Glyco-Gold Nanoparticles: Exploiting Multivalent Sugars for Addressing Rare Lysosomal Storage Disorders

Francesca Buco[1], Camilla Matassini[1], Francesca Clemente[1], Francesca Cardona[1], Amelia Morrone[2] and Marco Marradi[1]

[1]DICUS - UNIFI, via della Lastruccia 13, 50019-Sesto Fiorentino (FI), Italy
[2]AOU Meyer and NEUROFARBA (UNIFI), Viale Pieraccini n. 24, 50139 Firenze, Italy

francesca.buco@unifi.it

Lysosomal Storage Disorders (LSDs) are a family of genetic and pediatric pathologies caused by a lysosomal enzyme misfolding and dysfunction that lead to accumulation of unmetabolized substrates in the lysosomes [1].

Enzyme replacement therapy (ERT) is a therapeutic strategy for LSDs consisting of the infusion of the enzyme involved in the disorder in its recombinant form. This therapy shows some crucial disadvantages like the low stability *in vivo* of the recombinant enzyme and the high cost.

An emerging therapy for LSDs involves the use of pharmacological chaperones (PC), molecules capable of stabilizing mutated enzymes and restoring their physiological activity [2]. The identification of new PCs is also useful for the PC/ERT combined therapy, a strategy already investigated for some LSDs with the aim of reducing the dose of the infused recombinant enzyme and the administration frequency with great benefits for the patients' life quality [3].

Most PCs are identified among molecules able of mimicking the natural substrates of the enzyme involved in the pathology. Particular attention is on sugar molecules and their nitrogen-containing analogues since most of the enzymes involved in LSDs are carbohydrate-processing enzymes.

In addition, some of these enzymes, such as β-glucocerebrosidase (GCase) and *N*-acetylgalactosamine-6-sulfatase (GALNS) recently demonstrated enhanced affinities for multivalent ligands [4]. In particular, gold nanoparticles (AuNPs) have already been used as scaffolds for the multimerization of sugars, leading to biocompatible and water dispersible systems and guaranteeing the possibility of the simultaneous grafting of different thiol-ending ligands in a controlled manner [5]. In this context, AuNPs were selected as valuable scaffolds for the design and synthesis of multivalent nanosystems decorated with sugars and/or sugars analogues, properly chosen to mimic specific lysosomal enzyme substrates. After the chemical-physical characterization of the AuNPs, the biological evaluation towards enzymatic targets will be presented, to prove their affinity for lysosomal enzymes as well as their ability to stabilize the enzyme tertiary structure, acting as PCs (Figure 1).

References

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Figure 1

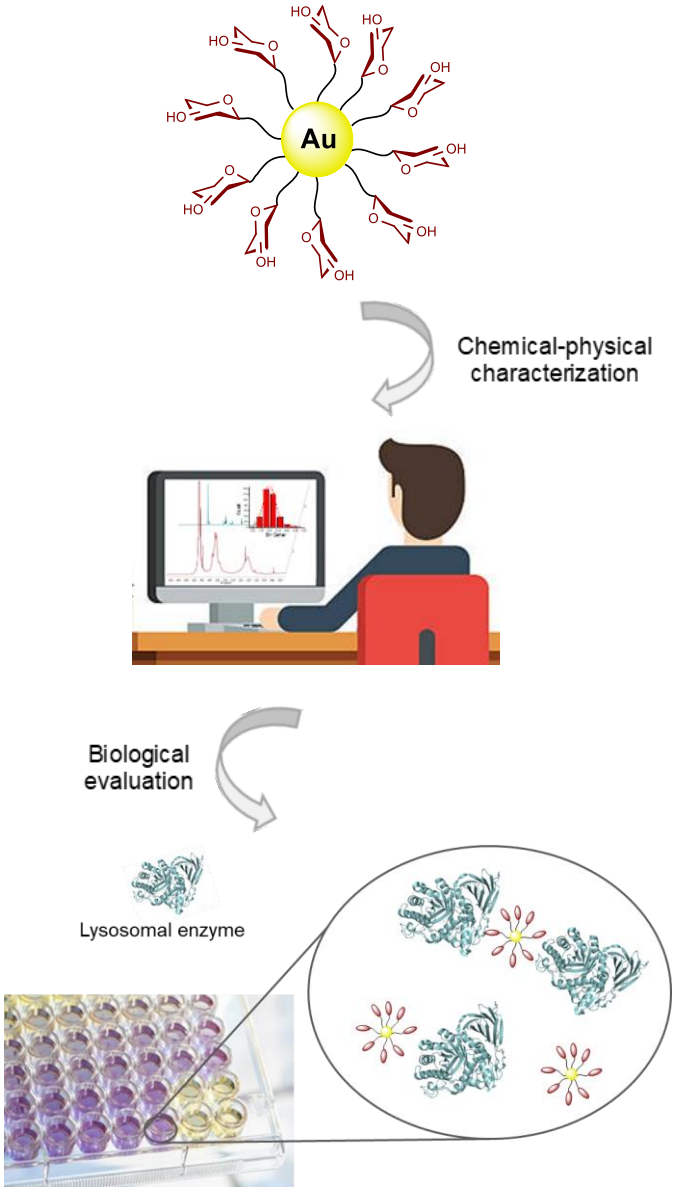

Figure 1. Graphical abstract