Excessive activation of the inflammasome is a common feature of numerous inflammatory diseases, including rheumatoid arthritis, colitis, and atherosclerosis. **Inflammasome** is a large protein complex that, when activated, evokes overexpression of various pathogenic proteins leading to mass production of **proinflammatory cytokines**; **IL-1*β* and IL-18**. Although their significant importance in defence mechanisms during short-term inflammatory responses, overproduction of these cytokines leads to chronic inflammation and tissue damage. This suggests an attractive opportunity to target inflammasome in pursuit of effective therapeutic strategies towards inflammatory diseases. Unfortunately, some of the proteins involved in inflammasome activation posses up to 3 distinct binding pockets, which highly hampers the use of traditional inhibitors for the purposes above.

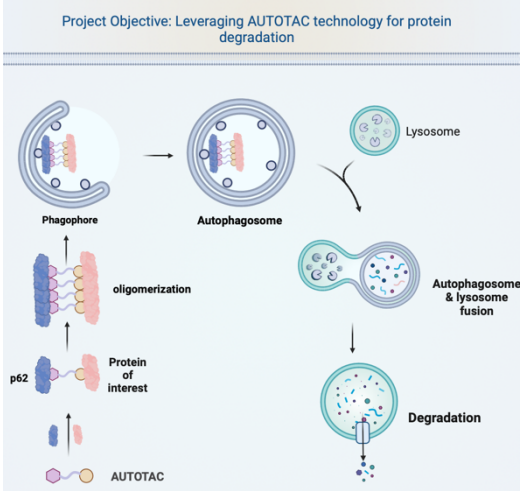

Fig 1. AUTOTAC as an example of targeted protein degradation technology

A solution to this problem can be brought to life by **TPD** (**Targeted Protein Degradation**), being a rapidly developing set of techniques that aim to induce proximity between a pathogenic protein, and a cellular machinery able to induce **proteolysis** thereof. The most viable TPD strategies, such as **PROTAC** (PROteolysis TArgeting Chimeras), **AUTOTAC** (AUTOphagy TArgeting Chimeras) or **LYTAC** (LYsosome TArgeting Chimeras) use bifunctional molecules to create a linkage between a protein of interest, and a larger cellular complex responsible for protein recognition and degradation (Fig 1). The main advantage of TPD is a possibility to **totally eradicate a target protein**, being a paradigm shift in comparison to conventional inhibitors which only block their target for a limited time. Morover, this strategy solves common pharmacotheraeutic problems associated with multiple binding pockets, their hindered availability or impaired inhibitor affinity.Recent years have seen a strong scientific interest in designing novel TPD strategies engaging lysosomes – ubiquitous organelles naturally able to degrade damaged DNA, dysfunctional proteins or their large, insoluble aggregates. Physiology of lysosomes is highly associated with **autophagy** – a process of bringing cytoplasmic debris up to lysosome, for subsequent digestion by lysosomal hydrolases and other enzymes.

In this project hereby, we intend to focus on induced protein degradation employing autophagy processes. Our aim is to **neutralize a protein of interest, associated with inflammasome activation and chronic inflammatory disease states**, e.g. **colitis.**

We will obtain new molecules which, after initial physicochemical analyses will be further evaluated *in vitro* and *in vivo.* We will assess the influence of these compounds on degradation of a target protein and consequential changes in inflammatory cytokine IL-1*β* secretion. Next, the most promising compounds will be tested against a knockdown cell line (such, with immobilized expression of a certain protein) to confirm the molecular mechanism of action, followed by detailed analysis of induced autophagy process using advanced *live cell imaging* techniques. The study will be finalized by *in vivo* investigation of the new degraders in an experimental model of endocolitis.

Our project will enable a rise of new pharmacological tools based on AUTOTAC technology, contributing to wider understanding of autophagy processes and their potential in treatment of chronic inflammatory diseases. Molecular degraders constitute one of the most promising, worldwide trends in searching for new therapeutic strategies for a myriad of diseases states.