Design and Synthesis of Linkers for Glycan-Coated Gold Nanoparticles Used in Drug Discovery

Pampín, B.; Codesido, E.; Masse, J.; Cruces, J.
Galchimia, S.A. R&D Department. Cebreiro s/n 15823 O Pino, A Coruña, Spain

Introduction

The structure of a nanoparticle

Metallic nanoclusters functionalized with biomolecules have been a subject of sustained interest for several years. To obtain this nanoparticle, the **nanocore is covered** by a **mixture of different linkers (Illustration 1)**.

This work was focused on the design, synthesis and optimization of different **carbohydrate and glycan linkers**, which were attached, via gold-sulphur bonds, to the gold core of the nanoparticle. Indeed, gold nanoparticles protected with self-assembled monolayers of carbohydrates antigens (GNPs) open up a novel promising multivalent platform for biological application, representing the latest generation of nanomedicines[1].

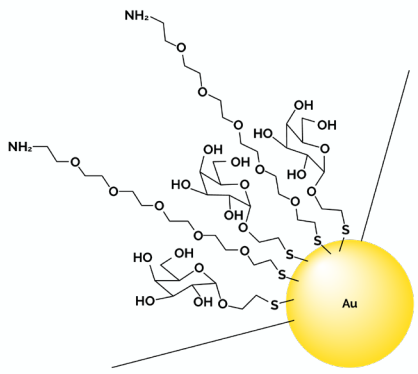


Illustration 1. *Nanogold particle covers by sulfure and carbohydrate linkers.*

Linkers and Drug Discovery

The linkers influence directly the efficacy of the GNPs.

The type of linkers and their distribution will impact directly on the **therapeutic index** of the novel medicine[2]. In general:

- the final chemical group will determine the **type of biomolecule** that can be bound to the metal core.
- the type of chemical bond between the linker and the biomolecule can give a certain **control on the release** of the drug.
- the charge of the linkers can help **controlling biodistribution**, determining how much time the GNPs will last in the circulation.
- for carbohydrates/glycans, these linkers **stabilize** the metallic core and make the particle water-soluble and biocompatible.

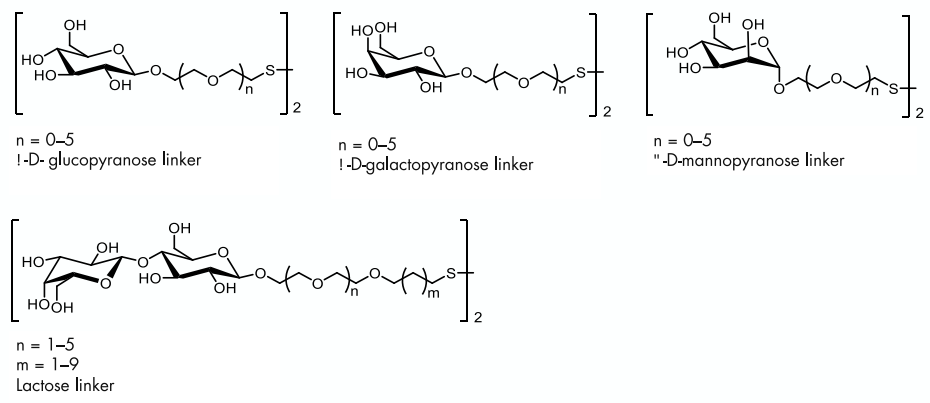
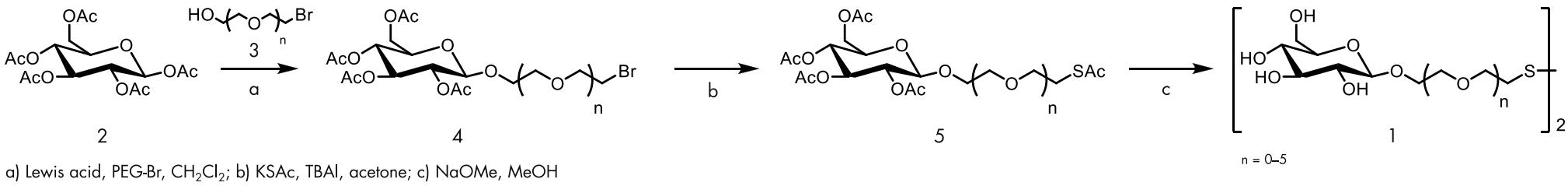


Illustration 2. *Carbohydrate linkers prepared in this work.*

Synthetic Strategy

In this work a simple and versatile methodology is described for the preparation of different **carbohydrate and glycan linkers.**

The synthesis of glucose derivatives **1** is used as example:



a) Lewis acid, PEG-Br, CH_2Cl_2; b) KSAc, TBAI, acetone; c) NaOMe, MeOH

Glycosides **4** have been prepared with good stereoselectivity using standard glycoside synthetic methods, starting from conveniently protected oligosaccharide **2**, commercially available, wich reacts with bromo polyethylene glycol **3** in the presence of a Lewis acid. The nature of the protecting group at the **C-2** position of the glycosyl donor is a major determinant of the anomeric selectivity. A protecting group at **C-2** that can perform neighbouring group participation, as acetyl or benzyl group, will give during the glycosilation **1**, 2-trans-glycosidic linkates. Nucleophilic displacement of bromide with potassium thioacetate yielded derivatives **5**, which in turn were submitted to deprotection of the sugar hydroxyl and thioacetate groups with sodium hydroxide. Finally, oxidation of the terminal thiol afforded disulfides **1** in good yield.

Conclusions

The development of synthetic routes for a series of linkers terminated with a sugar motif allow the fine tuning of the GNPs technology. The synthesis of these linkers has been succesfully scalated. The applications for such nanoparticles are huge. GNPs technology developed in the Nanofacturing project can be applied to solve a range of problems in drug delivery[4].

Keywords: *nanotechnology, carbohydrate linker, GNP, drug discovery.*

References

[1] *Nanomedicine*, **2010**, *5* (5), 777–792
[2] *Biochimica et Biophysica Acta*, **2006,** *1760*, 636–651
[3] According to Midatech data.
[4] *Molecules*, **2017**, *22*, 857

nanofacturing

This project has received funding from the EU H2020 research and innovation program under grant agreement 646364.