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Dynamic precision cancer nanomedicine

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Dynamic precision medicine enables preemptive cancer therapy switching in response to emerging resistance. Owing to their modular architecture and tumour-targeting capabilities, nanomedicines are theoretically well-suited to support such adaptive strategies. However, the questions remain whether modular design can consistently yield durable therapeutic responses, and whether the temporal constraints imposed by tumour evolution allow the practical implementation of dynamic nanomedicine.

Dynamic precision medicine[1] relies on continuous biomarker monitoring to allow preemptive therapy adaptation when resistance emerges. For example, the aromatase inhibitor and palbociclib therapy (PADA-1) clinical trial demonstrated that switching therapy upon detection of *ESR1* mutations in plasma circulating tumour DNA (ctDNA) (before radiographic progression) doubled progression-free survival in patients with breast cancer[2]. Similar biomarker-guided strategies are emerging across other modalities.

Nanomedicines, with their modular architectures, potential to carry several drugs and, importantly, capacity to target tumour tissues, seem ideally suited to adaptive strategies. However, despite demonstration of tumour accumulation in both preclinical and clinical settings[3], no targeted nanomedicine has gained regulatory approval thus far. This contrasts with antibody–drug conjugates, which achieved clinical success through systematic optimization of antibody selection, linker chemistry and payload potency[4]. Therefore, the question remains whether nanomedicine could be designed to enable biomarker-guided adaptation, or whether delivery and timing constraints prevent such an approach from succeeding. In particular, modular conjugation chemistry, multi-drug polymer architectures and circulating biomarker detection could make nanomedicines suitable for dynamic precision nanomedicine approaches.

Inadequate delivery versus resistance

Clinical trials of human epidermal growth factor receptor 2 (HER2)-targeted liposomal doxorubicin (MM-302) showed that nanoparticles can reach tumours but provided no survival benefit compared with conventional therapy[3]. This has been attributed to poor delivery, with less than 1% of injected dose reaching tumour cells[5]. However, it remains unclear whether these outcomes are a result of inadequate delivery or delivery to resistant cell populations. An alternative interpretation draws from precision oncology: static formulations cannot adapt to resistance, just as monotherapies fail when resistance mechanisms emerge. Therefore, nanomedicine failures may reflect therapeutic inflexibility rather than delivery inadequacy alone.

Tumour heterogeneity compounds this challenge. Beyond temporal resistance, spatial heterogeneity within tumours, including pharmacologically isolated subclones, distinct microenvironments (hypoxic zones and vascular regions) and differences between primary and metastatic sites, creates barriers to a uniformed response. Spatially resolved biomarkers from multi-region sequencing or imaging could theoretically guide adaptive nanoparticle design. However, this adds complexity to already challenging temporal constraints: reformulation must account for several simultaneous targets with potentially different resistance mechanisms while operating within tumour evolution timescales.

This distinction carries crucial implications. If failures arise from resistance in adequately exposed tumours, payload switching could provide benefit. However, if delivery is inherently insufficient regardless of resistance status, no amount of adaptation will be effective. Therefore, intratumoral drug concentrations should be measured alongside resistance biomarkers to determine whether tumours fail therapy owing to inadequate exposure or acquired resistance.

Technical capability and timing

Adaptive nanomedicine can be based on various building blocks. In particular, modular nanoparticle platforms enable ligand exchange through bioorthogonal chemistry[6]. In addition, high drug-loading capacity and multi-drug co-delivery can be achieved using bottlebrush polymers, which can load over 100 drug molecules[7,8]. Nanomedicine can also be designed to maintain fixed drug ratios for synergistic efficacy. Importantly, nanomedicines could be combined with ctDNA-guided adaptive therapy, which has demonstrated improved outcomes in randomized clinical trials[9]. Such ctDNA assays can detect resistance mutations weeks before imaging shows progression.

However, pharmacokinetic and manufacturing realities impose temporal constraints that may prove decisive. Small molecules achieve therapeutic levels within hours, enabling rapid response to emerging resistance. By contrast, nanoparticles typically require several days for tumour accumulation, cellular uptake and cargo release. If resistant clones double every 3–5 days, as is common in aggressive cancers, intervention windows may close before reformulated nanoparticles can take effect. Manufacturing logistics compound this challenge: successful adaptive therapy depends on immediately available alternative agents, as demonstrated in endocrine therapy trials[2]. Nanoparticle reformulation, by contrast, requires new batch production, comprehensive characterization and quality control under stringent regulatory standards. Even with optimized workflows, producing and validating new formulations takes weeks, during which resistant clones may proliferate from a minor subpopulation to dominant disease.

Several approaches could reconcile these pharmacokinetic timescales with adaptive requirements. Pre-manufactured libraries of alternative formulations could enable rapid switching without custom production delays. Modular platforms that allow point-of-care conjugation could reduce reformulation time from weeks to hours. Machine learning models that integrate resistance kinetics and nanoparticle pharmacokinetics could predict optimal intervention windows[10]. Such models may distinguish therapeutic scenarios for which

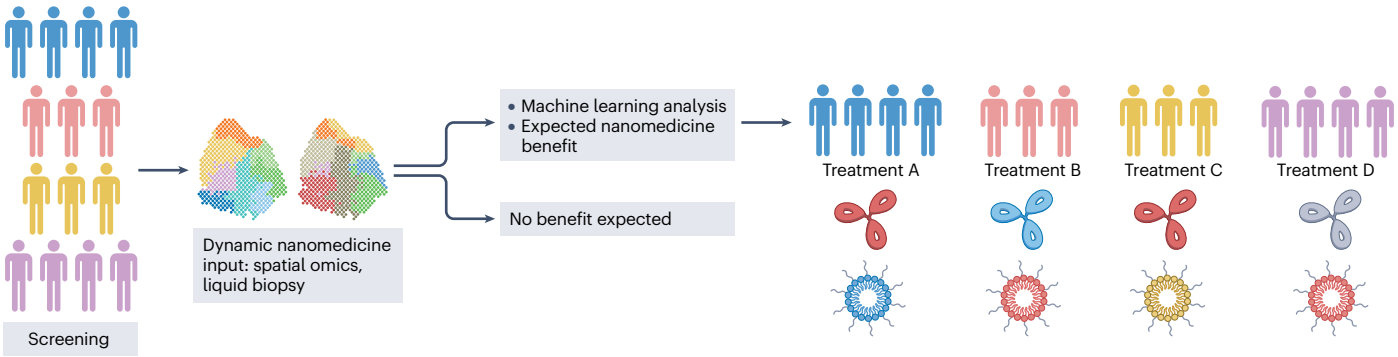

Fig. 1 | Conceptual overview of dynamic precision nanomedicine. Adaptive nanomedicine relies on early biomarker detection (through spatial omics and liquid biopsies) and preemptive switching to improve outcomes for patients.

adaptive strategies are viable from those that necessitate alternative approaches. Importantly, early biomarker-triggered switching, before resistant clones become dominant, may provide sufficient lead time for reformulation and intervention. The challenge is not only scientific but also operational, raising questions about whether these solutions could reconcile nanoparticle development timescales with the pace of tumour evolution.

Empirical testing approach

Systematic empirical validation can resolve this question. Pilot studies should establish whether reformulated nanoparticles can be produced and validated within clinically relevant windows, and whether they deliver therapeutic drug levels to tumours. These could define go and no-go criteria before committing resources to full trials.

Adaptive therapy could then be tested in preclinical models by initiating treatment with targeted nanoparticles, monitoring for emerging resistance biomarkers and switching payloads or targeting moieties upon detection. Such studies would reveal whether adaptation can prolong response or whether delivery and timing constraints remain limiting factors. Machine learning approaches could accelerate this development process by modelling nanoparticle pharmacokinetics, resistance evolution kinetics and intervention window compatibility[10]. This computational layer would identify optimal reformulation strategies and predict clinical feasibility before resource-intensive manufacturing.

Toward adaptive nanomedicine

Tumour accumulation of nanomedicines alone does not ensure therapeutic benefit. Systematic testing of adaptive nanomedicine through biomarker-triggered reformulation trials will determine whether modular design can convert delivery into durable response (f).

Such adaptive nanomedicine approaches could then build on the validated platforms, monitoring technologies and adaptive therapy strategies that have already been established in precision oncology. Beyond primary tumour resistance, adaptive nanomedicine could also address metastatic heterogeneity, facing the same temporal and logistical constraints; here, secondary lesions typically have distinct molecular profiles indicative of poor prognosis. Fig. 1.

The question is not whether adaptation is theoretically possible, but whether it is practically achievable within tumour evolution timescales. This question admits definitive experimental resolution. Importantly, either answer would substantially advance the field. A positive result would position nanomedicine as the first therapeutic platform able to evolve with tumours through modular design and biomarker-guided switching, potentially transforming treatment of resistant cancers. A negative result would redirect resources towards approaches better matched to evolutionary timescales, clarifying which engineering principles can translate from concept to clinic and which remain aspirational despite technical feasibility.

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Competing interests

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