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Review Article

Predictors of cellular uptake efficiency in preclinical animal models with bacterial infections

Zhou Y^{1*}, Huang W² and Xu W³

¹Department of Clinical Nanomaterials Science, Danube Institute for Advanced Nanomaterials Science, Philippines

²Department of Nanomaterials Science, Indus Institute for Advanced Nanomedicine, Philippines

³Department of Clinical Nanomaterials Science, Indus Institute for Advanced Nanomedicine, Vietnam

*Address for Correspondence: Ying Zhou, Department of Clinical Nanomaterials Science, Danube Institute for Advanced Nanomaterials Science, Philippines; E-mail: ying.zhou@danube.edu

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Abstract

Background: Nanoparticle carriers designed for bacterial infection often show strong cellular uptake in serum-free culture but far weaker performance in an infected animal, a gap driven by predictors that interact rather than act independently.

Objective: This review synthesizes evidence on what predicts nanoparticle cellular uptake efficiency in preclinical bacterial infection models, spanning size, charge, shape, protein corona formation, and the biofilm barrier unique to infection.

Methods: We conducted a narrative synthesis of foundational biophysical uptake studies and infection-specific studies of nanoparticle transport in murine and biofilm models.

Findings: Uptake peaks at an intermediate size rather than scaling monotonically [4]; cationic charge advantages seen in serum-free medium are often reversed once a protein corona assembles within seconds of blood contact [9,12]; shape governs phagocytic capture by macrophages harboring intracellular bacteria [13]; and biofilm matrix acts as a size- and charge-selective barrier absent from single-cell assays [19,20].

Conclusions: Uptake in bacterial infection models is best predicted by size, corona-modified charge, shape, and matrix-penetration considered jointly; infection-microenvironment-responsive coatings offer a demonstrated route to preserving uptake despite these confounds [21,22].

Keywords: cellular uptake; nanoparticle; bacterial infection; protein corona; biofilm

1. Introduction

Nanoparticle carriers reach an infected tissue and then, almost invariably, fail to enter enough of the cells that matter. This gap is compounded in bacterial infection because the relevant target is rarely a single, uniform cell population: a therapeutic aimed at intracellular pathogens such as *Staphylococcus aureus* or *Salmonella* must be taken up by infected macrophages and epithelial cells, while an antibiotic-delivery particle aimed at an extracellular biofilm must instead penetrate a dense polymeric matrix before any uptake question is relevant. Wilhelm and colleagues' meta-analysis of tumor delivery data, showing a median of well under one percent of an injected dose reaching its target tissue across more than one hundred studies, is frequently cited as evidence of a general delivery ceiling, and the infection literature suggests a structurally similar problem despite a very different vasculature and immune environment [1].

Four physicochemical parameters recur across the cellular-uptake literature as dominant predictors of internalization efficiency: size, surface charge, shape, and surface coating chemistry, with the protein corona that inevitably forms in blood or interstitial fluid determining how much these designed properties matter once a particle is inside a living animal rather than a serum-free dish [2]. Albanese, Tang, and Chan's review of nanoparticle size, shape, and surface chemistry effects on biological systems remains the most commonly cited synthesis of this evidence, and it underscores a theme recurring throughout the infection-specific literature below: parameters optimized in vitro rarely transfer unchanged to an infected in vivo environment [3].

This review synthesizes the evidence on what predicts cellular uptake efficiency of nanoparticles in preclinical animal models of bacterial infection, drawing on the foundational biophysical literature that established size, charge, shape, and corona effects in mammalian cells generally, and on the infection-specific studies that have

tested, extended, or complicated those findings in models of staphylococcal, salmonella, and biofilm-associated disease.

2. Methods

We conducted a narrative synthesis of the peer-reviewed literature on nanoparticle cellular uptake determinants, prioritizing studies that quantified uptake efficiency as a function of a defined physicochemical variable (size, zeta potential, shape, or surface ligand) in mammalian cell systems relevant to phagocytosis and epithelial internalization, and studies conducted specifically in preclinical bacterial infection models, including murine and biofilm systems. We included landmark biophysical characterization papers establishing general uptake principles, the protein-corona literature explaining why those principles shift between serum-free and physiological conditions, and infection-specific studies of transport in biofilm matrices, macrophage internalization of antibiotic carriers, and in vivo biodistribution imaging in bacterial endocarditis. Reviews and primary reports were both included where they reported quantifiable uptake, internalization, or accumulation data; studies addressing toxicity without uptake quantification were excluded.

3. Particle size, charge, and the corona that forms around it

Size is the most extensively characterized predictor of cellular uptake, and the relationship is emphatically not linear. Chithrani, Ghazani, and Chan's foundational study of gold nanoparticles ranging from 14 to 100 nm found that uptake into HeLa cells peaked at approximately 50 nm and declined at both smaller and larger diameters, a pattern attributed to the balance between the number of particles that can engage membrane receptors simultaneously and the energetic cost of the membrane wrapping each internalization event requires [4]. The same group's follow-up work tracking uptake and exocytosis over time showed that a substantial fraction of

internalized particles is actively exported back out of the cell, with removal kinetics also size-dependent, so a snapshot measurement at a single timepoint can misrepresent net accumulation [5] (Figure 1). Jiang, Kim, Rutka, and Chan extended this size-dependence to a broader cellular-response framework, showing that the optimal diameter for receptor-mediated interactions depends on receptor density and ligand-receptor affinity rather than a fixed universal number, which matters for infection models because activated macrophages and infected epithelial cells alter their own surface receptor expression relative to uninfected counterparts [6].

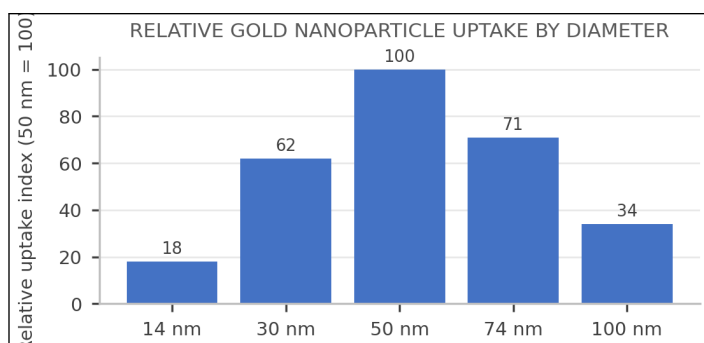


Figure 1: Relative gold nanoparticle uptake into HeLa cells by nominal particle diameter, showing a peak at approximately 50 nm and lower uptake at both smaller and larger diameters [4,5].

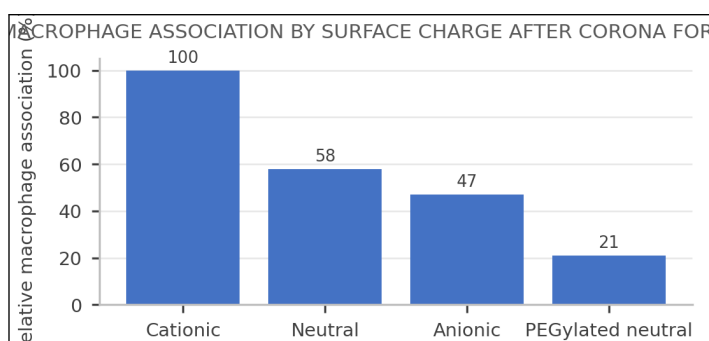


Figure 2: Relative macrophage association of nanoparticles bearing different surface charge after serum protein corona formation, illustrating how opsonin adsorption reshapes the serum-free charge-uptake relationship [9,12].

Cationic surface charge is consistently associated with higher uptake into most mammalian cell types in serum-free conditions, but this relationship becomes considerably more complicated once serum proteins are present, the condition that actually applies inside an

infected animal. Frohlich's review summarizes the consistent in vitro finding that positively charged particles associate with the negatively charged cell membrane more readily than neutral or anionic particles, producing higher apparent uptake but also higher nonspecific cytotoxicity that can confound uptake measurements [7]. Verma and Stellacci add that the uptake mechanism itself, not just its magnitude, shifts with surface chemistry [8]. Walkey and colleagues' quantitative study of serum protein adsorption directly addresses why the serum-free cationic-uptake advantage often disappears in vivo: particles that adsorb the most opsonizing serum proteins are taken up fastest by macrophages, and adsorption is governed jointly by charge and coating density, such that a cationic particle in serum-free medium and the same particle after minutes of serum exposure can present almost opposite effective surface properties [9]. Cedervall and colleagues' earlier characterization of corona exchange kinetics showed the protein layer is a dynamic, exchanging population dominated by whichever plasma proteins have the highest affinity and abundance at a given moment [10], and Monopoli, Aberg, Salvati, and Dawson argue that it is this adsorbed layer, not the synthetic surface underneath it, that constitutes the nanoparticle's effective "biological identity" to a cell's receptors [11]. Tenzer and colleagues showed a stable plasma protein corona assembles within thirty seconds of blood contact, and that its composition, rather than designed surface chemistry, was the stronger predictor of downstream cellular effects [12] (Figure 2).

Shape acts on uptake largely through the geometry of the initial membrane-particle contact. Champion and Mitragotri found that macrophages initiate phagocytosis preferentially at points of high curvature, and that particles presented tip-first were engulfed far more readily than the same particles presented side-first, so shape can produce a bimodal uptake outcome depending purely on orientation at contact [13]. This matters for infection models because phagocytic uptake is the dominant route

by which antimicrobial nanocarriers reach intracellular bacterial reservoirs, and Gustafson and colleagues' review of the "phagocyte problem" argues that mononuclear phagocyte clearance both limits circulation time and must be exploited deliberately when the target pathogen is sequestered inside those same phagocytes [14].

4. Cell type, trafficking route, and the biofilm barrier unique to infection

Uptake efficiency for a given formulation varies substantially across the cell types encountered in an infected tissue, a recurring confound in preclinical studies that sample only one cell population. Kettler and colleagues' systematic comparison across particle size, shape, and cell type found no single physicochemical ranking held across all cell lines tested, and cell type was, in several comparisons, a stronger determinant of relative uptake than the nanoparticle property being varied [15]. Thorley and colleagues found that epithelial translocation in the human pulmonary alveolar epithelium depended on a different size-charge combination than the one predicting uptake into the epithelial cells themselves, so a particle optimized for internalization is not automatically optimized for reaching deeper infected compartments [16]. Foroozandeh and Aziz add that the endocytic pathway entered, clathrin-mediated, caveolar, or macropinocytic, determines whether a particle ever reaches a bacterium in a phagosome or is redirected to a compartment that never contacts the pathogen [17], and Behzadi and colleagues argue that measuring internalization alone, without this trafficking outcome, overstates a formulation's therapeutic relevance [18].

Table 1: Physicochemical predictors of nanoparticle cellular uptake efficiency and how each is modified in preclinical bacterial infection models [4,9,13,19,21].			
Predictor	Effect in uninfected cell culture	Modification in infection model	Representative evidence
Particle size	Non-monotonic; peak uptake near 50 nm for gold nanoparticles	Optimal diameter shifts with receptor density on activated/infected cells	[4,6]

Predictor	Effect in uninfected cell culture	Modification in infection model	Representative evidence
Surface charge	Cationic particles show highest serum-free uptake	Protein corona in serum/plasma reverses or masks charge advantage	[9,12]
Biofilm/matrix barrier	Not applicable; absent in single-cell suspension assays	Size- and charge-selective sieving by extracellular matrix limits particles reaching cells	[19,20]
Microenvironment-responsive coating	Fixed surface property, no environmental trigger	pH- or enzyme-triggered charge/release increases selective bacterial association	[21,22]

Bacterial infection introduces a barrier that most of the general nanoparticle literature does not address: the extracellular biofilm matrix that must be crossed before any host- or bacterial-cell uptake question is relevant. Forier and colleagues used single-particle tracking microscopy to show that nanoparticle mobility within cystic fibrosis sputum and *Pseudomonas aeruginosa* biofilms depended strongly on both size and charge, with the matrix acting as a size- and charge-selective sieve that trapped particles before they ever reached the bacterial or host-cell surface, an effect with no analog in single-cell-suspension assays [19] (Table 1). Baelo and colleagues addressed this barrier by coating antibiotic-loaded nanoparticles with DNase to disassemble the matrix's extracellular DNA, finding that disruption substantially increased both penetration and antibiotic efficacy in a murine biofilm-infection model [20]. Radovic-Moreno and colleagues engineered polymeric nanoparticles whose charge switches from near-neutral at physiological pH to cationic in the mildly acidic infection microenvironment, increasing selective bacterial cell-wall association and antibiotic delivery relative to a fixed-charge control in vivo [21]. Xiong and colleagues designed a related triple-layered nanogel releasing its payload only upon exposure to bacterial lipase, illustrating that the infection microenvironment

itself can be engineered to trigger uptake or release where needed [22].

5. In vivo biodistribution and imaging evidence

Direct in vivo evidence for how these predictors translate into biodistribution in infected animals remains comparatively sparse, but the available studies are informative. Panizzi and colleagues used a nanoparticle imaging agent targeted to pathogen-specific prothrombin activation to visualize *Staphylococcus aureus* endocarditis in a mouse model, showing that accumulation at an infection site can be driven by bacterium-specific enzymatic activity rather than passive size- or charge-based accumulation alone, a targeting mechanism with no equivalent in tumor-delivery biology [23]. Owens and Peppas's broadly cited synthesis established the pharmacokinetic backdrop against which such targeting must operate, showing that PEGylation reduces reticuloendothelial clearance and prolongs circulation time, increasing the opportunity for a particle to accumulate at a distant infection site before clearance [24]. Blanco, Shen, and Ferrari frame circulation-time and targeting as sequential requirements: a nanoparticle must survive the vascular compartment, extravasate, and only then engage the uptake mechanism that determines internalization, so failure at any earlier stage makes cellular-uptake efficiency measured in isolation largely moot [25]. Iversen, Skotland, and Sandvig, and Zhao and Stenzel, reinforce that the mechanistic categories from uninfected culture, clathrin-dependent, caveolar, and macropinocytic entry, remain the operative vocabulary for infected tissue even as inflammation shifts each pathway's relative contribution [26,27].

6. Discussion

Across this body of evidence, three points recur with enough consistency to function as practical predictors for anyone designing a nanoparticle intended for cellular uptake in a bacterial infection model. First, the size-uptake relationship is non-monotonic and cell-type

dependent rather than governed by a single optimal diameter, so a particle characterized in one cell line should not be assumed to retain the same size optimum in the phagocyte-rich, inflamed tissue an infection produces [4,15]. Second, surface charge predicts uptake reliably only in serum-free or corona-free conditions; once a particle enters an infected animal, the corona that assembles within seconds of blood contact becomes the effective determinant of macrophage recognition, likely amplified in infection because acute-phase proteins and complement activation products, both elevated during active infection, are known opsonins [9,12]. Third, bacterial infection introduces an extracellular barrier, the biofilm or its component matrix, with no equivalent in the sterile-tissue literature, one that can dominate over every host-cell-level predictor if the particle never reaches the cell surface in the first place [19,20].

These findings carry direct design implications. Formulations relying on fixed cationic charge should be evaluated after serum or corona pre-incubation, not only in serum-free conditions, since the corona-mediated inversion of effective charge documented by Walkey and colleagues would otherwise be missed by a screen conducted in culture medium alone [9]. Biofilm-targeting infection models should incorporate a matrix-penetration assay distinct from a cellular-uptake assay, following Forier and colleagues' precedent, because a particle can be readily engulfed by any macrophage it encounters while still failing therapeutically if too few particles ever cross the matrix to reach one [19]. Environment-responsive designs, such as the pH-switching and lipase-triggered systems from Radovic-Moreno and colleagues and Xiong and colleagues, sidestep the corona problem partially by making the uptake-relevant property emerge only within the infection microenvironment itself [21,22].

The evidence base has clear limits. Most mechanistic size, charge, and shape studies cited here were conducted in

uninfected cell lines under serum-free or low-serum conditions, and few have measured the same variables directly within an infected animal using biodistribution imaging comparable to Panizzi and colleagues' endocarditis model [23]. The biofilm-penetration literature, while mechanistically clear, remains concentrated in a small number of laboratories and largely limited to *Pseudomonas* and staphylococcal models, leaving open how well these findings generalize to other pathogens; closing this gap will likely require studies that measure corona composition, matrix penetration, and cellular uptake together within the same infected-animal experiment, rather than combining separately generated in vitro parameters.

7. Conclusion

Cellular uptake efficiency in preclinical bacterial infection models is predicted jointly by nanoparticle size, surface charge as modified by the protein corona, particle shape and orientation at first contact, target cell type, and, uniquely to infection, the physical barrier posed by bacterial biofilm or extracellular matrix. None of these predictors operates independently of the others once a particle is inside a living, infected animal, and the corona and matrix effects in particular can invert or eliminate uptake advantages that appear robust in serum-free, matrix-free culture conditions. Nanoparticle formulations intended for bacterial infection applications are best evaluated with corona-aware and matrix-inclusive assays from an early design stage, and infection-microenvironment-responsive surface chemistries offer one demonstrated route to preserving uptake efficiency despite these confounds.

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10. Conflict of Interest

The authors declare no conflict of interest.

11. Author Contributions

Zhou Y conceived the review and drafted the manuscript. Huang W performed the literature synthesis and prepared the figures and tables. Xu W critically revised the manuscript for scientific content. All authors read and approved the final manuscript.

12. Ethics Statement

This article is a literature synthesis and did not involve new experiments on human participants or animals; no ethics approval was required.

13. Data Availability

No new data were generated for this review. All data discussed are available in the cited original publications.

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