New anti-inflammatory and pro-apoptotic photosensitizers against arthritis

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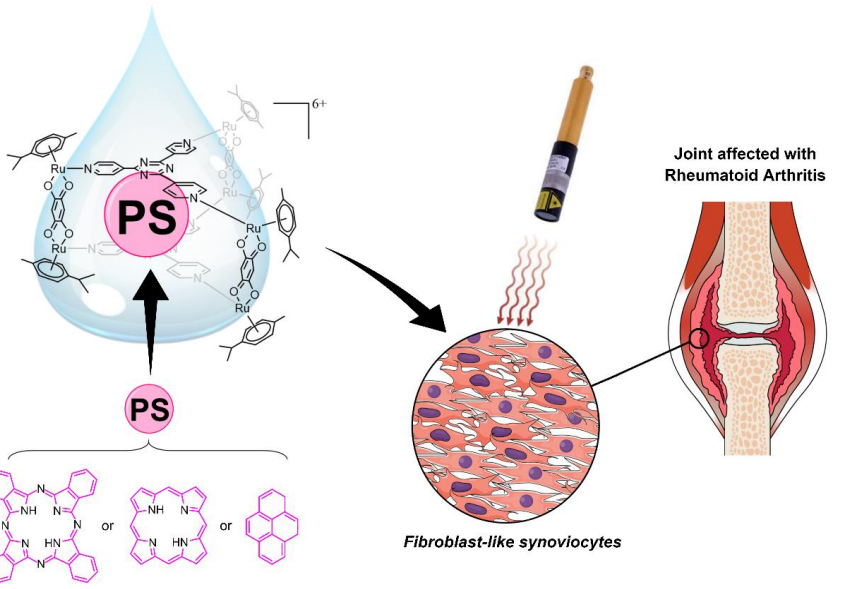
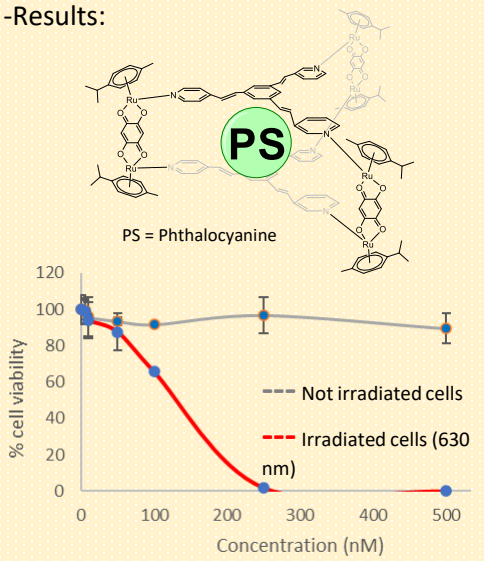
Contrary to popular belief, rheumatoid arthritis (RA) is not a disease only associated with aging, since it can also affect young people.[1] It is an autoimmune pathology that, although mainly affecting joints, can also attack other organs such as kidneys, lungs or heart. If left untreated, it can lead to a serious prognosis.[2] The most common treatment remains synovectomy, which is an invasive treatment and involves long periods of postoperative rehabilitation. In recent years, promising results have been achieved using non-invasive treatments such as anti-tumor necrosis factor drugs, Janus kinase inhibitors, and especially photodynamic therapy (PDT).[3] The latter involves a photoactive compound, a photosensitizer (PS), and light activation. The simplicity and non-invasiveness make PDT an ideal treatment to alleviate the pain or disability caused by RA. Unfortunately, conventional PSs often have some drawbacks related mainly to their low solubility in biological media and undesirable side effects such as light hypersensitivity.[4] We believe that it may be possible to solve the poor water solubility of PSs using ruthenium metallacages. These metallacages are soluble in biological media and have an inner cavity in which the PS can lodge. Such ruthenium metallacages have already been tested in vitro on cancer cells, demonstrating their potential.[5]



Insoluble PSs could be placed inside the cavity of the metallacage to transport it in biological media

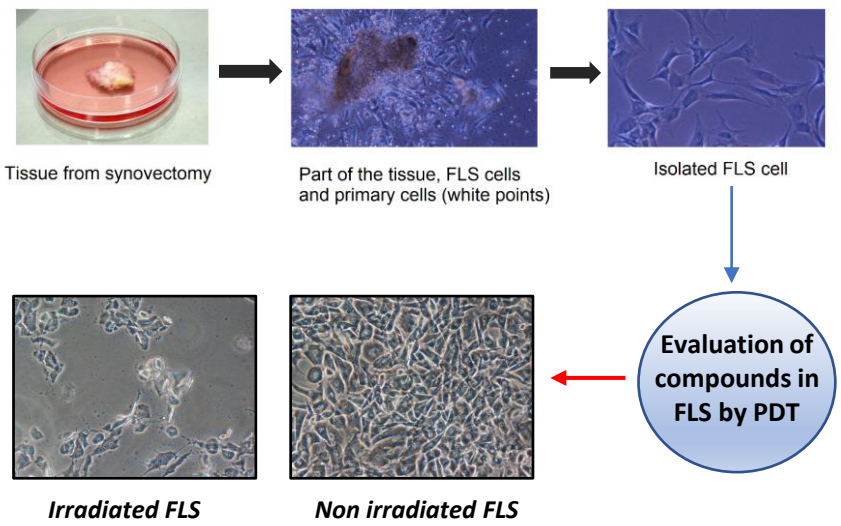
References: [1] Stuart M.J., Rand J.A., *J. Bone Joint Surg*, **1988** 70, 84-87. [2] Maradit-Kremers, H., Crowson, C.S., Nicola, P.J., Ballman, K.V., Roger, V.L., Jacobsen, S.J., Gabriel, S.E., *Arthritis Rheumatol*, **2005**, 52, 402-411. [3] Gallardo-Villagrán, M., Leger, D. Y., Liagre, B., Therrien, B., *Int J Mol Sci*, **2019**, 20, 3339. [4] Koderhold, G., Jindra, R., Koren, H., Alth, G., Schenk, G., *J Photoch Photobio B*, **1996**, 36, 221-223. [5] Schmitt, F., Freudenreich, J., Barry, N. P., Juillerat-Jeanneret, L., Süss-Fink, G., Therrien, B., *J Am Chem Soc*, **2012**, 134, 754-757.

-Results:

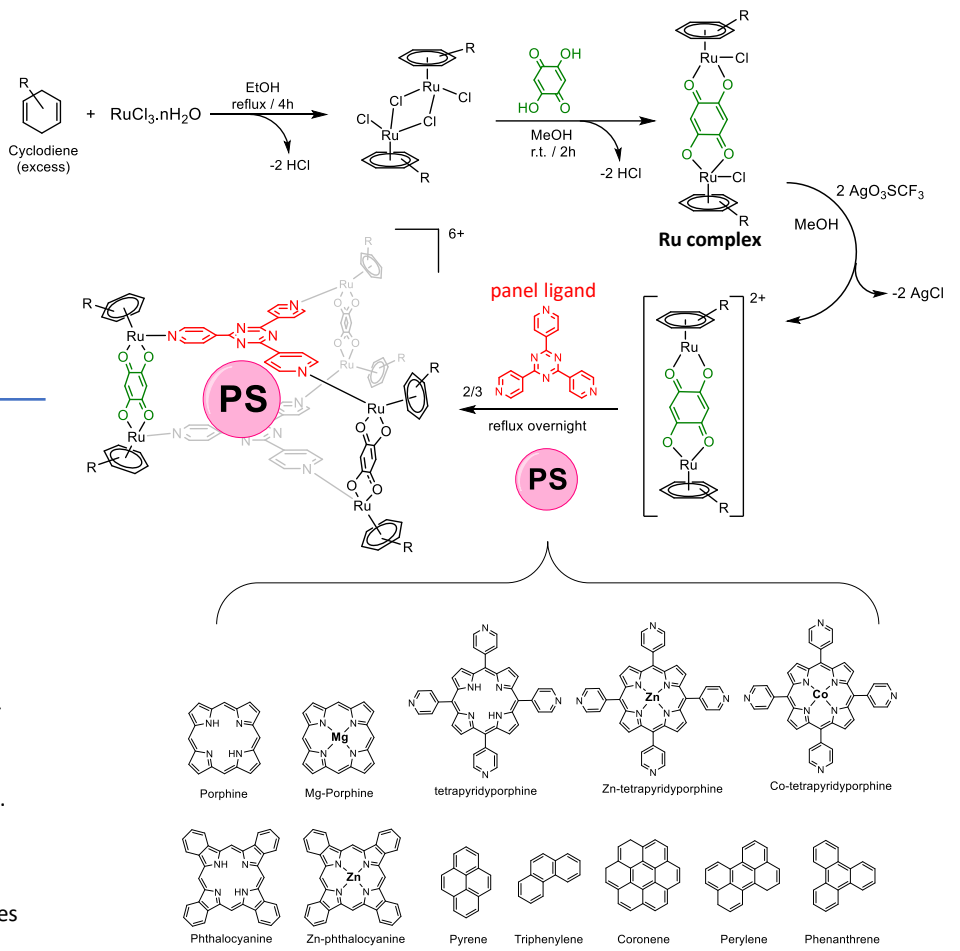


We have tested the photocytotoxicity of 25 different compounds, including cages of different structure (prismatic and cubic) with different PS in their interior cavity (porphine, Mg-porphine, phthalocyanines, tetrapyridylporphyrins, pyrene, coronene, perylene, triphenylene and phenanthrene), achieving results excellent with 15 of them (the example above, prismatic cage + phthalocyanine inside). Now we are working on the anti-inflammatory evaluation (COX-2 expression, cytokines and PGE_2) to confirm the admirable potential of these compounds against rheumatoid arthritis using PDT.

Fibroblast-like synoviocytes (FLS) are isolated by digestion from tissue removed in synovectomies in people with rheumatoid arthritis. The cells are subsequently cultured to increase their number and are used to test the compounds by PDT. After treatment, photocytotoxicity is tested and the anti-inflammatory capacity of the treatment is evaluated.



The organometallic ruthenium cages are synthesized in the faculty of Chemistry of the University of Neuchâtel (Switzerland). Depending on the type of ligand used, we can synthesize cages with different volume and shape (cubic and prismatic), varying the size of their interior cavity to host different photosensitizers. In this way we have synthesized 11 different cages combined with 12 different PSs, achieving a total of 25 compounds.



Conclusions after photocytotoxicity tests (by MTT assays):

1. When the Ru complex is bulkier photocytotoxicity is much better using Porphine.
2. Using the same Ru complex, bigger panel ligands, on the top and bottom, work better.
3. Porphine works better than Mg-porphine.
4. There are not significant different between Porphine and Phthalocyanine using the same cage, their photocytotoxicity look similar.
5. Phthalocyanine was very good with the two prismatic cages but did not work with the cubic cage.
6. Zn-Phthalocyanine showed cytotoxicity in not irradiated cells, less than irradiated but close to these.
7. Pyrene, Coronene, Perylene, triphenylene and phenanthrene did not show photocytotoxicity with red light (630 nm).
8. Empty cubic cage with tetrapyridylporphine as panel (on the top and bottom) showed the higher photocytotoxicity (IC50 = 14 nM). As with porphine and Mg-porphine, adding a metal (Zn or Co) reduces the photocytotoxicity.

We are currently working on the evaluation of the anti-inflammatory activity of the treatment.