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Multivalent iminoglyco-NPs for theranostic applications

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Gaucher disease (GD) is a rare autosomal recessive disorder due to mutations in the *GBA* gene which cause a deficiency in the activity of the enzyme glucocerebrosidase (GCase). This enzyme has indeed multiple roles. Deficiency of GCase has also been linked to Parkinson's disease, and GCase is aberrantly activated in cancer, suggesting that therapeutic approaches to modulate GCase activity could play an important role in treating multiple diseases [1,2]. An innovative therapeutic strategy for the treatment of metabolic disorders which, however, has not yet reached the market for GD, is the use of pharmacological chaperones (PCs), compounds which can be found among competitive inhibitors of GCase but are able to rescue the enzyme activity when they are used in sub-inhibitory concentrations. In this regard, iminosugars, carbohydrate analogues with a nitrogen replacing the endocyclic oxygen of sugars, are promising candidates as PCs for GCase [3]. Since the blood-brain barrier (BBB) represents an obstacle for the classic enzymatic replacement treatment of neuronopathic forms of GD, the synthesis of new iminosugars functionalized with specific ligands (e.g. glucose, galactose) capable of enhancing brain uptake through the GLUcose Transporters (GLUT) is being investigated. In addition, since the overexpression of GCase reduces the toxicity of chemotherapy, the effect of co-administration of iminosugars with chemotherapeutic agents in different cancer cell lines is being studied. Both these applications can be further investigated, by exploiting the enhanced affinity recently demonstrated by GCase for multivalent iminosugars. Therefore, multimerization of iminosugars on different types of nanoparticles (NPs), e.g. metallic (Au) and fluorescent (quantum dots), is carried out to combine the properties of inhibitors with the multivalence of NPs, thus obtaining intelligent systems having the simultaneous ability to transport and track molecules both *in vitro* and *in vivo*.

[1] G. M. Riboldi et al., *Cells*. **2019**, *8*, 364.
[2] X. Zhou et al., *Biomed. Pharmacother*. **2017**, *91*, 504–509.
[3] E.M. Sánchez-Fernández et al., *ChemCommun*. **2016**, *52*, 5497.

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