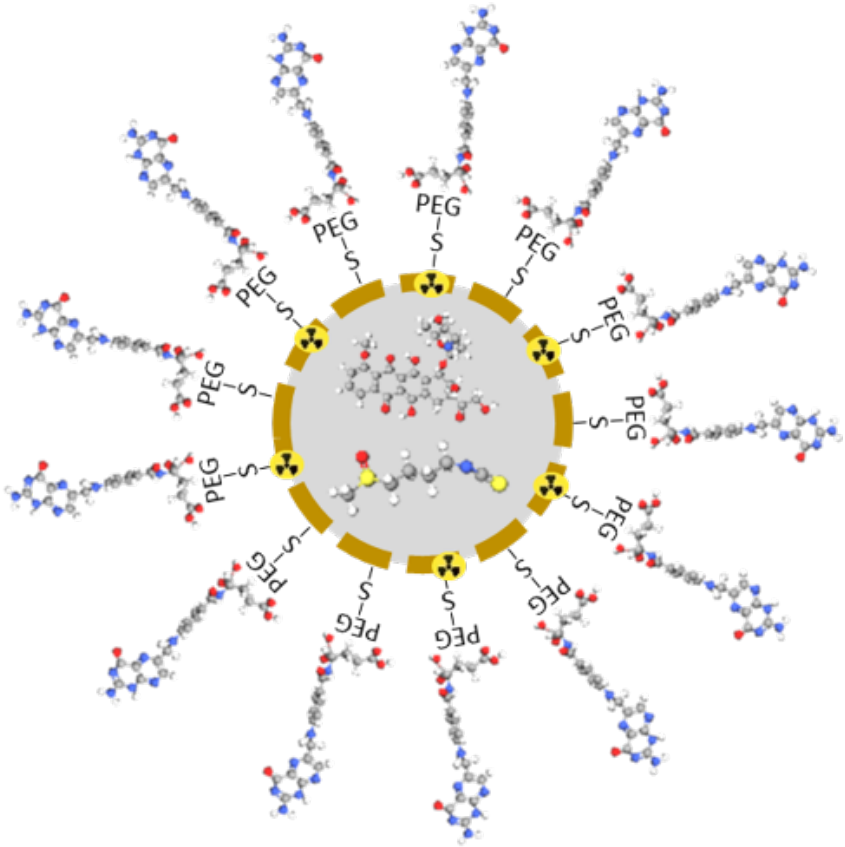
Cancer treatment is currently one of the central problems of medicine, accounting for more than ten percent of all deaths worldwide. The treatment of cancer is typically difficult, and therapies are associated with severe side effects. While there are a number of various methods to treat cancer diseases, the most effective and most common is chemotherapy. Chemotherapy involves the application of drugs that inhibit growth or cause the death of cancer cells. These drugs are typically administered through intravenous or oral routes. Although new drugs are instantly introduced to the medical market, severe disadvantages to treatment via chemotherapy remain, as the current therapies are typically non-specific, and the drugs used are toxic to both tumor and healthy tissues in the body. Consequently, when the cancer cells are killed, the normal cells are also harmfully affected, leading to secondary illnesses. Moreover, many tumors might develop resistances to multiple drugs; thus, treatment becomes non-effective or requires applications of higher doses. One of the most potent chemotherapy agents is doxorubicin. This pharmaceutical is derived from daunorubicin, a natural product initially isolated from the fungus *Streptomyces peucetius* . Doxorubicin is effective against leukemias and cancers of the breast, stomach, lung, ovaries and thyroid, but reveals extremely severe side effects with serious cardiotoxicity, potentially leading to death. We have recently observed, however, that the addition of another natural product, sulforaphane (obtained from broccoli and cabbage), can enhance the anticancer properties of doxorubicin, while lowering the negative effects on healthy cells.

In the current project, we will examine mixtures of doxorubicin with sulforaphane. To further lower the adverse effects and enhance therapeutic efficacy of this mixture, we will encapsulate both drugs inside polymer particles. The idea is that the drugs will travel through the body enclosed and will subsequently be released when they reach the tumor. The role of the encapsulating particles is to isolate the drug from healthy tissues, thereby reducing the adverse effects. The polymer particle might even serve additional functions. The modification of the surface of the particle using molecules that recognize the tumor could facilitate the precise targeting of the drug to malignant tissue. This approach, called targeted delivery, will be achieved in the present study by anchoring folic acid molecules onto the surface of the particles. The membranes of cancer cells typically contain receptors that interact with folic acid, and this interaction is the basis for targeted delivery. However, the attachment of folic acid molecules onto the surface of the polymer particle is a challenge. To accomplish this task, we plan to decorate polymer drug carriers with ultrasmall gold particles (called nanoparticles because the diameter of these particles is in the range of several nanometers). These nanoparticles, located on the surface of drug carriers, will be used as specific anchors that fix the folic acid molecules.

As described above, these modified polymer particles can perform several tasks, including the transport and targeting of drug molecules to the tumor. These tasks are responsible for enhanced therapeutic efficacy of the encapsulated drugs. However, hybrid particles can perform yet another function, as these molecules can also be employed for diagnostic purposes. Such integration of therapy and diagnosis into a single structure is called theranostics, an acronym derived from the words "therapy" and "diagnostics". In this scenario, the drug carrier not only cures the disease but also determines the causation. In an ideal situation, the smart theranostic particle enters the body, searches for the illness, determines how to treat it, and finally cures the disease. This level of advanced therapy, although considered science fiction at this stage, might become a reality in the future.



Scheme 1. The structure of the multifunctional hybrid organic-inorganic particle.

The idea of the current project is slightly less visionary, but more realistic. Herein, we propose a project to monitor hybrid drug carriers traveling through the body. The point is that that, when the drug is administered to the patient (i.e., intravenously), we do not know how it circulates in the blood system and where it is eventually delivered. This lack of information about the fate

of the drug is a considerable problem and diminishes the effectiveness of the treatment. For this reason, we decorated the hybrid particles with radioactive gold nanoparticles. The radioactive gold (^{198}Au isotope) emits gamma rays (a type of high energy electromagnetic radiation), which can be detected using a medical imaging system called Single Photon Emission Computed Tomography (or SPECT). SPECT is routinely used in clinical practice for the diagnosis of malignant tissues in the body. Thus, we will employ this instrument to monitor the fate of the encapsulated drug in the body.

We propose that this multidisciplinary study will establish a new paradigm in the field of smart drug delivery systems, and these findings will provide a foundation for new revolutionary medical treatments of the future.