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# Exploring 'new' bioactivities of polymers at the nano–bio interface

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**A biological system is essentially an elegant assembly of polymeric nanostructures. The polymers in the body, biomacromolecules, are both building blocks and versatile messengers. We propose that non-biologically derived polymers can be potential therapeutic candidates with unique advantages. Emerging findings about polycations, polysaccharides, immobilised multivalent ligands, and biomolecular coronas provide evidence that polymers are activated at the nano–bio interface, while emphasising the current theoretical and practical challenges. Our increasing understanding of the nano–bio interface and evolving approaches to establish the therapeutic potential of polymers enable the development of polymer drugs with high specificities for broad applications.**

## Biological systems: elegant assemblies of polymeric nanostructures

If we could see all biological events taking place at the nano scale, we would recognise biological systems as natural assemblies of polymeric nanomaterials. Cellular components consist of biopolymers, such as proteins, polysaccharides, nucleic acids, and their complexes, with sizes ranging from a few to hundreds of nanometres. Cells function by way of various interactions between these nanostructures, typified by protein binding events, such as receptors recognising ligands, integrins adhering to the cell matrix, and antigens binding antibodies. Collectively, biopolymers elegantly combine to orchestrate cell functions and mediate crucial physiological events.

Dissecting biological systems into interactions between polymeric nanostructures inspired investigations into whether non-biological polymers can be used as therapeutic agents [1]. Conventionally, most polymers, apart from a few classes of biologically derived macromolecules like collagen, are hardly considered bioactive and rarely top the list of drug candidates. They are useful biomaterials tools to support tissue regeneration, resist pathogens, or deliver drugs, chiefly because of their physical advantages [2,3]. However, increasing evidence has emerged that many polymers, either natural or synthetic, can acquire new, mostly unpredicted bioactivities when they interact with living systems [4,5]. Even the so-called 'bio-inert' materials, such as gold or high-molecular-weight polyethylene, gain significant bioactivities when they form nanoparticles [6,7]. Polymers can be 'activated' at the nano–bio interface, no matter how active or inert their constituents. The notion that polymers, especially those that are non-tissue derived, should be bio-inert is now proving incorrect. Polymers can act as drugs and may offer unique advantages over smaller compounds. For instance, their interaction with the biological interface emulates the natural interplay between biomacromolecular complexes in the body. They may also be more specific than smaller compounds, as the latter usually have more diverse targets [8]. Investigation and active control of the nanoscopic interactions between polymers and native biomolecules may open up enormous possibilities for development of polymer drugs with unique, high, and specific therapeutic activities.

## Polymers are activated at the nano–bio interface: cases and inspirations

Polymers should have several essential features in order to gain various bioactivities at the nano–bio interface. The polymers must be sufficiently large, usually measuring between tens of nanometres and a few micrometres. Additionally, the biological effects exhibited by the polymers should not be present or be much weaker in their monomers or oligomers. The monomers or oligomers may have no activity at all or other activities that disappear after polymerisation. The polymers could interact with cell receptors, antigens, or growth factors, creating or changing an existing nanostructure and thereby activating or blocking cell signalling. Fourth, apart from a few carbohydrates, the polymers do not have specific antigens/receptors, but utilise the antigens/receptors that are specific to other antibodies/ligands (Figure 1A).

The cationic polymer polyethyleneimine (PEI), long used as a carrier tool for gene transfection, was recently found to be a promising adjuvant [9,10] and was used as a direct therapeutic agent for immunotherapy [11–13]. As a potent mucosal adjuvant against viral subunit glycoprotein antigens [9,10], PEI co-administrated with viral vaccine antigen gp140 increased the production of antigen-specific IgG

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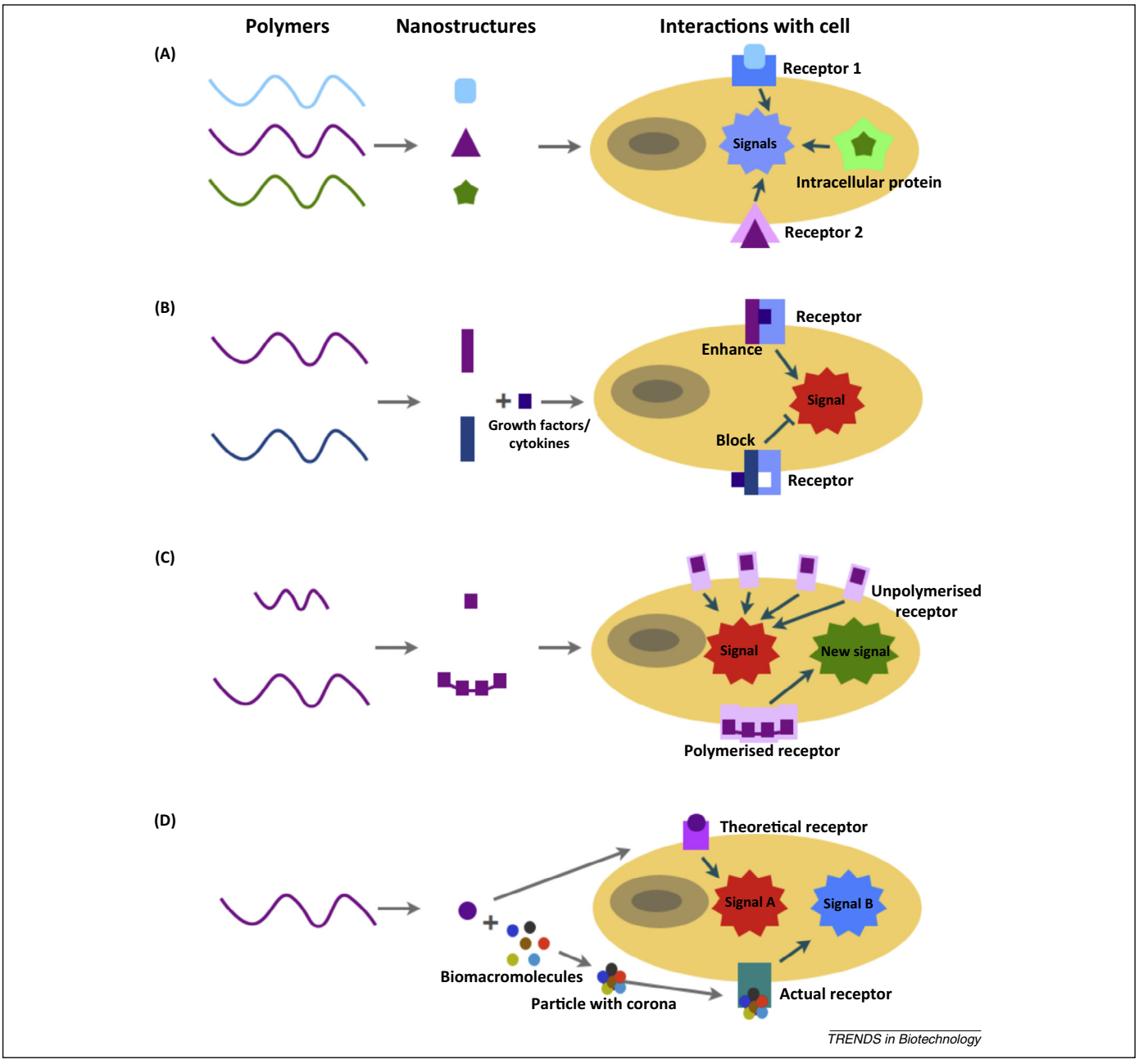


**Figure 1**. Four major mechanisms through which polymers are activated at the nano–bio interface. **(A)** A polymer can directly bind and activate a biomolecule, such as an antigen, a receptor, or an intracellular protein, and thereby trigger downstream cellular signals. These biomolecules are not specific to the polymer (and usually have their own specific antibodies or ligands) but are efficiently used by the polymer. **(B)** Instead of directly binding to a receptor, a polymer can bind a growth factor or cytokine, and form complexes with the receptor for this growth factor, thus enhancing or blocking the function of this growth factor. **(C)** A polymer can be engineered to conjugate ligands to form a multivalent conjugate, with high specificity and efficacy to activate cellular receptors and control cell behaviour. **(D)** In the body, a nanoscale polymer can be encapsulated by biomolecular coronas, and its 'original' function may be redefined by the corona activities. The corona can be very stable.

approximately 100 fold, compared to gp140 alone. Size was crucial for the activity of PEI, because PEI of higher molecular weight (750 kDa) and in branched form acted more powerfully than lower molecular weight PEI and its linear form. PEI and the antigen formed a relatively large complex (750 nm). The complex was internalised by antigen-presenting cells (APCs) that subsequently induced non-proinflammatory cytokine release, which may be a major mechanism for the immune activity of PEI [10]. In addition to its adjuvant role, PEI was also able to induce cytokine expression that recruited APCs [9], inhibit the development of arthritis [12], as well as promote the response of type 1 T helper cells *in vivo* [11]. None of these diverse, immune-modulating activities of PEI has been found in its monomers. Similarly, another set of polycations, 'viologen' (*N*-alkylated 4,4′-bipyridinium)-based dendrimers, were designed to modulate immune cells [14,15]. Some viologen-based polycation macromolecules, those with 10–90 charges per molecule, can directly bind the chemokine receptor CXCR4 [15] and exert activity against the human immunodeficiency virus type 1 (HIV-1) in primary human cell cultures [14]. Cationic polymers that can interact with antigens or receptors have emerged as promising candidates for therapeutic agents with broad applications.