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Synthetic polymer receptors for cold-chain-free paper diagnostics

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Paper-based diagnostics remain constrained by the thermodynamic fragility of biological recognition elements. Synthetic polymers, such as molecularly imprinted polymers, offer a synthetic route to storage-resilient, cold-chain-independent platforms.

Decentralized paper-based diagnostics, particularly lateral flow assays, are a cornerstone of point-of-need testing during global health emergencies. However, recent outbreaks of diseases caused by high-consequence zoonotic pathogens, such as Crimean–Congo haemorrhagic fever, a tick-borne viral disease, and hantavirus disease, a rodent-borne viral infection, have exposed a structural vulnerability of lateral flow assays. Their biological recognition elements are inherently thermodynamically unstable, leading to reduced assay performance in resource-limited settings, in which reliable cold-chain infrastructure is unavailable.

Paper-based diagnostic platforms typically rely on mammalian cell-derived monoclonal antibodies that bind to specific antigens on pathogens. Although these biological receptors offer high affinity under controlled laboratory conditions, their proteinaceous nature makes them vulnerable to environmental stress, such as high temperature (Fig. 1a). For example, gold-standard immunoglobulins (IgG) undergo irreversible structural alterations, aggregation and loss of binding capacity when subjected to temperature fluctuations or pH shifts during prolonged storage[1]. Recognition element denaturation leads to reduced test sensitivity and false-negative results, compromising diagnostic test performance. Therefore, a strict 2–8 °C cold chain must be maintained during shipping and storage. However, a continuous cold chain might not be achievable in resource-limited settings.

Furthermore, the reliance on biological manufacturing that requires protracted animal immunization, cell culture scaling and complex purification steps can delay deployment of diagnostic tests based on biological recognition elements. Although smaller biological fragments, such as nanobodies, have been explored to circumvent some of these production hurdles[2], they remain proteinaceous entities and thus do not address the fundamental vulnerabilities of thermal degradation and cold-chain dependence. Alternatively, field resilience and outbreak readiness could be improved by paper-based diagnostics that rely on molecularly imprinted polymers (MIPs).

Molecularly imprinted polymers

MIPs, also termed 'synthetic antibodies', can be engineered by polymerizing functional monomers around a target template, thereby creating stable and specific recognition cavities after template removal[3]. Importantly, MIPs can be produced by chemical synthesis without reliance on cell lines or animal hosts, allowing rapid and scalable adaptation to emerging viral threats[4]. In particular, the in situ synthesis of MIP nanoparticles within continuous-flow micro-reactor systems exemplifies the scalability of synthetic manufacturing, enabling rapid, high-yield production of uniform synthetic receptors[5].

Importantly, rationally designed MIPs, particularly those based on customized amino acid-based monomers, which benefit from structural flexibility and high affinity, exhibit thermal and chemical stability[6]. Furthermore, in contrast to paper-based platforms that contain biological elements, which have limited shelf lives, MIP-based platforms offer indefinite storage capabilities. They maintain their structural integrity and binding capacity even when exposed to high temperatures or during prolonged storage, thereby reducing cold-chain dependence.

Engineering the paper–MIP interface

Paper–MIP systems can be engineered to remain selective under clinically relevant flow, storage and matrix conditions[7] (Fig. 1b). For example, plasmonic nanoscale MIPs can be reproducibly integrated into lateral flow architectures as optical probes, eliminating lot-to-lot variability inherent to biological production[8]. Importantly, these MIP-based probes enable sensitive viral detection on cellulose matrices, while circumventing autofluorescence interference[9].

However, unlike soluble antibodies, the rigid and cross-linked nature of MIP particles makes their uniform distribution difficult, as irregular aggregation can obstruct capillary flow and sterically hinder access to the binding cavities. Furthermore, in samples such as whole blood or serum, MIPs remain susceptible to non-specific adsorption, which can compromise selectivity and diagnostic accuracy. These challenges may be addressed by optimizing the interfacial chemistry between the paper matrix and the MIP. For example, hydrophilic co-monomers can be added to passivate the MIP surface and repel non-target proteins. In addition, controlled covalent anchoring techniques can be applied to ensure that the synthetic receptors are firmly immobilized onto the cellulose fibres without altering their capillary wicking properties[10]. This ensures that specificity and signal transduction remain robust outside controlled laboratory environments.

Operational durability and rapid deployment

In addition to analytical sensitivity, operational durability and rapid deployability are key considerations in the design of paper-based, point-of-care diagnostic platforms to ensure pandemic preparedness[11]. In particular, cold-chain independence should be considered in the research and development of decentralized diagnostic systems and should be accounted for by funding agencies and regulators.

Importantly, diagnostic success should not be measured solely by the limit of detection, but by 'diagnostic yield', that is, the proportion

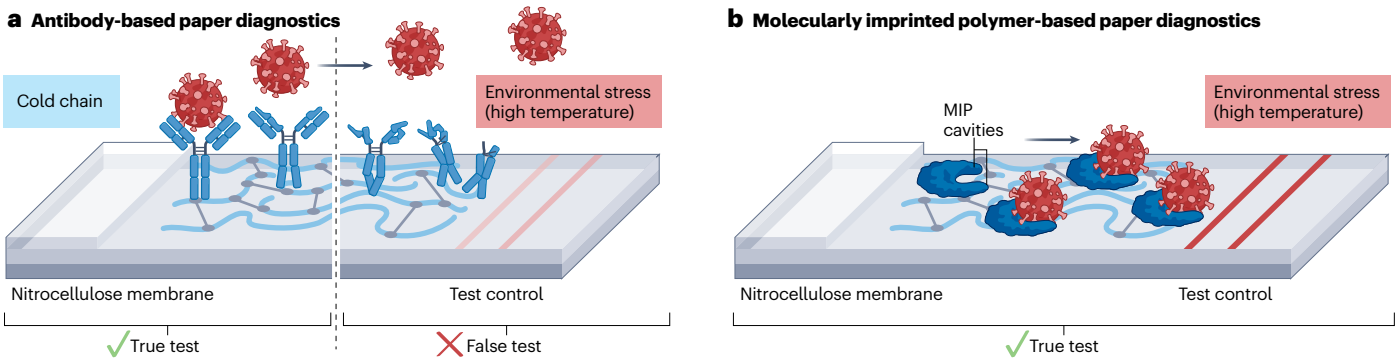

Fig. 1 | Biological receptors versus synthetic polymers in paper-based diagnostics. a, The performance of antibody-based diagnostics can be negatively affected by real-world conditions, such as temperature fluctuations and prolonged storage, which can cause denaturation of these proteinaceous receptors. **b**, Synthetic receptors, such as molecularly imprinted polymers (MIPs), can be engineered using rationally designed monomers. These cavities maintain their structural integrity and high affinity for viral targets under temperature fluctuations, ensuring diagnostic sensitivity in all settings.

of accurate results obtained under real-world conditions, in which temperature fluctuations and logistical delays are often unavoidable[12]. By shifting investment towards synthetic recognition elements, such as MIPs, diagnostic platforms can be built to ensure that reliable testing is rapidly available to all communities across the globe.

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Competing interests

The authors declare no competing interests.