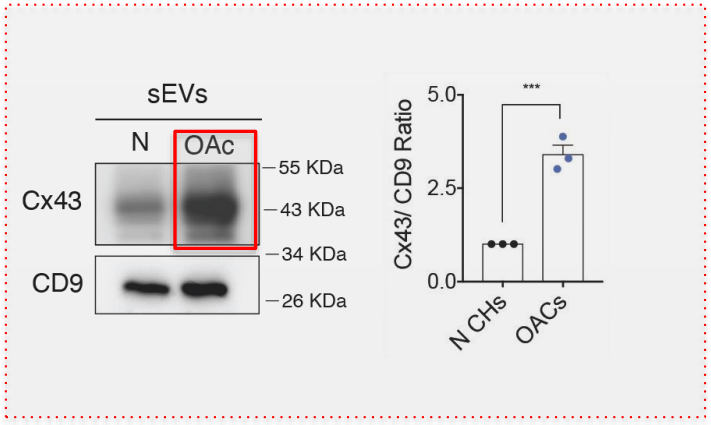
OA chondrocytes contain higher levels of Cx43 in the sEVs compared to sEVs from healthy chondrocytes





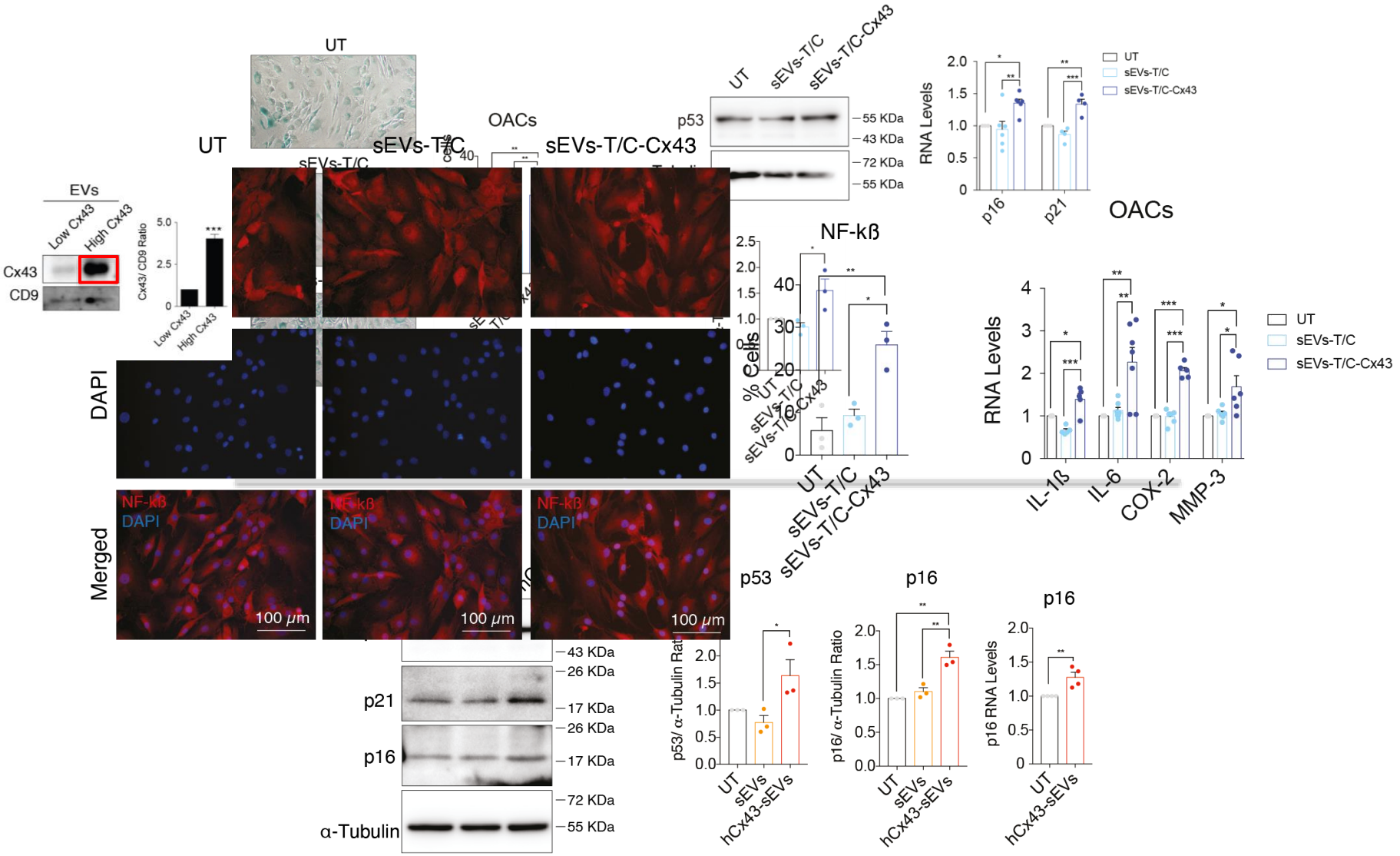






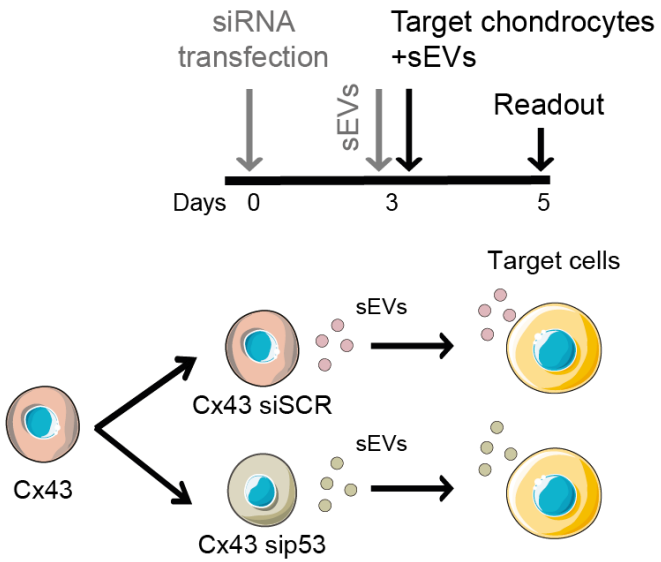
Cell Death and Disease. 2022 August 13(8):681. doi: 10.1038/s41419-022-05089-w

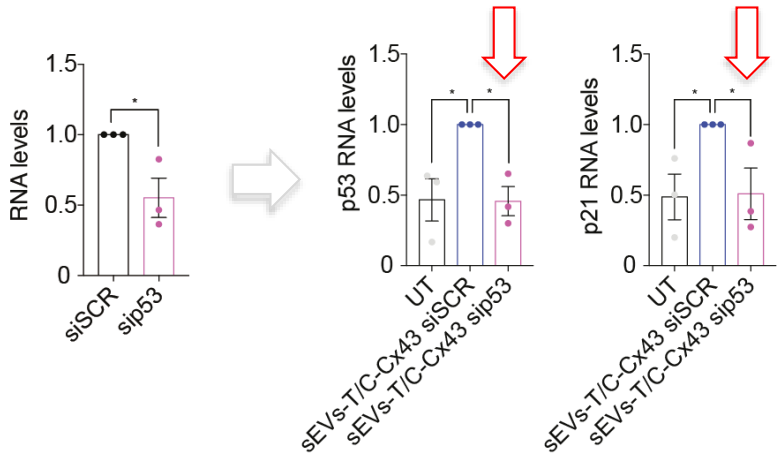
Exosomal Cx43 induces cellular senescence turning chondrocyte into pro-inflammatory cells

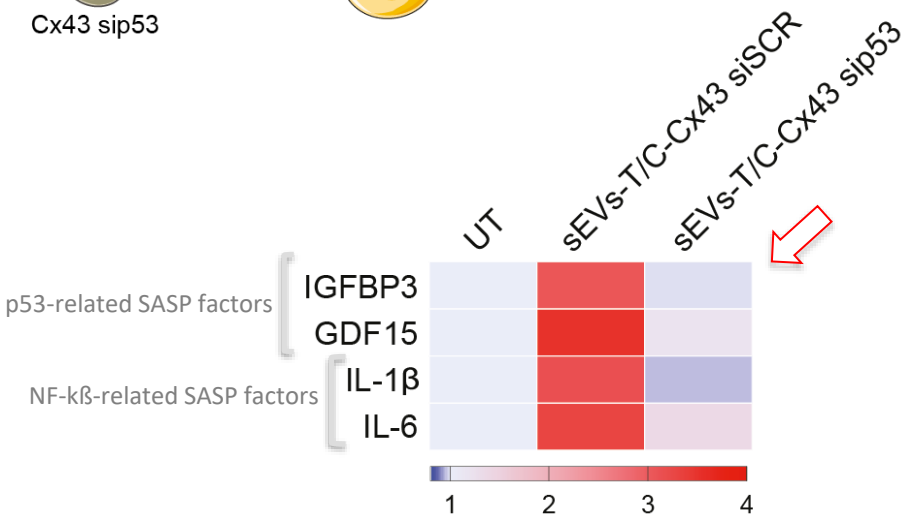


Cell Death and Disease. 2022 August 13(8):681. doi: 10.1038/s41419-022-05089-w

Exosomal Cx43 induces cellular senescence in a p53 dependent pathway

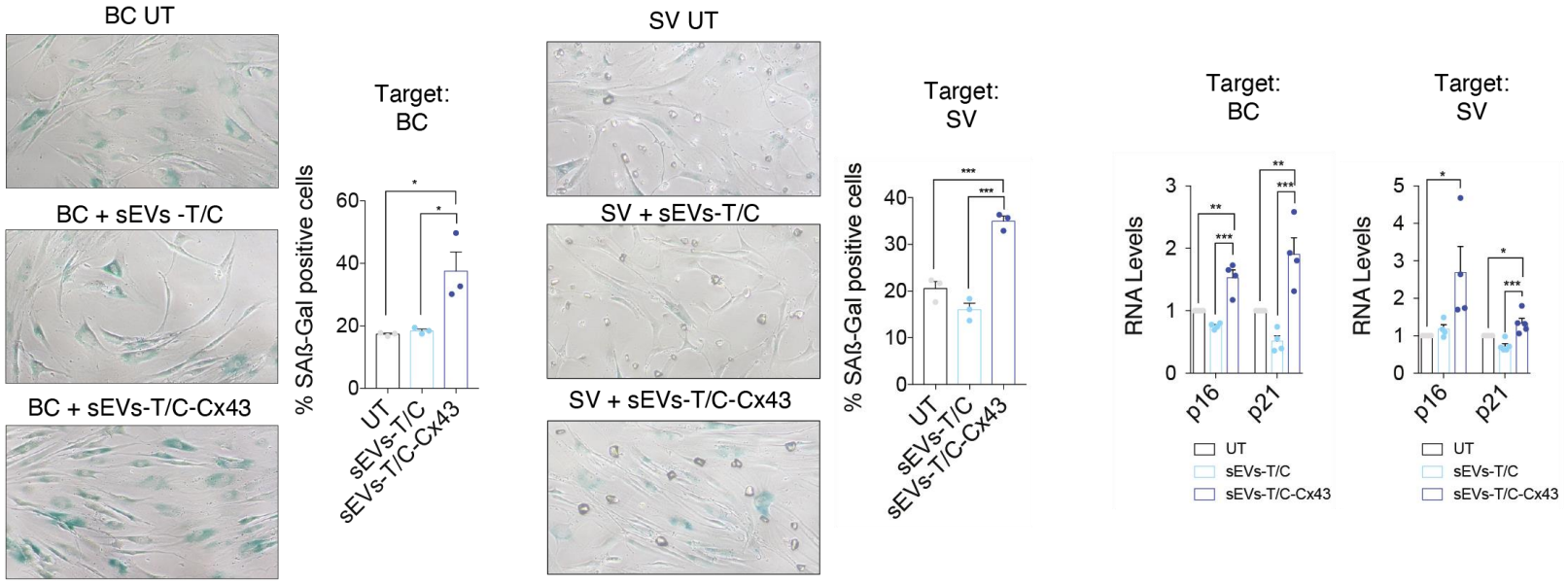


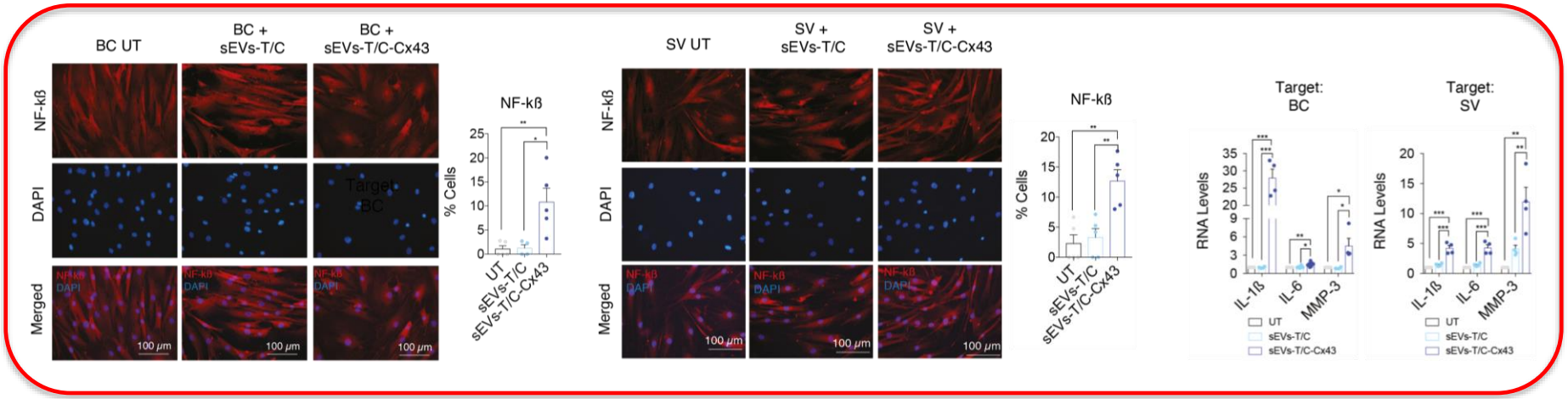




Cell Death and Disease. 2022 August 13(8):681. doi: 10.1038/s41419-022-05089-w

sEVs enriched in Cx43 induce cellular senescence in bone and synovial cells



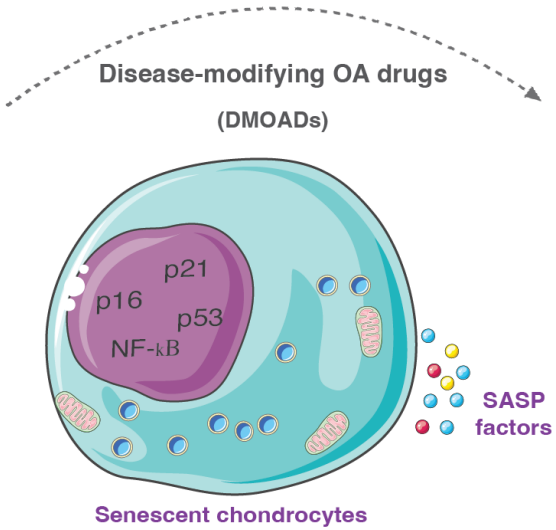


Cell Death and Disease. 2022 August 13(8):681. doi: 10.1038/s41419-022-05089-w

Take-home message

Senescence endotype

- Endogenous markers
- SASP factors
  - Cytokines
  - Proteases
  - Growht factors
- ↑Cx43 & Channel activity
- Acummulation of sensescent cells



Potential therapy

- Gene therapy
- SASP modulators
  - ILs receptor antagonists (IL-1Ra)
  - Metalloproteinases inhibitors (MIV-711)
  - Growth factors (Sprifermin, TissueGene-C)
  - Wnt signaling antagonist (Lorecivivint)
- Cx43 modulating drugs
- Senolytic drugs

Carpintero-Fernandez et al., February 2022 **Bioelectricity** DOI:10.1089/bioe.2021.0039

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Among others

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