Funded by the European Union
under the MSCA GA No 956544

January 2023

Coating of inorganic nanoparticles in Biomedicine

The nanoscale synthesis of inorganic materials has revolutionized chemistry, physics, biology, and medicine [1-4]. The useful physicochemical properties of inorganic nanoparticles (NPs) are unique to their size and arise, in part, from the large fraction of atoms situated at the surface [5] .
The size and composition of inorganic nanomaterials result in magnetic, conductive, radioactive, (photo)thermal, plasmonic, and photoresponsive features. Based on these qualities, inorganic NPs are increasingly applied in biomedicine (e.g. as drug carriers, contrast agents in MRI or in immune targeting applications) [6-9].

In the biological milieu, surface composition determines the extent of nanoparticle recognition by the innate immune system and regulates the NP biodistribution [10, 11]. Moreover, the choice of surface modification is a critical design factor governing the colloidal stability, biocompatibility, and function of inorganic NPs for biomedical application [12].

Non-fouling polymer coating

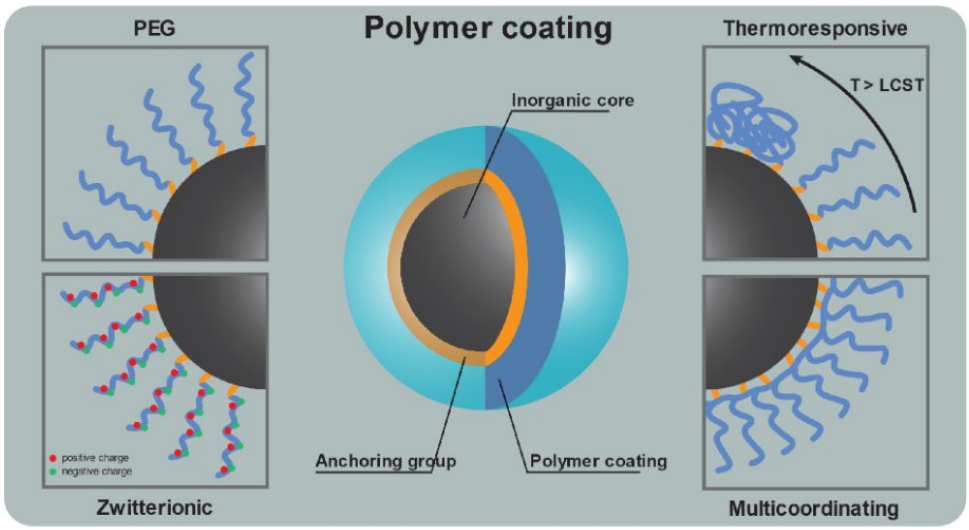
Non-fouling polymers are employed in various biomedical applications to prevent unwanted adsorption of proteins, macromolecules and microorganisms [1-3]. Their non-fouling capability is highly related to the formation of a strong surface hydration layer [4, 5].

The most extensively studied polymer in this area is poly(ethylene glycole) (PEG). PEG remains the gold standard polymer for surface coating of biomedical NPs due to its biocompatibility, ease of application on surfaces, and fouling-resistant abilities (Figure 2a) [13, 14].
The properties of PEG-based coatings can be tuned by changing the coating layer thickness, polymer architecture, and end-group chemistry. However, the usage of PEG is mainly limited by its propensity to oxidize but also the possible formation of anti-PEG antibodies [6]. These limitations of PEG motivated the development to alternatives [7, 8].

Zwitterionic coatings, based on polymers with positive and negative charges,

have also been explored based on their capacity to create thick hydration layers that are similar to or stronger than PEG coatings [13, 15, 16].
The differences are caused by the nature of the formed intermolecular interactions between water and the polymer: zwitterionic coatings interact electrostatically with water whereas PEG molecules form hydrogen bonds.

To further improve the functionality of the non-fouling polymer coatings, stimuli-responsive behaviors can be introduced into the surface. Stimuli-responsive polymers undergo physicochemical changes upon alterations in their environment, such as temperature, pH, or light [14].
Polyalkyloxazolines (PAOXA) are thermoresponsive polymers that have attracted interest for biomedical use [17]. In complex physiological media, salinity and additives affect the thermoresponsive behavior [18].
Below the lower critical solution temperature (LCST), the polymer is soluble in aqueous conditions. When the temperature increases above the LCST, the polymer undergoes a phase transition from an extended hydrated state to a collapsed dehydrated and insoluble state.



A further step in the design of tunable polymer coatings was developed using multicoordinating polymeric ligands [19].
Herein, the polymer ligands offered multisite coordination through the incorporation of several anchoring groups in the backbone.
Additionally, secondary polymers can be grafted on the backbone to provide colloidal stability and the desired properties to the NPs.
This system enables additional design control and tuning of the properties for specific applications [19].

The prevention of unwanted adsorption of proteins, macromolecules and microorganisms plays a pivotal role in the utilization of NPs in biomedicine.
Therefore, various polymeric coatings are tested within the DIRNANO network to fine tune the interaction between NP and the innate immune system.

DIRNANO NEWS

My project focuses on developing a mulitcoordinating polymer (based on the SuSoS AG's PAcrAm™ technology), which serves two distinct purposes.
Firstly, the coating should render surfaces non-fouling. Secondly, the coating should contain multiple functional groups providing the coating with a targeting function. This would allow the attachment of only specifically chosen moieties via click-chemistry. The developed coating shows already suppression of >90% unwanted protein adhesion on gold surfaces while simultaneously being able to participate in azide click-chemistry.

Srđan Tadić (ESR 7) is currently in Newcastle in Prof. Moghimi's group to learn how to test complement activation by the NPs.

The DIRNANO team is meeting again at the end of February in Verona (Italy) for the 3rd regular Meeting.

Stay tuned and follow all updates on our website and on our LinkedIn page!

Tobias Komsthöft
ESR SuSoS AG

REFERENCES

1. Chiozzi V, Rossi F. Inorganic–organic core/shell nanoparticles: progress and applications. Nanoscale Advances. 2020;2: 5090–5105.

2. Wang H, Liang X, Wang J, Jiao S, Xue D. Multifunctional inorganic nanomaterials for energy applications. Nanoscale. 2020;12: 14–42.

3. Wu W. Inorganic nanomaterials for printed electronics: a review. Nanoscale. 2017;9: 7342–7372.

4. Wang X, Zhong X, Li J, Liu Z, Cheng L. Inorganic nanomaterials with rapid clearance for biomedical applications. Chem Soc Rev. 2021;50: 8669–8742.

5. Auffan M, Rose J, Bottero J-Y, Lowry GV, Jolivet J-P, Wiesner MR. Towards a
definition of inorganic nanoparticles from an environmental, health and safety perspective. Nat Nanotechnol. 2009;4: 634–641.

6. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov.

2021;20: 101–124.

7. Luther DC, Huang R, Jeon T, Zhang X, Lee Y-W, Nagaraj H, et al. Delivery of drugs, proteins, and nucleic acids using inorganic nanoparticles. Adv Drug Deliv Rev. 2020;156: 188–213.

8. Krystina L. Hess, Igor L. Medintz, Christopher M. Jewell. Designing inorganic nanomaterials for vaccines and immunotherapies. Nano Today. 2019;27: 73–98.

9. Ni D, Bu W, Ehlerding EB, Cai W, Shi J. Engineering of inorganic nanoparticles as magnetic resonance imaging contrast agents. Chem Soc Rev. 2017;46: 7438–7468.

10. Sapsford KE, Algar WR, Berti L, Gemmill KB, Casey BJ, Oh E, et al. Functionalizing nanoparticles with biological molecules: developing chemistries that facilitate nanotechnology. Chem Rev. 2013;113: 1904–2074.

11. Zheng L, Sundaram HS, Wei Z, Li C, Yuan Z. Applications of zwitterionic polymers. React Funct Polym. 2017;118: 51–61.

12. Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. Adv Drug Deliv Rev. 2020;154-155: 163–175.

13. Zheng L, Sundaram HS, Wei Z, Li C, Yuan Z. Applications of zwitterionic polymers. React Funct Polym. 2017;118: 51–61.

14. Maan AMC, Hofman AH, Vos WM, Kamperman M. Recent developments and practical feasibility of polymer-based antifouling coatings. Adv Funct Mater. 2020;30: 2000936.

15. Sanchez-Cano C, Carril M. Recent Developments in the Design of Non-Biofouling Coatings for Nanoparticles and Surfaces. Int J Mol Sci. 2020;21. doi:10.3390/ijms21031007

16. Erfani A, Seaberg J, Aichele CP, Ramsey JD. Interactions between Biomolecules and Zwitterionic Moieties: A Review. Biomacromolecules. 2020;21: 2557–2573.

17. Morgese G, Benetti EM. Polyoxazoline biointerfaces by surface grafting. European Polymer Journal. 2017. pp. 470–485. doi:10.1016/j.eurpolymj.2016.11.003

18. Kurzhals S, Gal N, Zirbs R, Reimhult E. Controlled aggregation and cell uptake of thermoresponsive polyoxazoline-grafted superparamagnetic iron oxide nanoparticles. Nanoscale. 2017;9: 2793–2805.

19. Wang W, Mattoussi H. Engineering the Bio-Nano Interface Using a Multifunctional Coordinating Polymer Coating. Acc Chem Res. 2020;53: 1124–1138.