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Hypothesis

Metabolically Enhanced pH-Dependent Conformational Switching of Polymers for Selective Chemotherapy of Solid Tumors: A Hypothesis

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Abstract

The selectivity of chemotherapy remains limited by systemic toxicity. pH-sensitive polymeric nanocarriers exploit the acidic extracellular environment of solid tumors as a drug-release trigger, but they respond passively to a pre-existing pH gradient that is modest and heterogeneous. We hypothesize that controlled glucose priming, temporally coordinated with nanocarrier administration, may transiently widen the tumor-to-normal extracellular pH differential sufficiently to trigger release from a sharply tuned ultra-pH-sensitive (UPS) carrier in responsive tumor regions. Historical animal studies and limited human observations report tumor-associated extracellular pH decreases of approximately 0.17–0.20 units under selected conditions, while UPS micelles can dissociate cooperatively across a window narrower than 0.25 units and have tunable transition pH thresholds (pHt). The carrier would be tuned below the baseline extracellular pH (pHe) of the target tumor (with a pHt of approximately 6.5–6.6), remaining assembled where local pHe remains above pHt until a priming-induced pH excursion crosses the threshold. The central uncertainty is the accompanying effect on tumor perfusion and carrier delivery: tumor blood flow was unchanged at 1 g/kg in one animal study and reduced by 31% at 4 g/kg, while perfusion at 2 g/kg and the net effect across the proposed 1–2 g/kg testing range remain insufficiently characterized. Human evidence is limited and heterogeneous. Recent intracellular pH imaging associated glucose-induced pH changes with the lactate-to-pyruvate ratio but not with fluorodeoxyglucose standardized uptake value; fluorodeoxyglucose positron emission tomography avidity is therefore retained only as an exploratory candidate biomarker. A previous pH-low insertion peptide (pHLIP)-modified liposomal study supports the general principle of glucose-enhanced pH-responsive delivery but uses a mechanistically distinct carrier. The present work formulates a class-level, falsifiable framework for conformational UPS polymers. The essential next step is simultaneous measurement of tumor extracellular pH, perfusion, nanocarrier accumulation, and cargo release across glucose doses and administration sequences in tumor-bearing animals. Until those variables are measured together, the strategy should be regarded as a falsifiable preclinical proposal rather than a clinically feasible protocol.

Introduction

Classical chemotherapy continues to be limited by a fundamental lack of selectivity: cytotoxic agents damage healthy tissues alongside tumor cells. Stimulus-responsive drug delivery systems, particularly pH-sensitive polymer nanocarriers, have emerged as a promising approach to overcome this limitation.[1,2] The biological rationale for pH targeting is well established. Solid tumors are characterized by an acidic extracellular pH (pHe 6.2–6.8) compared with the normal physiological pH of blood and tissues (7.2–7.4). This acidosis is closely linked to the Warburg effect: even under adequate oxygen supply, many tumor cells preferentially utilize aerobic glycolysis, generating lactate and protons that contribute to extracellular acidification.[3-7]

Recent pH-sensitive nanocarriers include ultra-pH-sensitive (UPS) micelles, poly(L-histidine)-based mixed micelles, phenylboronic acid-modified polymers, and dual pH/redox-responsive platforms.[8-13] In these systems, the carrier generally acts as a

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passive sensor of an already established microenvironmental signal. The present hypothesis instead asks whether the activating signal can be transiently amplified in a controlled manner before or during carrier exposure.

A previous experimental study using MDA-MB-435S tumor xenografts demonstrated that combining glucose administration with a pH-responsive DVar7-modified doxorubicin liposome enhanced tumor-targeted delivery and antitumor efficacy.[14] That work provides proof of principle for metabolically enhanced pH-responsive delivery in one specific system. Its mechanism, however, differs from polymeric micelle drug release: pHLIP undergoes pH-driven insertion into lipid bilayers as a transmembrane alpha helix, whereas UPS polymeric micelles undergo cooperative dissociation from assembled micelles into hydrophilic unimers across a narrow pH window.[15-17] These mechanisms operate on different molecular scales, depend on different protonatable groups, and impose different design constraints. The present work therefore extends the metabolic priming concept to a distinct carrier class and develops a quantitative framework incorporating the dose–perfusion trade-off, candidate metabolic stratification, carrier-threshold matching, and explicit falsifiable predictions.

Literature basis: This hypothesis paper was informed by a targeted narrative search of PubMed, Scopus, and Web of Science covering the period 1980–2026, using combinations of the terms tumor pH, Warburg effect, glucose infusion, pH-responsive, UPS, nanocarrier, fluorodeoxyglucose positron emission tomography (FDG-PET), and chemical exchange saturation transfer magnetic resonance imaging (CEST-MRI). Foundational studies of glucose-induced tumor acidification were included because of their direct relevance to the dose–response relationship, while recent studies were prioritized for imaging methodology and translational context. This was not a formal systematic review or meta-analysis. Studies of unrelated pH-modulation strategies were included only where they served as conceptual comparators in the Discussion.

Hypothesis

The principal practical implication of the present work is that the Warburg phenotype may be used as an experimentally inducible therapeutic lever rather than only as a diagnostic signature. Existing pH-responsive carriers exploit the pre-existing tumor pH gradient passively; that gradient is modest, spatially heterogeneous, and may be subthreshold for a deliberately under-tuned sharp-transition carrier. Beyond the single experimental demonstration cited above,[14] to our knowledge, this strategy has not been explicitly formulated as a class-level approach for conformational UPS carriers. The hypothesis advanced here is therefore conceptual rather than protocol-level.

Hypothesis: Controlled glucose priming may transiently widen the tumor-to-normal extracellular pH differential sufficiently to trigger cargo release from a sharply tuned UPS polymeric nanocarrier whose transition threshold is set below the baseline extracellular pH of the target tumor. The hypothesis fails if the induced pH displacement is too small, too short-lived, or insufficiently tumor-selective to cross the carrier threshold; if substantial baseline release occurs before priming; or if glucose-associated changes in perfusion reduce carrier accumulation enough to offset the gain in triggering. Within this framework, tumor glycolysis acts as the biological amplifier and the pH-responsive carrier as the chemical transducer.

Three falsifiable claims follow from this hypothesis:

(i) Selectivity: A controlled glucose load will produce a larger extracellular pH displacement in highly glycolytic tumor tissue than in surrounding normal tissues, although the magnitude and spatial distribution of this selectivity must be measured directly.

(ii) Magnitude: Within the proposed 1–2 g/kg preclinical range, the induced pH displacement may be sufficient to carry responsive tumor regions across the threshold of a UPS carrier tuned just below baseline tumor pHe (with a pH thresholds (pHt) of approximately 6.5–6.6), provided that the carrier transition is sharp and baseline pHe and pHt are appropriately matched. Whether perfusion is preserved sufficiently for net delivery to improve is an untested premise requiring direct validation.

(iii) Biomarker-anchored translation: Direct measures of glycolytic flux, such as the lactate-to-pyruvate (Lac:Pyr) ratio, may correlate with the magnitude of glucose-induced acidification and may support prospective tumor stratification. FDG-PET avidity will be evaluated as an exploratory comparator but is not assumed to be a reliable predictor. These relationships are testable predictions rather than established clinical associations.

A scheme for testing the hypothesis: The two-stage scheme below is one proposed glucose-first schedule for initial testing, not a demonstration of clinical efficacy and not a predetermined optimal protocol. Carrier-first, glucose-first, and simultaneous administration should ultimately be compared. The scheme specifies conditions under which the claims above become experimentally decidable, initially in tumor-bearing animal models. The illustrated glucose-first testing sequence is summarized in Figure 1.

Stage 1 — Metabolic priming: For an initial glucose-first experiment, a controlled intravenous glucose load within the proposed 1–2 g/kg range is administered, and tumor pHe and perfusion are followed dynamically. Based on earlier studies, the pH nadir is expected to occur within approximately 30–60 min, but both the magnitude and timing must be established in each model. Normal-tissue pH is expected to change less than tumor pH, an expectation that also requires direct measurement.

Stage 2 — pH-triggered release: A UPS polymeric carrier with a transition threshold below the baseline extracellular pH of the target tumor (with a pHt of approximately 6.5–6.6) is administered during priming or administered beforehand to allow tumor pre-accumulation, so that carrier exposure overlaps with the induced pH excursion. The micelle should remain assembled while local pH is above pHt and dissociate cooperatively only in tumor regions where priming drives pHe below the threshold. Regions in which local pHe does not cross pHt are expected to retain the assembled carrier and sequestered cargo.

The critical distinction from conventional pH-responsive systems lies not in the polymer chemistry alone but in the deliberate, transient manipulation of the activating signal. The strategy therefore links a controlled metabolic perturbation to a fixed chemical threshold and makes the success or failure of that linkage experimentally measurable.

Evaluation of the hypothesis

The hypothesis is evaluated below from five perspectives: a

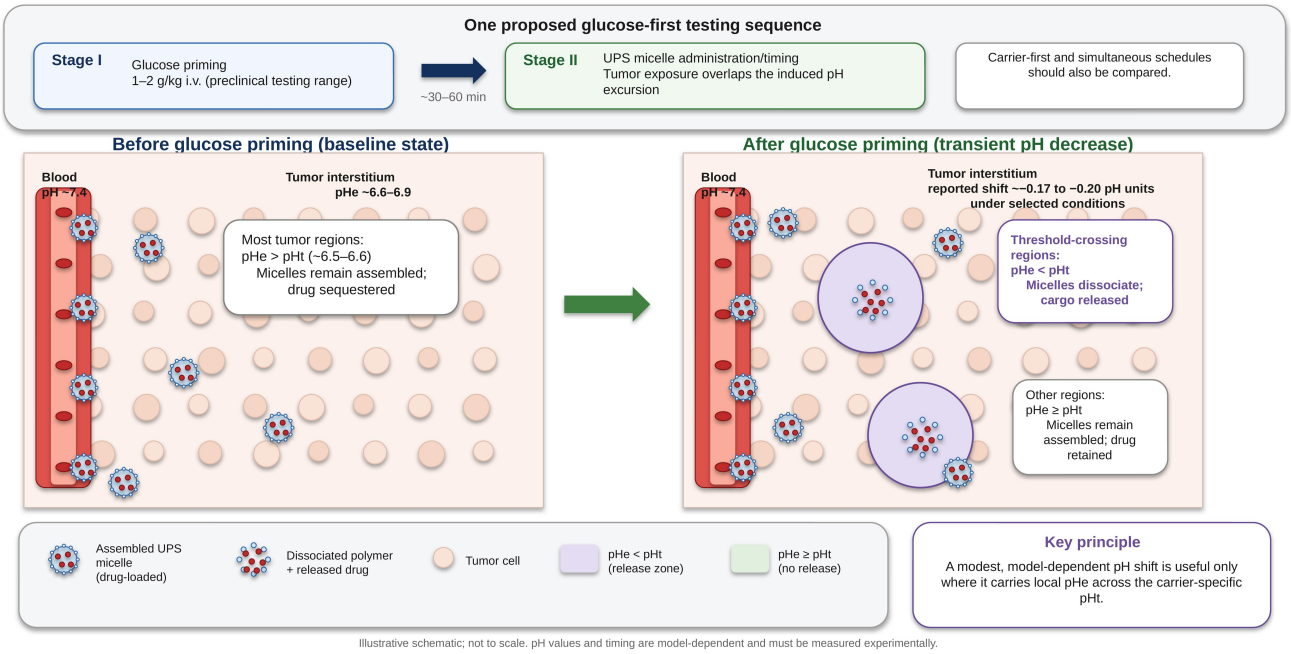

Fig. 1. Schematic of one proposed glucose-first testing sequence for selective chemotherapy delivery. Stage 1 — Metabolic priming: an intravenous glucose load is used to induce a transient, model-dependent decrease in tumor extracellular pH; normal-tissue pH and tumor perfusion must be measured concurrently. Stage 2 — pH-triggered release: a UPS polymeric carrier is selected with a transition threshold below the measured baseline tumor pHe distribution and administered or timed so that tumor exposure overlaps the induced pH excursion. Micelle-to-unimer dissociation and cargo release are expected only in tumor regions where local pHe falls below pHt; regions remaining above the threshold retain the assembled carrier and sequestered cargo. The pH values shown in the schematic are illustrative and must be determined experimentally for each tumor model and carrier. Carrier-first and simultaneous schedules should be evaluated alongside the illustrated glucose-first sequence. The central before-and-after panels illustrate carrier states relative to local pH-threshold crossing and are not intended to depict the exact chronological presence of the carrier before glucose administration.

quantitative assessment of the achievable pH shift against the polymer switching window; a conceptual model of the polymer-state transition; a differentiation from existing work; the operating envelope (limitations, risks, and safety considerations); and a balanced discussion of failure modes and adjacent strategies.

Quantitative assessment: ΔpH amplification and its effect on selectivity

Baseline pH differential

The pHe gradient between tumor and normal tissue in the absence of intervention has been measured *in vivo* across human and animal solid tumors using increasingly resolved techniques. Classical *in vivo* fluorescence-ratio measurements demonstrated heterogeneous interstitial pH profiles in human tumor xenografts, with pHe decreasing to approximately 6.7 at increasing distances from tumor blood vessels.[5] Rat glioma models likewise showed spatially heterogeneous intratumoral–peritumoral pHe differences that varied substantially with tumor type and region.[6] Modern noninvasive imaging refines this picture at the patient level: ioversol-based CEST-MRI at clinical 3 T reported a mean pHe of 6.66 ± 0.19 in hepatocellular carcinoma compared with 7.34 ± 0.09 in hemangioma (n = 15 and 5 patients, respectively),[7] while pH-weighted amine CEST-EPI distinguished infiltrating glioblastoma from normal brain tissue.[18] Hyperpolarized carbon-13 pyruvate magnetic resonance imaging provides complementary real-time information on glycolytic flux rather than a direct measurement of extracellular pH.[19,20] The baseline gradient is real but heterogeneous. Mean tumor pHe values around 6.66–6.9 lie above a carrier threshold set at approximately 6.5–6.6, but local regions may already approach or cross that threshold. Priming is therefore expected to shift only part of the tumor pH distribution into the activation range, making spatially resolved pHe measurement essential.

Magnitude of the glucose-induced pH shift

Experimental evidence for glucose-associated tumor acidification spans more than four decades. Continuous intravenous glucose infusion in tumor-bearing rats reduced mean tumor pH to 6.7 at a serum glucose concentration of 27 mM and to 6.1 at 50 mM, while brain and kidney pH were not significantly altered.[21] Raising blood glucose to approximately 14 mM lowered mean tumor pH across four human tumor xenograft models.[22] A dose-response study reported tumor pH changes of −0.17 units at 1 g/kg and −0.60 units at 4 g/kg.[23] Spatial and temporal profiling showed that pH approached its nadir within 30–60 min and returned toward baseline by approximately 90 min after a glucose bolus.[24] Among 25 fasting, nondiabetic patients given 100 g oral glucose, 14 developed transient hyperglycemia and had a mean tumor pHe change of −0.17 ± 0.04 units, but the response across the full cohort was heterogeneous.[25] A recent amine and amide

Table 1. Evidence relevant to the glucose dose–pH–perfusion trade-off. Different routes, species, and experimental settings are shown separately; the proposed testing range is identified as an inference rather than a measured integrated regimen

Intervention / setting	Tumor-pH evidence	Tumor-perfusion evidence	Implication for delivery
1 g/kg i.v., animal study	−0.17 units (measured[23])	No measurable change in tumor blood flow (measured[23])	Supports lower-dose testing without an observed perfusion penalty, but nanocarrier accumulation and release were not measured
100 g oral glucose, 25 patients	Mean −0.17 ± 0.04 units in 14 patients with transient hyperglycemia; heterogeneous response across the full cohort (measured[25])	Not measured	Limited human evidence for acidification; does not establish an i.v. dose or delivery benefit
4 g/kg i.v., animal study	−0.60 units (measured[23])	31% reduction in tumor blood flow (measured[23])	Potential risk of impaired carrier delivery; accumulation and release were not measured
Proposed 1–2 g/kg i.v. preclinical range	Not characterized as an integrated regimen; inferred from heterogeneous prior studies	No change measured at 1 g/kg; not characterized at 2 g/kg or as an integrated dose range	Central testing range for simultaneous pHe, perfusion, accumulation, and release measurements

i.v., intravenous; pHe, extracellular pH.

concentration-independent detection (AACID)-CEST-MRI study in C6 rat glioma found that glucose-associated changes in intracellular tumor pH correlated with the Lac:Pyr ratio but not significantly with fluorodeoxyglucose (FDG) standardized uptake value (SUV).[26] This supports a relationship with glycolytic flux but does not directly validate the extracellular pH displacement required by the present hypothesis. Contemporary simultaneous measurements of glucose-induced tumor pHe and perfusion remain lacking.

Dose–perfusion trade-off

The same evidence that supports pH amplification also identifies a potential perfusion-related limitation. In the cited dose-response study, 1 g/kg intravenous glucose produced a tumor pH decrease of approximately 0.17 units without a measurable change in tumor blood flow, whereas 4 g/kg produced a decrease of approximately 0.60 units accompanied by a 31% reduction in tumor blood flow.[23] These findings suggest that lower-dose acidification may be achievable without the perfusion penalty observed at the higher dose. However, perfusion has not been characterized at 2 g/kg or across the proposed 1–2 g/kg range as an integrated regimen, and neither nanocarrier accumulation nor cargo release was measured at either dose. The proposed range should therefore be regarded as an initial preclinical testing range rather than an established optimum. Higher doses may be counterproductive, but the net effect of glucose dose on nanocarrier delivery remains untested. The available evidence is summarized in Table 1.[23,25]

Pharmacokinetic alignment

The glucose-induced pH displacement is transient. Earlier spatial and temporal measurements placed the nadir within approximately 30–60 min and showed recovery toward baseline by about 90 min.[24] A glucose-first schedule therefore requires carrier delivery and extravasation to overlap this short pH excursion. UPS micelle accumulation kinetics are expected to depend on particle size, chemistry, tumor vascularity, and the experimental model. The hypothesis does not predetermine the optimal sequence of administration. Carrier-first, glucose-first, and simultaneous schedules should be compared experimentally. Pre-accumulation of an intact, subthreshold carrier followed by glucose-induced switching may widen the effective release window and reduce the dependence of initial carrier delivery on glucose-associated perfusion changes, thereby partially separating the delivery problem from the switching problem.

Correspondence with the UPS switching window

Contemporary UPS micelles undergo cooperative micelle-to-unimer dissociation across a sharp pH window narrower than approximately 0.25 units, with pHt tunable across the physiological range through polymer composition.[16,17] The widely characterized UPSe imaging variant, with a pHt of approximately 6.9, was designed to activate within the untreated tumor-pH band.[15] It is therefore not the preferred carrier for a priming-dependent strategy. The present hypothesis instead requires a deliberately lower pHt, approximately 6.5–6.6, selected in relation to the measured baseline pHe distribution of the target tumor. A glucose-associated displacement of 0.17–0.20 units could then become functionally important in regions that cross the threshold. Poly(L-histidine)-based mixed micelles have shown composition-dependent destabilization as pH falls and may be considered an exploratory alternative.[13] Their suitability for the present extracellular switching strategy would still require carrier-specific validation of transition sharpness, baseline leakage, and activation in untreated tumor tissue. Classical poly(acrylic acid)-based systems

Table 2. Polymer candidate classes

Polymer class	pH-sensitive mechanism	pH transition window	Suitability
Ultra-pH-sensitive (UPS) polymeric micelles (for example, PEG-based ionizable block copolymers or polycarbonate-based systems)	Cooperative micelle-to-unimer dissociation driven by protonation of ionizable groups	Sharp; transition narrower than approximately 0.25 units; pHt tunable by polymer composition[16,17,27]	Primary candidate. A modest pH displacement may become decisive when pHt is matched below the measured baseline tumor-pHe distribution. The UPSe imaging variant, with a pHt of approximately 6.9, is unsuitable because untreated acidic tumor regions can already activate it[15]
PEG-b-poly(L-histidine)-containing mixed micelles	Imidazole protonation disrupts hydrophobic core packing	Composition-dependent; a representative mixed-micelle formulation was stable at pH 7.4–7.0 and destabilized as pH decreased further[13]	Exploratory candidate. Baseline leakage, transition sharpness, and carrier-specific pHt must be shown to prevent substantial activation in untreated tumor tissue

PEG, polyethylene glycol; pHt, transition pH threshold; UPS, ultra-pH-sensitive.

can show gradual release even at physiological pH,[11] making them less suitable for a strategy that depends on a narrow induced excursion.

Quantitative conclusion

Reported glucose-associated tumor-pH displacements of approximately 0.17–0.20 units are of the same order as the transition width of sharply responsive UPS systems. This establishes quantitative plausibility, not *in vivo* sufficiency. The pH measurements were obtained under heterogeneous animal and human conditions, while the UPS transition characteristics were measured in separate carrier systems. Although tumor blood flow was unchanged at 1 g/kg in one animal study, perfusion has not been characterized at 2 g/kg or across the proposed range, and preservation of sufficient carrier accumulation for priming to improve net drug delivery remains untested. The available evidence therefore supports a testable intersection of biological and chemical thresholds but does not establish that the complete sequence will operate *in vivo*. The decisive experiment is simultaneous, spatially resolved measurement of glucose-induced extracellular pH, tumor perfusion, carrier accumulation, and cargo release across doses and administration sequences. Clinical translation should not be considered before this relationship has been established preclinically and the substantial heterogeneity of tumor response has been characterized.

Conceptual model

The hypothesis is realized mechanistically through cooperative pH-driven conformational switching in polymeric self-assemblies. In UPS micelles, protonation of ionizable groups along the hydrophobic block destabilizes the assembled core, producing a cooperative transition from micelles to hydrophilic unimers across a narrow pH interval.[16,17] This response differs from the gradual chain expansion and leakage of classical polyanions. A small, tumor-associated shift in pHe could therefore drive coordinated switching in regions that cross a carrier-specific threshold, while regions remaining above pHt would retain the assembled state.

Polymer candidates

The governing requirement is not pH responsiveness alone but a carrier-specific transition threshold below the baseline pHe distribution of the target tumor, combined with sufficiently sharp switching and low baseline leakage for a modest induced displacement to matter. UPS micelles are the primary candidate class; poly(L-histidine)-based mixed micelles remain an exploratory alternative requiring direct carrier-specific validation (Table 2).[13,15-17,27]

Mechanism of action

The strategy operates by shifting the tumor pH distribution downward relative to a fixed carrier threshold. Before priming, a correctly tuned micelle should remain assembled in blood, normal tissues, and most untreated tumor regions. After priming, dissociation is expected only where local pHe falls below pHt. Because both baseline pHe and the induced displacement are heterogeneous, switching and release are predicted to be spatially incomplete rather than uniform throughout the tumor (Table 3).[6,23,25]

Novelty and differentiation from existing work

The novelty of the present work lies not in the polymer platform itself but in a class-level hypothesis linking controlled metabolic modulation to threshold-dependent carrier switching, together with the experimental framework proposed for testing it (Table 4).[1,2,8-12,14,23,26]

Discussion

The Warburg effect is routinely exploited in oncological diagnostics. The present hypothesis asks whether this metabolic signature can also serve as a transient pharmacological lever for controlling drug release: the same property of the disease that allows it to be visualized could potentially be used to activate treatment within responsive tumor regions.

Table 3. Polymer state across anatomical compartments under metabolic priming

Compartment	Baseline pH	pH after priming	Expected polymer state	Expected drug status
Blood / normal tissue	Approximately 7.35–7.45	Expected to change little; must be measured	Assembled micelle because pH remains well above pHt	Predominantly sequestered
Tumor interstitium	Mean approximately 6.6–6.9, with substantial local heterogeneity[6]	Model- and region-dependent; historical shifts approximately −0.17 to −0.20 units under selected conditions[23,25]	Assembled before priming in regions above pHt; after priming, dissociates only where local pHe falls below pHt	Released in threshold-crossing regions; retained elsewhere
Endosome / lysosome after uptake	Approximately 4.5–6.0	Not applicable	Further protonation and dissociation expected	Release may continue after endocytosis

pHe, extracellular pH; pHt, transition pH threshold.

Table 4. Differentiation of the present hypothesis from existing work

Feature	State of the field	Present hypothesis
pH-responsive nanocarriers	Extensively realized in preclinical systems[1,2,8]	Uses an established sharp-transition platform deliberately tuned below baseline tumor pHe
Glucose as a pH amplifier for delivery	Demonstrated in one pHLIP-modified doxorubicin liposome model[14]	Extends the principle to mechanistically distinct conformational UPS polymers
Multi-stimulus systems	pH/redox and direct glucose-responsive systems demonstrated experimentally[9-12]	Adds a metabolically induced extracellular-pH layer to a single pH-threshold carrier
Dose–perfusion trade-off	Not integrated with UPS delivery measurements	Proposes a 1–2 g/kg preclinical testing range; tumor blood flow was unchanged at 1 g/kg and reduced by 31% at 4 g/kg, but the net effect on carrier delivery remains unknown[23]
Metabolic-response stratification	No validated predictor of glucose-induced extracellular acidification; FDG SUV did not significantly correlate with glucose-induced intracellular-pH change in one study[26]	Direct glycolytic-flux measures and FDG-PET as an exploratory comparator to be tested prospectively
Class-level metabolic priming	To our knowledge, not explicitly formulated as a class-level approach for conformational UPS carriers	Core novel element and falsifiable experimental framework

FDG, fluorodeoxyglucose; FDG-PET, fluorodeoxyglucose positron emission tomography; pHe, extracellular pH; pHLIP, pH-low insertion peptide; SUV, standardized uptake value; UPS, ultra-pH-sensitive.

Failure modes

Three major scenarios limit the applicability of this strategy. Poor tumor perfusion, extensive necrosis, elevated interstitial pressure, or aberrant vasculature may limit carrier delivery regardless of pH amplification. Low glycolytic activity may be associated with a smaller acidification response, but no imaging biomarker has yet been validated to predict that response. Metabolic plasticity may also allow tumors to shift between glycolytic and oxidative phenotypes over repeated cycles. Metabolic and vascular stratification may eventually help identify tumors in which the first two limitations are less pronounced, but this approach will require prospective validation; the third remains an empirical question.

Comparators

Several adjacent strategies manipulate tumor pH for therapeutic purposes. Sodium bicarbonate nanoparticles can alkalinize tumor pH to support immunotherapy,[28] which is the inverse direction of the present proposal. Mitochondrial pyruvate-carrier inhibition and dichloroacetate can promote tumor acidification through metabolic redirection rather than substrate loading.[29,30] The present hypothesis is distinct in using endogenous tumor glycolysis as a transient amplifier, but the magnitude, tumor selectivity, vascular consequences, and net therapeutic benefit of that amplification remain to be demonstrated.

Mechanistically distinct carrier classes

Phenylboronic-acid-modified polymers respond directly to glucose through reversible boronate-ester formation rather than through metabolically induced extracellular acidification.[9,10] Such systems may respond in blood or other glucose-exposed compart-

ments and therefore test a different mechanism. They are useful mechanistic comparators but are not candidate carriers for the specific priming-dependent pH-switching hypothesis proposed here.

Metabolic stratification as a testable extension

The human study linked the magnitude of change in tumor pHe indirectly to glucose handling.[25] A recent study found that glucose-induced intracellular pH changes correlated with the Lac:Pyr ratio but not significantly with FDG SUV.[26] These findings support a relationship with glycolytic flux while indicating that FDG-PET avidity itself may not be a reliable predictor. Whether FDG-PET predicts glucose-induced extracellular acidification remains unknown. To our knowledge, FDG uptake and glucose-induced extracellular pH change have not been measured prospectively in the same tumor. FDG-PET should therefore be treated as an exploratory comparator within a broader metabolic stratification program rather than as an established selection biomarker.

A note on the polymer requirement

The hypothesis does not require invention of a new polymer class. It requires an established sharp-transition system to be retuned below the measured baseline pHe distribution of the target tumor and then tested under controlled metabolic perturbation. This lowers the barrier to initial validation while placing stringent requirements on carrier threshold, leakage, kinetics, and biocompatibility.

Limitations, risks and safety considerations

The hypothesis makes specific quantitative claims and therefore has definable limits. Some arise from tumor biology, including heterogeneity of glycolysis, pHe, and perfusion; others arise from carrier pharmacology and systemic glucose exposure. At present, these considerations define priorities for preclinical testing rather than validated clinical eligibility criteria.

Patient heterogeneity

The principal human evidence is a 1994 study of 25 patients given 100 g oral glucose.[25] Only 52% showed a tumor-pHe decrease of at least 0.1 unit, and 24% reached a decrease of at least 0.2 unit. No contemporary clinical study has repeated this measurement using modern extracellular pH imaging together with perfusion assessment. Modern imaging studies support associations among tumor acidity, glycolytic activity, and tumor distribution, while glucose-associated intracellular pH changes have been linked to the Lac:Pyr ratio but not significantly to FDG SUV.[18,26] These studies do not establish the extracellular response required here or validate FDG-PET as a predictor. This heterogeneity suggests that only a subset of lesions may be responsive and makes prospective biomarker validation essential.

Systemic glucose exposure

Published acidification studies used heterogeneous intravenous and oral regimens in animals, xenografts, and patients.[21-25] The principal human observation used a 100 g oral load, whereas the 1–2 g/kg intravenous range proposed here is intended only for initial animal testing. Oral and intravenous administration cannot be assumed to be pharmacokinetically or physiologically equivalent. Before any clinical consideration, contemporary studies would need to characterize glycemic exposure, tumor pHe, tumor perfusion, and systemic metabolic effects under the exact proposed regimen.

Diabetes and insulin resistance

Altered insulin responses could prolong systemic hyperglycemia and may change both tumor metabolism and baseline pHe. These populations would therefore require dedicated investigation if the strategy progresses beyond preclinical testing. Appropriate dose, infusion rate, eligibility criteria, and monitoring cannot be specified from existing evidence.

Repeated administration

If metabolic priming were eventually paired with repeated chemotherapy cycles, cumulative metabolic and vascular effects would need to be assessed. The consequences of intermittent glucose boluses separated by days or weeks have not been studied in this delivery context, and analogies with oral glucose tolerance testing or imaging procedures are insufficient to establish safety.

Tumor-growth stimulation by transient hyperglycemia

Acute glucose exposure supplies additional substrate to tumor cells and may transiently intensify glycolysis. Whether the accompanying cytotoxic release would outweigh any short-term protumor metabolic effect cannot be inferred and should be measured directly through tumor growth, pharmacodynamic, and survival endpoints.

Gluco-immunometabolic effects

Glucose and lactate influence immune-cell metabolism, monocarboxylate transport, and the immunosuppressive tumor microenvironment. Priming may therefore alter responses to immunotherapy or other immune-dependent treatments. These effects remain uncertain even when the delivered cargo is a conventional cytotoxic agent and should be incorporated into later combination studies.

Carrier biocompatibility and clearance

UPS polymer systems have undergone extensive preclinical evaluation, and polycarbonate-based variants have been developed to improve biodegradability and therapeutic window.[27] Nevertheless, carrier-specific clearance, degradation, immunogenicity, and cumulative exposure must be assessed together with pHt suitability. A chemically appropriate threshold alone is insufficient for translational use.

A note on what these limits define

These considerations identify the most informative starting conditions for preclinical testing: highly glycolytic tumor models, direct pHe and perfusion imaging, sharply tuned UPS carriers, and metabolically characterized hosts. They should not be interpreted as established clinical selection criteria. Whether direct glycolytic-flux measures, FDG-PET avidity, diabetic status, baseline pHe, or vascular parameters can ultimately guide patient selection requires prospective validation.

Future directions

The hypothesis can be confirmed or refuted through a preclinical program centered on integrated measurement rather than on a

fixed treatment protocol. Numerical doses, timing intervals, particle sizes, and biomarker cutoffs should be refined in pilot studies. The central experiment should compare several glucose doses and administration sequences while simultaneously measuring tumor extracellular pH, tumor perfusion, carrier accumulation, and spatially resolved cargo release, with appropriate metabolic, osmotic, and carrier controls. Six linked predictions define this program.

In vivo extracellular-pH amplification

At least one low-to-moderate intravenous glucose dose within the proposed 1–2 g/kg testing range will produce a reproducible extracellular-pH decrease in responsive tumor regions that exceeds any change in matched normal tissue. Tumor perfusion must be measured concurrently rather than assumed. Controls: saline; matched normal tissue; repeated baseline imaging.

Metabolic-response stratification

Direct measures of glycolytic flux, including the Lac:Pyr ratio, are predicted to correlate with the magnitude and spatial extent of glucose-induced extracellular acidification. FDG-PET avidity should be tested in parallel as an exploratory comparator because it was not significantly associated with glucose-induced change in intracellular pH in a prior study.[26] Controls: tumor models spanning low and high glycolytic phenotypes; saline challenge; blinded pHe analysis.

Administration-sequence dependence

Carrier-first, glucose-first, and simultaneous schedules will produce different relationships among perfusion, tumor accumulation, and cargo release. Pre-accumulation of an intact subthreshold carrier followed by glucose is predicted to reduce the dependence of initial carrier delivery on glucose-associated perfusion changes. Controls: carrier without glucose; glucose plus a matched non-pH-responsive carrier; free drug; vehicle.

Threshold fidelity and cargo retention

A suitable carrier will remain predominantly assembled and retain cargo at blood pH and within the measured baseline tumor-pHe distribution but will dissociate rapidly when pH is shifted by approximately 0.17–0.20 units across its predefined pHt. Control carrier formulations should have pHt values that bracket the intended transition threshold and include a gradual-response polymer comparator.

Glycolysis dependence

Inhibition of glucose metabolism will attenuate the glucose-induced extracellular-pH displacement and the associated UPS release response, distinguishing metabolic acidification from osmotic or direct chemical effects. Controls: saline; mannitol-matched osmotic load; glycolysis inhibitor alone; glucose without carrier.

Mechanistic distinction from direct glucose responsiveness

A phenylboronic-acid-based carrier may respond directly to glucose in plasma or buffer, whereas a UPS carrier should respond only when local pH crosses its threshold. Parallel testing under controlled glucose and pH conditions will separate chemical glucose sensing from metabolically mediated pH switching.

Conclusions

We propose a class-level hypothesis in which controlled glucose priming, appropriately timed relative to nanocarrier administration, transiently shifts the tumor extracellular pH distribution across the activation threshold of a UPS polymeric carrier deliberately tuned below the baseline tumor pHe distribution. Historical animal studies and limited human observations show that glucose can produce tumor-associated pH changes of approximately 0.17–0.20 units under selected conditions, a magnitude quantitatively compatible with the narrow transition window of UPS systems. Compatibility does not establish sufficiency: the relevant pH measurements and carrier transitions were obtained in separate settings, the human response was heterogeneous, tumor blood flow was unchanged at 1 g/kg in one animal study but has not been characterized at 2 g/kg or across the proposed range, and nanocarrier accumulation was not measured. Direct measures of glycolytic flux may prove more informative for stratification than FDG-PET avidity, which remains an exploratory candidate rather than a validated predictor. No administration sequence should be assumed optimal. The essential next step is simultaneous, spatially resolved validation of tumor pHe shift, perfusion, carrier accumulation, and cargo release across doses and administration sequences in tumor-bearing animals. Until those variables are measured together, the strategy should be regarded as a falsifiable preclinical proposal rather than a clinically feasible protocol.

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Conflict of interest

The author was the sole inventor on a U.S. patent application filed in 2005 (U.S. Patent Application No. 11/100,105; Publication No. US 2005/0074424 A1; filed April 5, 2005; subsequently abandoned and never granted) describing an early conceptual precursor of the present hypothesis. The application is disclosed solely as a competing-interest declaration; it is not offered as scientific evidence or as a claim of priority over the hypothesis advanced in this manuscript, which rests entirely on peer-reviewed literature. The author holds no intellectual-property rights related to the subject matter of this manuscript. The author is an independent researcher affiliated with InterceptAge LLC; the work reported here was conducted independently and received no financial support from the company. InterceptAge LLC has no commercial activity or financial interest in pH-responsive drug delivery. Apart from this disclosure, the author declares no conflict of interest.

Author contributions

LS is the sole author of the manuscript.

Ethical statement

Not applicable. This is a hypothesis paper involving neither human subjects nor animal experiments.

Data sharing statement

No new data were generated for this hypothesis paper. All data analyzed are available in the cited publications.

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