Concept Note: Development of Redox-Targeted Gold-Core MIP Nanoparticles for Treatment of Multiple Myeloma

Multiple myeloma (MM) is a malignancy of plasma cells in which relapse and treatment resistance remain major clinical challenges. A particularly attractive therapeutic opportunity is to exploit the altered **redox metabolism of malignant plasma cells**. Myeloma cells experience elevated oxidative and endoplasmic-reticulum stress associated with their high metabolic activity and immunoglobulin production, while relying on antioxidant systems, including glutathione (GSH), thioredoxin/thioredoxin reductase (Trx/TrxR) and other redox-regulating pathways, to maintain cellular redox homeostasis. This dependence creates a potential therapeutic vulnerability: further disruption of redox balance may push malignant plasma cells beyond their oxidative-stress tolerance and induce cell death.[1–4]

We propose to develop **gold-core molecularly imprinted polymer nanoparticles (Au@MIP NPs**) as a new class of targeted, redox-active therapeutic agents for MM. The central hypothesis is that targeted delivery of gold nanoparticles to malignant plasma cells will enhance their interaction with intracellular redox-regulating systems and catalytic pathways, resulting in oxidative stress and selective cancer-cell death. The MIP shell will provide the molecular recognition element, while the gold core will provide redox-active and catalytic functionality. Importantly, metallic gold nanoparticles have previously been shown to inhibit the proliferation of multiple myeloma cell lines in a dose-dependent manner, establishing a direct precedent for the anti-myeloma activity of Au nanoparticles.[5]

A further important foundation for the proposed programme is our recent development of **gold-core MIP nanoparticles with integrated molecular recognition and catalytic activity**. Abdulsada et al. demonstrated a generic strategy for preparing highly specific Au/MIP nanozymes in which a molecularly imprinted polymer shell is generated around a gold nanoparticle core through a gold-catalysed Fenton-like reaction. The resulting nanoparticles combined target-specific molecular recognition with peroxidase-like catalytic activity and demonstrated nanomolar analytical performance in complex biological matrices.[6] This provides a strong technological foundation for translating the Au/MIP platform from molecular detection towards targeted therapeutic applications, where the recognition properties of the MIP shell could direct the catalytic and redox properties of the gold core towards malignant cells.

A key innovation will be the use of **snapshot imprinting to identify disease-associated epitopes directly from the surface of malignant plasma cells and their associated immunoglobulins**. In particular, we will investigate **κ (kappa) light-chain antibodies and kappa-restricted myeloma plasma cells** to identify exposed epitopes of **kappa myeloma antigen (KMA)** that can distinguish malignant cells from normal plasma-cell populations. KMA has recently been characterised as an antigen expressed on malignant plasma cells but not normal bone-marrow plasma cells, arising from conformational epitopes in the constant region of lipid-associated immunoglobulin light chains. This makes KMA a potentially attractive target for selective therapeutic recognition.[7]

Snapshot imprinting provides a powerful strategy for this objective. The approach uses intact cells as templates for molecularly imprinted nanoparticles, followed by proteomic analysis to identify protected, surface-accessible peptide sequences. It has been demonstrated for mapping

cancer-cell surfaces and identifying exposed epitopes that can subsequently be converted into selective nanoMIP recognition elements.[8] Complementary studies of epitope imprinting have established that exposed peptide sequences can be used to generate synthetic recognition sites for proteins, providing an alternative to antibody-based molecular recognition.[9,10]

The programme will therefore first apply **snapshot imprinting to κ antibodies and κ-restricted malignant plasma cells**, followed by proteomic analysis and identification of disease-associated KMA epitopes. Where appropriate, patient-derived material will be used to determine whether structurally distinct or patient-associated epitopes can be identified. Selected surface-accessible epitopes will then be used to generate high-affinity nanoMIPs, which will subsequently be assembled around optimised gold nanoparticle cores. The resulting Au@MIP NPs will combine **synthetic molecular recognition with a catalytically active gold core**, creating a potentially stable and tuneable alternative to antibody-based targeting.

Following cellular binding and internalisation, the **Au core will be exploited for redox-mediated cytotoxicity**. Gold has a strong affinity for thiol- and selenol-containing biomolecules, providing a potential mechanism for interaction with intracellular GSH and the Trx/TrxR system. Gold nanoparticles have been reported to perturb intracellular glutathione homeostasis and increase oxidative stress, while gold-based compounds can directly inhibit TrxR.[11,12] Importantly, inhibition of TrxR has demonstrated anti-myeloma activity, including activity against drug-resistant myeloma cells.[2,12] We therefore hypothesise that selective delivery of Au cores to malignant plasma cells will amplify an existing redox vulnerability and generate cytotoxicity through disruption of antioxidant defence.

The **catalytic properties of the Au core** provide an additional opportunity. The recent Au/MIP nanozyme work demonstrated that gold-core MIPs can catalyse peroxide-dependent reactions through a Fenton-like mechanism, generating reactive oxygen species at the nanoparticle surface.[6] In the proposed therapeutic system, this catalytic activity could potentially be exploited to enhance oxidative stress locally following selective binding and internalisation by myeloma cells. Thus, the gold core may provide **two complementary mechanisms of action: interaction with intracellular redox systems and catalytic generation of reactive oxygen species.** The relative contribution of these mechanisms will be experimentally determined rather than assumed.

The effects of Au@MIP NPs on **ROS production, GSH/GSSG balance, thioredoxin/thioredoxin reductase activity, mitochondrial function, lipid peroxidation and downstream cell-death pathways** will be quantified. The relationship between gold-core size, MIP recognition affinity, catalytic activity, cellular uptake and redox response will be systematically investigated. Particular attention will be given to **intracellular trafficking and endosomal escape,** since access of the Au/MIP nanoparticles to intracellular redox systems may be critical for therapeutic efficacy. Studies using normal plasma cells and other relevant blood-cell populations will establish whether targeted delivery produces a therapeutically useful selectivity window.

The ultimate objective is to establish a **precision nanomedicine platform for personalised treatment of myeloma** in which snapshot imprinting identifies patient- and disease-relevant molecular targets, MIPs provide selective cellular recognition, and gold nanoparticles exploit the intrinsic redox vulnerability and oxidative-stress sensitivity of malignant plasma cells. The combination of **disease-specific molecular recognition, gold-mediated catalytic activity**

and intracellular redox disruption represents a novel therapeutic strategy. The platform could subsequently be adapted to different myeloma subtypes and combined with existing therapies, with particular potential for targeting relapsed or treatment-resistant disease.

References

1. Lipchick BC, Fink EE, Nikiforov MA. Oxidative stress and proteasome inhibitors in multiple myeloma. *Pharmacological Research*. 2016; 105: 210–215. DOI: 10.1016/j.phrs.2016.01.029.
2. Raninga PV, Di Trapani G, Vuckovic S, et al. Cross-talk between two antioxidants, thioredoxin reductase and heme oxygenase-1, and therapeutic implications for multiple myeloma. *Redox Biology*. 2016; 8: 175–185. DOI: 10.1016/j.redox.2016.01.007.
3. Zheng Z, Fan S, Zheng J, et al. Inhibition of thioredoxin activates mitophagy and overcomes adaptive bortezomib resistance in multiple myeloma. *Journal of Hematology & Oncology*. 2018; 11: 29. DOI: 10.1186/s13045-018-0575-7.
4. Starheim KK, Holien T, Misund K, et al. Intracellular glutathione determines bortezomib cytotoxicity in multiple myeloma cells. *Blood Cancer Journal*. 2016; 6: e446. DOI: 10.1038/bcj.2016.56.
5. Bhattacharya R, Patra CR, Verma R, Kumar S, Greipp PR, Mukherjee P. Gold nanoparticles inhibit the proliferation of multiple myeloma cells. *Advanced Materials*. 2007; 19: 711–716. DOI: 10.1002/adma.200602098.
6. Abdulsada SH, Garcia Cruz A, Zaleski C, Piletska E, Ulker D, Piletsky S, Piletsky SA. Generic strategy for the synthesis of highly specific Au/MIP nanozymes and their application in homogeneous assays. *Materials Advances*. 2025; 6: 378–387. DOI: 10.1039/D4MA00917G.
7. Sartor M, Lemarchand TX, Britz L, et al. Expression of Kappa Myeloma Antigen (KMA) and Lambda Myeloma Antigen (LMA) on malignant but not normal plasma cells offers novel therapeutic targets for patients with myeloma, amyloidosis and other plasma cell dyscrasias. *Clinical Lymphoma Myeloma and Leukemia*. 2025; 25(10): e788–e798.e5. DOI: 10.1016/j.clml.2025.05.022.
8. Piletska E, Thompson D, Jones R, Garcia Cruz A, Poblocka M, Canfarotta F, Norman R, Macip S, Jones DJL, Piletsky S. Snapshot imprinting as a tool for surface mapping and identification of novel biomarkers of senescent cells. *Nanoscale Advances*. 2022; 4: 5304–5311. DOI: 10.1039/D2NA00424K.
9. Piletsky S, Canfarotta F, Poma A, Bossi AM, Piletsky SA. Molecularly imprinted polymers for cell recognition. *Trends in Biotechnology*. 2020; 38: 368–387. DOI: 10.1016/j.tibtech.2019.10.002.
10. Pasquardini L, Bossi AM. Molecularly imprinted polymers by epitope imprinting: a journey from molecular interactions to the available bioinformatics resources to scout for epitope templates. *Analytical and Bioanalytical Chemistry*. 2021; 413: 6101–6115. DOI: 10.1007/s00216-021-03409-1.
11. Wang X, Chen G, Zhang P, Jia Q. Advances in epitope molecularly imprinted polymers for protein detection: a review. *Analytical Methods*. 2021; 13: 1660–1671. DOI: 10.1039/D1AY00067E.

12. Mateo D, Morales P, Ávalos A, Haza AI. Oxidative stress contributes to gold nanoparticle-induced cytotoxicity in human tumor cells. *Toxicology Mechanisms and Methods*. 2014; 24(3): 161–172. DOI: 10.3109/15376516.2013.869783.
13. Sze JH, Raninga PV, Nakamura K, et al. Anticancer activity of a Gold(I) phosphine thioredoxin reductase inhibitor in multiple myeloma. *Redox Biology*. 2020; 28: 101310. DOI: 10.1016/j.redox.2019.101310.
14. Piletsky SS, Piletska EV, Poblocka M, et al. Snapshot imprinting: rapid identification of cancer cell surface proteins and epitopes using molecularly imprinted polymers. *Nano Today*. 2021; 41: 101304. DOI: 10.1016/j.nantod.2021.101304.