This project was designed as a scientific response to a fashion, out of a concern that the history is going to repeat itself. Again. Too many times products of scientific discoveries made their way to human environment and consumer products before full (or any) consequences of their adverse effects could be realized. Let us recollect the radium hype of the early 20th century – when radioactivity was supposed to be a cure-all, but soon brought cancer and radiation disease to avid users. Let us consider leaded gasoline which helped develop the human mobility, but polluted the world with a neurotoxic element. Let us remember, or actually look around to see asbestos roofs, which prevented house fires, but brought lung cancer and melanoma to their inhabitants. Finally, let us think about antibiotics, which temporarily freed the humanity from bacterial infectious diseases as the main cause of death before 1950ies, but used unreasonably helped create and spread the multidrug resistant bacteria to which there is no cure. So let us look at silver. This precious metal has accompanied humankind since early antiquity and its uses in fighting infections (silver plates and later also silver nitrate) and as food and drink preservative (silver vessels) is documented for ancient Persia, Greece and Rome. Such uses have continued over centuries and went out of fashion only in 1940ies, when first sulfonamides and then the first modern antibiotics were made available. As the history likes to play tricks, the emergence and spread of antibiotic resistance in the 21st century resulted in the renaissance of antiseptic applications of silver, but now mainly as metallic silver nanoparticles, tiny spheres of silver – typically 10 to 100 nanometers in diameter, containing hundreds of thousands to tens of millions of silver atoms apiece.

Silver has been used in coins and household objects for the millennia (hence the name silverware) with obvious benefits, such as durability and mild antiseptic properties, and with no apparent side effects. Hence, the introduction of modern silver-made materials including nanoparticles has been neither legally regulated nor controlled – by assumption that silver is all right. Along with the grand career of silver coatings in the health care system, particularly in antibacterial and antifungal coatings and in the treatment of burns, and also in water purification, medical devices, cancer therapies, and air quality management, silver nanoparticles have made it to the human environment with consumer products, as antimicrobial component of cosmetics, bedding, sportswear, protective gear (such as face masks heavily used during COVID-19 pandemics), and food containers. At the same time, but without making it to front pages, rigorous scientific studies on cell cultures and experimental animals started providing more and more evidence for the deposition of these nanoparticles, or silver ions derived from them, in body organs, which are directly toxic. We contributed to these studies, by finding out that exposure to silver nanoparticles in liver disease patients caused copper accumulation in their livers. This is a potentially dangerous mechanism of toxic synergy which will be studied independently by the clinicians. Still, we are confident that benefits of responsible use of silver nanoparticles in combatting infections difficult to treat otherwise, prevail over the currently recognized hazards, but the research must continue with respect to the scope and duration of such treatment. This is not necessary the case, however, for unregulated and not rigorously tested non-medicinal consumer products.

The mentioned toxicological studies of silver have not been adequately accompanied by chemical research into the specific causes of various manifestations of silver nanoparticle toxicity. Trying to fill this gap, we also discovered that silver very easily displaces zinc from certain zinc fingers – protein structures responsible for the proper use of cellular genetic code. The specific aims of this project build on this finding, and are directed at filling the gaps in the chemical, molecular understanding of ways the silver atoms harm the cells. This knowledge will help us to invent and propose the ways and means one might use to protect themselves from toxicity of silver nanoparticles, of course in addition to avoiding excessive exposure to them.

In particular, we are going to elucidate the mechanism of according to which the nanoparticles are dissolved in cell cytosol, yielding Ag^{+} ions. Next we will study how these ions interact with glutathione, the abundant cellular antioxidant and a potential silver detoxifying agent. Upon establishing this chemistry, we will use it to find out which zinc-dependent proteins (e.g. belonging to the groups of transcription factors, DNA repair proteins, enzymes etc.) are particularly susceptible to silver toxicity and, in consequence which metabolic pathways are most vulnerable to it. These studies will be supported by the research stay of the doctoral student in the collaborating Grenoble laboratory, specialized in cellular studies of zinc toxicity. The priority of this stay will be to confirm or deny the role of glutathione in protection of cells against silver toxicity. In this fashion the project will deliver a comprehensive view of chemical mechanisms underlying those aspects of cellular toxicity of silver nanoparticles which regard the zinc metabolism. This will empower us to collaborate with physicians in the development of recommendations, regarding the protection against chronic exposure to these nanoparticles, perhaps including diet supplementation.