

Immune-Interactive Photopolymer Materials: Protein Adsorption, Innate Response, Foreign-Body Reaction and Design Limits

Qualification of surface-conditioned immune response in photocured and hydrogel materials

Juan Seguro

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Correspondence: info@3Dresyns.com · www.3Dresyns.com

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Abstract

Implanted photopolymer materials immediately acquire an adsorbed protein layer that mediates subsequent interactions with innate immune cells. The foreign-body response is therefore not a simple intrinsic material property and cannot be inferred from nominal polymer chemistry or short-term cytocompatibility. This review links protein adsorption, macrophage response, material modulus, surface chemistry and fibrous encapsulation, and defines design limits for immune-interactive photocured materials. It treats in vitro macrophage assays as mechanistic tools rather than substitutes for in vivo qualification.

Keywords: foreign-body response; macrophage; protein adsorption; hydrogel; photopolymer; innate immunity; fibrous capsule; biomaterial

1. Significance and scope

Any non-biological implanted material enters a protein-rich environment before immune cells contact the underlying polymer. Swartzlander and co-workers linked protein adsorption on PEG-based hydrogels to macrophage adhesion and the subsequent foreign-body response, demonstrating that surface-conditioned biology is central to interpretation [1]. Photopolymer qualification must therefore include the cured surface state, not only bulk composition.

2. Protein adsorption is the first changing interface

Adsorbed proteins depend on surface chemistry, hydration, charge, roughness and the biological fluid. The identity and conformation of that layer can influence complement activation and macrophage adhesion. A low-fouling formulation should be tested with relevant biological fluids rather than credited from nominal PEG or zwitterionic content alone.

Protein adsorption should be measured under a defined fluid composition and exposure time. Total adsorbed mass is useful but not always sufficient because different proteins and conformations can generate different cellular responses. Where possible, compositional analysis or at least a targeted panel should accompany a bulk adsorption metric, particularly when comparing surfaces with similar total adsorption.

3. Macrophage response is not a single M1/M2 number

Macrophages show mixed and time-dependent phenotypes during the foreign-body response. A single marker or a single time point cannot represent the full trajectory. Jansen and co-workers showed that both chemistry and modulus can influence protein adsorption and macrophage-associated foreign-body response in PEG-PC hydrogels [2].

Mechanical state is therefore part of immune material identity. Innate immune response is time-dependent and context-dependent. Early cytokine or macrophage-marker measurements should not be converted into a claim about long-term fibrous encapsulation without longitudinal or in vivo evidence.

Macrophage phenotype or cytokine concentration is only one level of the response. Recruitment, fusion into foreign-body giant cells, capsule formation and vascular or fibroblast behaviour occur on different timescales. A material that shows low acute cytokine release cannot automatically be called low-FBR. Where implantation is intended, the qualification endpoint should match the relevant service interval and include tissue-level evidence rather than relying only on short-term in-vitro assays.

Thompson and co-workers showed that TLR2/TLR4-dependent recognition of adsorbed proteins can contribute strongly to the foreign-body response [3], illustrating why surface-conditioned innate signalling and later tissue outcomes need to be linked experimentally rather than assumed.

4. Cure state and extractables are confounders

Residual monomer, photoinitiator fragments and incomplete post-cure can provoke responses that differ from the fully cured network. Extraction or post-cure may change both surface chemistry and modulus. Any comparison between formulations should therefore report cure conversion or a controlled post-cure proxy and the extraction history.

Cure state and extractables are additional variables unique to photopolymer systems. Incomplete conversion, leachable photoinitiator products and post-cure oxidation can change both cytotoxicity and protein adsorption. The biological test article should therefore be the

final washed/post-cured state intended for use, with extraction history reported and, where relevant, compared against an intentionally under-cured control.

5. In vitro assays do not substitute for foreign-body reaction

Protein adsorption and macrophage assays can identify mechanisms, but fibrous capsule formation involves multiple cell types, vascular events and tissue remodelling over time. The intended claim should determine the evidence level. A short-term viability or cytokine result can support screening but not a claim of reduced foreign-body response.

Mechanical properties can influence the foreign-body response independently of chemistry. The modulus-dependent results reported for PEG-PC hydrogels [2] make it unsafe to compare immune outcomes between formulations if their stiffness differs substantially. For printed objects, local geometry and surface area can add further confounding, so coupon and device-level studies answer different questions.

Axis	Measurement	Failure mode
Cured surface	post-cure, roughness/finish, hydration	bulk chemistry used as surface proxy
Protein layer	adsorbed mass/profile under relevant fluid	low-fouling claim without biological conditioning
Innate response	cell source, markers and time course	single marker treated as full phenotype
Mechanical state	modulus at test condition	chemistry compared at different stiffness
FBR claim	in vivo endpoint when required	in vitro screening presented as implantation outcome

Table 1. Domain-specific qualification matrix for immune-interactive photopolymer materials.

6. Device-level verification

For implant-facing photopolymers, qualify the final surface finish, sterilisation state, ageing history and mechanical state. Compare protein adsorption, relevant innate-cell responses and, when the claim requires it, an in vivo implantation endpoint.

This review does not qualify a material as clinically safe or biocompatible. It defines the engineering evidence needed to interpret protein adsorption and innate/foreign-body responses. ER-439 owns organ-on-chip measurement systems; such chips can be mechanistic tools, but they do not replace in vivo foreign-body evidence when an implant claim is made.

Testing hierarchy should be explicit. Protein adsorption and cell assays are mechanistic screens; subcutaneous or other in vivo models address a different level of evidence. Sterility, endotoxin and surface contamination must be controlled because they can dominate innate immune readouts and falsely attribute inflammation to the photopolymer chemistry.

For printed parts, roughness and geometry should be measured because they influence effective surface area and local tissue contact.

Post-processing belongs in the immunological material identity. Residual monomer, photoinitiator fragments, cleaning solvent, sterilisation and surface oxidation can alter protein adsorption and innate signalling. Therefore the final sterilised, washed and aged article should be tested whenever those operations are part of manufacture. Coupons printed from the same resin but processed differently are not automatically biologically equivalent.

7. Minimum qualification framework

Report matrix chemistry, cure/post-cure, extractables or wash state, modulus, surface condition, protein adsorption protocol, cell source and markers, time points, and the evidence level supporting any FBR claim. Separate design-screening data from translational or implantation data. The minimum dataset should therefore include final material state, extraction/post-cure history, surface chemistry or wettability metric, roughness, modulus, protein-adsorption condition, macrophage or innate-response assay with time points, and an in vivo endpoint when a foreign-body claim is made.

Results should be reported with biological variability and not collapsed into a single 'biocompatible' label. The engineering output is a bounded response profile under defined exposure conditions.

8. Engineering conclusions

Immune interaction is an emergent property of the cured material, the adsorbed biological layer and the host response. Photopolymer design can influence that chain, but no single chemical descriptor guarantees a favourable outcome. The engineering task is to control surface-conditioned protein interactions while maintaining the mechanical and chemical state needed for service, and to match the biological evidence to the strength of the claim.

References

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Competing interest

Juan Segurola is founder, CEO and CTO of 3Dresyns by Resyner Technologies S.L., which develops and commercialises photopolymer materials and related additive-manufacturing technologies. This review is an engineering analysis and does not constitute a product-performance claim or a device qualification.