Bioinert and Lubricious Surfaces by Macromolecular Design

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Abstract

The modification of a variety of biomaterials and medical devices often encompasses the generation of biopassive and lubricious layers on their exposed surfaces. This is valid when the synthetic supports are required to integrate within physiological media without altering their interfacial composition, and when minimization of shear stress prevents or reduce damage on the surrounding environment. In many of these cases, hydrophilic polymer brushes assembled from surface-interacting polymer adsorbates, or directly grown by surface-initiated polymerizations (SIP) are chosen.

While growing efforts by polymer chemists have been focusing on varying the composition of polymer brushes in order to attain increasingly bioinert and lubricious surfaces, the precise modulation of polymer architecture has simultaneously enabled to substantially broaden the tuning potential for the above-mentioned properties. This featured article concentrates on reviewing this latter strategy, comparatively analysing how polymer brush parameters, such as molecular weight and grafting density, the application of block copolymers, the introduction of branching and crosslinks, or the variation of polymer topology beyond the simple, linear chains determine highly technologically relevant properties, such as biopassivity and lubrication.

Introduction

The design of biomaterials, medical devices and sensors often encompasses surface functionalization strategies aiming to impart to them well-defined interfacial physicochemical properties. These determine the way the functionalized materials interact with their application medium, and in most of the formulations, largely influence their performance.

The assembly of functional polymers yielding "polymer brush" layers[1] or, alternatively, the growth of polymer brushes from pre-modified supports through surface-initiated polymerization (SIP)[2-3] methods have emerged amongst the most versatile and efficient strategies to generate surfaces with tunable properties.

During the last decade, we have dedicated intense efforts in establishing robust fabrication protocols to generate polymer brushes with precise architecture and well-defined composition, especially concentrating on the influence of these two parameters on the biopassive and tribological properties of the obtained coatings.

The combination of high resistance towards unspecific protein adsorption and lubrication is often highly required on the exposed surface of biomaterials. On the one hand, hampering the formation of a protein layer would prevent microbial contamination, or an adverse immune response towards a synthetic construct when this is applied within physiological environments.[4-7] On the other hand, the presence of a lubricious coating would increase the comfort and prevent wounding when a modified device is placed in contact with tissues, such as in the case of contact lenses or catheters.[8-10]

A large number of hydrophilic polymers forming dense brush assemblies on surfaces can meet these needs due to the interplay between enthalpic and entropic effects. These are respectively determined by the association of water molecules within the brush structure, and the distinctive, stretched conformation characterizing densely grafted chains.[11-14] Hence, dense and hydrated polymer brushes efficiently prevent unspecific adhesion of biomolecules (and larger

biomolecular entities), due to their unfavourable de-hydration and the loss of conformational entropy involved when biomolecules adhere to the surface.[4, 11-14]

In addition, the interplay between high water content and the osmotic pressure generated within the brush provides fluid lubrication and load-bearing capacity, substantially reducing friction when a shearing countersurface is applied (Figure 1).[15-19]

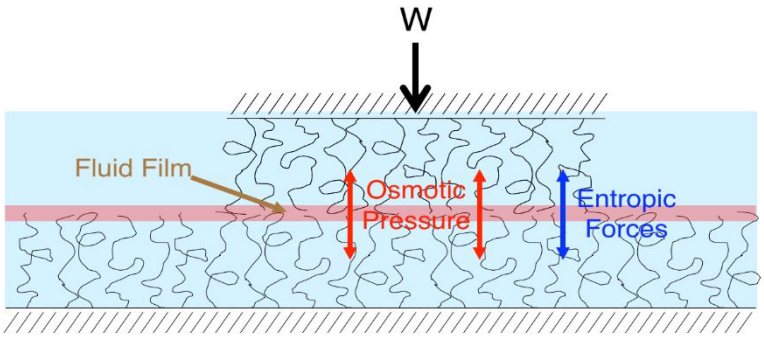

Figure 1. The lubricity of polymer brushes is due to a combination of osmotic pressure within the brush and the resistance to interpenetration of the two brushes due to entropic effects. (Reproduced with kind permission from Benetti et al.[20], Copyright 2019 John Wiley and Sons).

The design principle for biopassive and lubricious polymer brushes has primarily relied on a careful tuning of polymer composition, which allows one to enhance the hydration capacity of the assemblies while minimizing the presence of chemical functionalities that could trigger specific or unspecific interactions with the surrounding biological environment. Through this strategy, in addition to poly(ethylene glycol) (PEG)[13, 21-23] and its derivatives, several other polymers have progressively emerged as starting materials for fabricating brushes with improved antifouling properties and enhanced lubricity. These included polyzwitterions,[24-27] poly(acrylamide)s and poly(methacrylamide)s,[28-32] poly(2-alkyl-2-oxaoline)s (PAOXAs)[33-34] and very recently, poy(2-alkyl-2-oxazine)s (PAOZIs).[35]

However, besides their composition, polymer architecture (*i.e.* branching or topology) and structural properties (*i.e.* grafting density and/or thickness) represent additional parameters strongly affecting the physicochemical properties of brush assemblies, consequently

determining their resistance towards biological contamination, as well as their nanotribological properties.

In this paper, we summarize our recent efforts in the macromolecular design of polymer-brush interfaces, especially focusing on how polymer topology and the structural properties of the assemblies can be varied in order to modulate technologically relevant interfacial properties of the generated surfaces. In particular, we concentrate on bioinertness of polymer brushes, intended as protein and cell repellence, and lubrication properties of the grafted films.

While additionally reporting the most prominent, recent works by others, where polymer structure-brush properties relationships have been dissected, the main objective of this featured article is thus to derive from experimental works some general design principles, which for a given chemistry would enable to independently tune highly technologically relevant properties of polymer brushes, such as biopassivity and lubrication. Although we are aware that a comprehensive theoretical description of the brush structural parameters regulating these properties has been derived from several fundamental works, including simulations,[14-17, 36-42] to which we remand the reader, the focus of this report is rather on those studies that through experiments could rationalize the determinants for such interfacial properties of polymer brushes.

Modulation of Polymer-Brush Thickness and Grafting Density

The independent variation of the structural properties of homopolymer brushes represents a powerful tool to modulate both their interaction with biological environments, as well as to tune their lubrication properties. The main structural variables that can be readily adjusted in order to vary these characteristics are the molecular weight of the brushes, which directly correlates to brush thickness, and their grafting density (σ).[43-44, 14-16]

It is important to emphasize that the unspecific adhesion of proteins can provide an indirect indication about the way polymer-brush interfaces would interact with larger biological objects, such as cells or bacteria.[13-14, 41-42, 45] Nevertheless, enlarging resistance towards protein adsorption to a generalized antifouling behavior might be not valid for several systems.

The values of σ mainly determine the primary adsorption of proteins on polymer brushes, *i.e.* the unspecific interaction between the biomolecules and the underlying substrate.[14, 41-42] A variation of grafted-polymer coverage thus regulates the extent of protein intercalation within the brush assembly, with low-σ brushes enabling a relevant surface contamination especially by small globular proteins such as albumin (Figure 2).

In contrast, tuning of brush thickness, which for a given σ is directly correlated to the molecular weight of the grafted polymer, determines secondary protein adsorption.[14, 41-42] This phenomenon arises from long-range interactions between biomolecules approaching the brush-medium interface and the underlying substrate, and it can be efficiently hindered when brush thickness is finely adjusted, for instance by fabricating brushes via surface initiated controlled radical polymerizations (SI-CRPs).[2] Hence, the fabrication of sufficiently thick and densely grafted brushes can assure an efficient and durable resistance towards unspecific protein contamination.

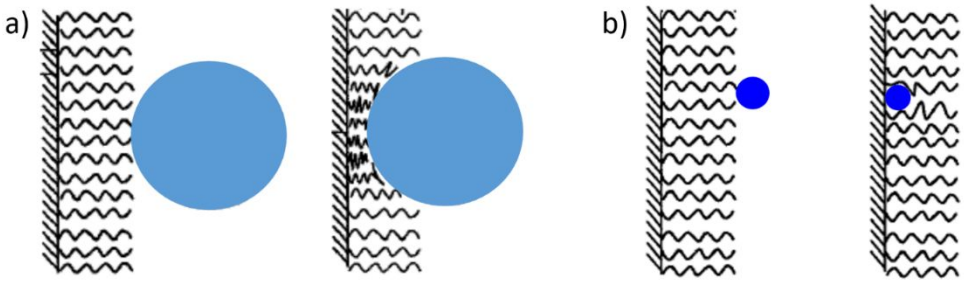

Figure 2. Large proteins can adsorb the outer edge on polymer brushes via secondary adsorption (a). In contrast, small proteins can intercalate within the brush structure undergoing primary adsorption (b). Reproduced from Halperin, A., Polymer Brushes that Resist Adsorption of Model Proteins: Design Parameters. *Langmuir* **1999,** *15* (7), 2525-2533, Copyright 1999 American Chemical Society.

When in addition to biopassivity high lubrication is sought, the composition of polymer brushes, *i.e.* their hydrophilic character, should be carefully considered while tuning the structural properties of the grafted assemblies. Friction progressively decreases with increasing brush thickness in the case of highly hydrophilic brushes, such as those based on polyzwitterions, due to the increment in the amount of water associated to the grafts with increasing their molecular weight (Figure 3).[46-49]

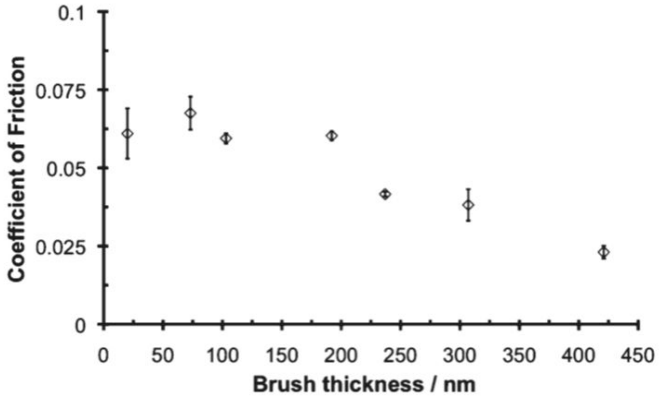

Figure 3. The coefficient of friction (μ) obtained by LFM on poly[2-(methacryloyloxy)ethylphosphorylcholine] (PMPC) brushes was shown to decrease with increasing brush thickness. Reproduced from Zhang, Z. Y.; Morse, A. J.; Armes, S. P.; Lewis, A. L.; Geoghegan, M.; Leggett, G. J., Effect of Brush Thickness and Solvent Composition on the Friction Force Response of Poly(2-(methacryloyloxy)ethylphosphorylcholine) Brushes. *Langmuir* **2011,** *27* (6), 2514-2521, Copyright 2011 American Chemical Society.

In contrast, brushes presenting an amphiphilic character, especially those based on poly(ethylene glycol) (PEG) and its derivatives, often showed an opposite behavior. This is the case of poly[(oligoethylene glycol)methacrylate] (POEGMA) brushes synthesized by surface-initiated atom transfer radical polymerization (SI-ATRP), which present an amphiphilic character in water, and showed a progressive increment in friction with increasing brush thickness when analyzed by lateral force microscopy (LFM) (Figure 4).[50] This phenomenon was ascribed to the increment in mechanical energy dissipation that arises while shearing

progressively thicker POEGMA brushes, which feature just a limited amount of solvent within their structure, and display adhesive hydrophobic interactions towards the atomic force microscopy (AFM) colloidal probe.

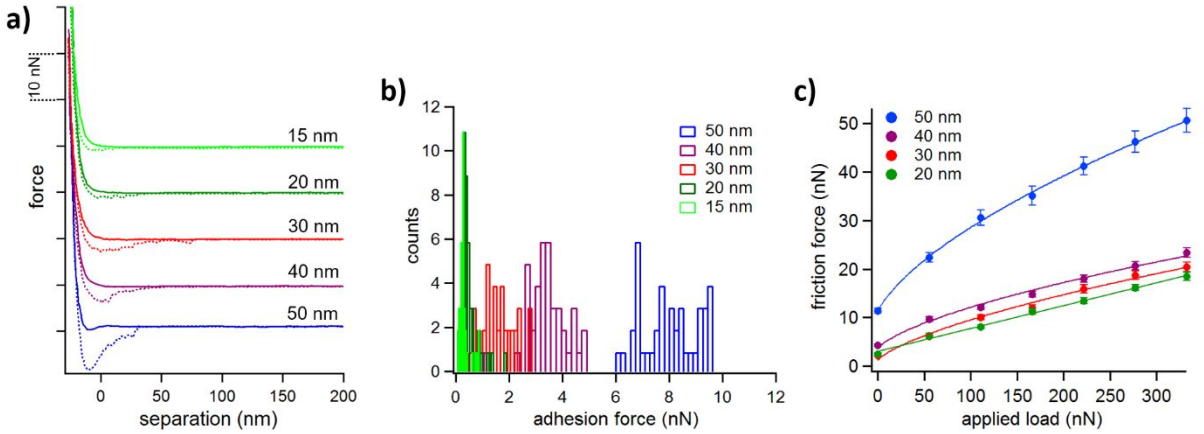

Figure 4. (a) Force-vs-separation (FS) profiles recorded on POEGMA brushes presenting different dry thicknesses (indicated in black along each FS profile). (b) Adhesion was shown to increase with brush thickness due to hydrophobic interactions between the silica-based AFM colloidal probe and POEGMA brushes. (c) Friction-vs-applied load profiles (F_fL) recorded by LFM highlighted how mechanical energy dissipation increased with increasing brush thickness, leading to a simultaneous increment in friction. Reproduced with permission from Ref. 50, Copyright 2015 John Wiley and Sons.

Similar results were recorded while studying the nanotribological properties of poly(N-isopropyl acrylamide) (PMIPAM) brushes below and above their lower critical solution temperature (LCST).[51] Below LCST, highly swollen PNIPAM brushes were characterized by an increment in lubricity with increasing thickness, due to the higher content of fluid lubricant incorporated within thicker brushes. In contrast, above LCST, PNIPAM brushes are poorly hydrated and friction increases with their thickness, due to the rising of dissipative forces when a shearing AFM probe is applied.

Differently from what has been observed while varying brush thickness, a variation of σ produced a similar effect on the nanotribological properties of hydrophilic and amphiphilic brushes. On both these types of assemblies, an increase in surface coverage of grafted chains

was mirrored by a concomitant reduction in friction. Generally, denser brushes displayed an augmented load-bearing capacity, due to the higher osmotic pressure generated within their structure with respect to that exerted by their more loosely grafted counterparts.[52-53] In addition, when polymer brushes are sheared against structurally identical brush-functionalized surfaces, an increment in grafting density translated into a reduction of interpenetration between opposing brushes,[16, 54] leading to a diminution of dissipative collisions between sheared chains, and a simultaneous decrease in the resulting friction (Figure 5).[52, 55-56]

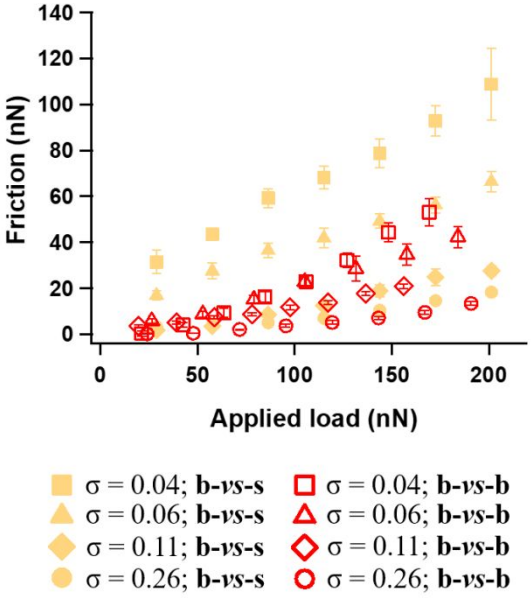

Figure 5. Friction-vs-applied load (F_fL) profiles recorded by LFM on poly(2-ethyl-2-oxazoline) (PEOXA) brushes presenting different values of σ. A reduction in friction was observed by increasing σ both when PEOXA brushes were sheared against a bare, silica-based colloidal AFM probe (b-*vs*-s), and when an identical brush was applied as countersurface (b-*vs*-b). Reproduced from Divandari, M.; Trachsel, L.; Yan, W. Q.; Rosenboom, J. G.; Spencer, N. D.; Zenobi-Wong, M.; Morgese, G.; Ramakrishna, S. N.; Benetti, E. M., Surface Density Variation within Cyclic Polymer Brushes Reveals Topology Effects on Their Nanotribological and Biopassive Properties. *ACS Macro Lett.* **2018,** *7* (12), 1455-1460, Copyright 2018 American Chemical Society.

Mixed and Copolymer Brushes

The fabrication of polymer brushes including compositionally diverse homopolymer, random or block copolymer grafts enables to precisely tune the biopassive and nanotribological properties of the generated surfaces.

After the seminal works by Stamm and Minko, where the morphological and interfacial physicochemical properties of mixed brushes in response to selective solvents were thoroughly investigated,[57-62] increasing efforts have been subsequently dedicated in synthesizing structurally similar assemblies capable of shifting their affinity towards proteins and/or their nanotribological properties.

Mixed brushes featuring tunable biopassivity were successfully synthesized following a general design principle, where two chemically different grafts are sequentially grafted to a functional surface,[61] or consecutively grown by SI-CRP from initiator-bearing substrates.[63-70] In most of these cases, mixed brushes comprised a biopassive component intercalated with an additional graft-type capable of changing its swelling properties or charge density in response to a variation in temperature, pH or ionic strength.

In the exemplary cases of ionizable poly(acrylic acid) or poly(methacrylic acid) (PAA and PMAA, respectively) grafts mixed with PEG[71-72] or poly(2-methyl-2-oxazoline) (PMOXA)[73-74] analogues, pH and ionic strength could be varied in order to modulate the exposure of the non-ionic and biopassive components at the interface, finally enabling the capture and successive release of proteins from the surrounding medium.

Through this strategy, and via the fine adjustment of molecular weight and relative content of PEG grafts within PAA/PEG mixed brushes, the selective and reversible physisorption of defined biomolecules from mixtures of different protein types could be additionally accomplished.[75]

Alternatively, by combining thermoresponsive poly(N-isopropylacrylamide) (PNIPAM) grafts with PAA analogues, switching of the affinity towards proteins could be triggered by varying the temperature of the medium, and it could further amplified by tuning of the relative content of each component at the surface.[76]

Switching of bioadhesion on polymer brushes could be also accomplished by synthesizing random copolymer grafts that incorporate different relative contents of amphiphilic, hydrophobic and charged co-monomers. Similarly to the case of mixed brushes, where the overall composition of the assemblies was tuned in order to amplify switching of properties, a careful adjustment of the relative content of each co-monomer was exploited to enhance the variation of interfacial properties of the generated brush in response to a temperature change, efficiently shifting the character of the surface from bio-repellent to bio-adhesive. This strategy was successfully exploited by Okano et al. in order to stimulate the adhesion of different cells and subsequently release them following proliferation, yielding freestanding cell sheets, or to trigger attachment and release from the surface of a particular cell type from mixtures.[77-83]

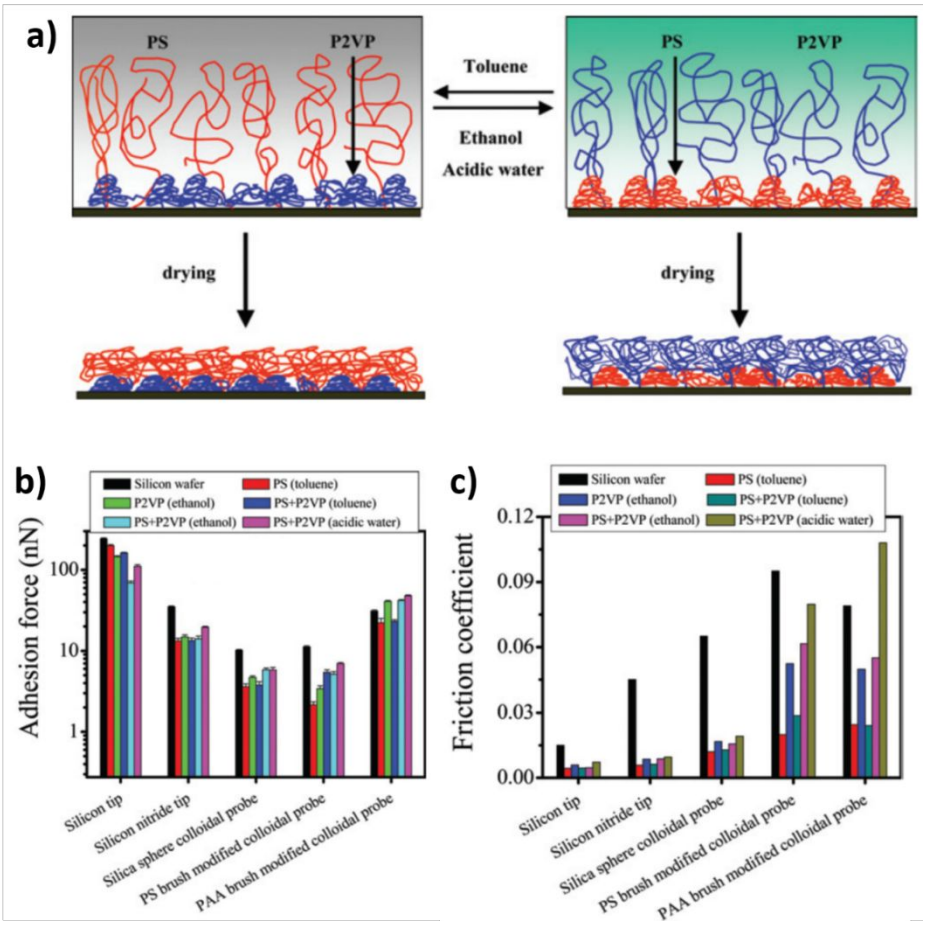

Figure 6. (a) The interfacial morphology of polystyrene (PS)-poly(2-vinylpyridine) (P2VP) mixed brushes was modulated by treating them with selective solvents. In this way, and by

simultaneously varying the composition of the brush grafted on the AFM colloidal probe, both adhesive properties (b) and friction (c) could be tuned. Reproduced from Ref. 84, Copyright 2008 Royal Society of Chemistry.

Mixed brushes featuring two immiscible polymer graft that can be selectively swollen in different solvent environments were additionally applied to modulate adhesion and friction at surfaces. In particular, grafted assemblies including polystyrene (PS) and poly(2-vinylpyridine) (P2VP) could significantly vary their morphology and interfacial composition in response to the exposure to selective solvents (toluene and ethanol/water) (Figure 6a).[84] In this way, adhesive and lubrication properties could be shifted by an order of magnitude, and further tuned as a function of the composition of the probe used as countersurface for the adhesion/friction force measurements (Figure 6b and 6c).

A significant alteration of the interfacial physicochemical properties of polymer brushes could be accomplished by mixing two non-ionic grafts that are both soluble in water, such as PEG and PMOXA or poly(2-ethyl-2-oxazoline) (PEOXA).[85] Surface dilution of a grafted component with a compositionally different analogue led to an increment in the hydration of the entire assembly, with a consequent improvement in its resistance towards protein contamination. Moreover, in combination with the increased brush swelling achieved through mixing, the inclusion of PEG grafts that are characterized by a low glass transition temperature (T_g) within PMOXA and PEOXA brushes (with $T_g \geq 70°C$) significantly reduced friction with respect to that measured on the corresponding homopolymer brushes, especially when relatively high pressures were applied (Figure 8).[35]

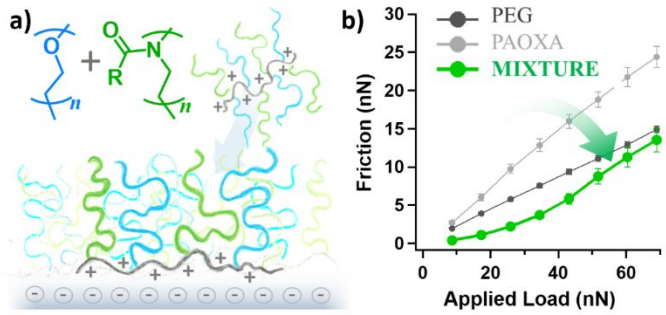

Figure 8. Mixed brushes featuring PEG and PAOXA grafts (a) showed an improved lubricity if compared to PEG- and PAOXA-based single-component brushes (b). Reproduced from Morgese, G.; Gombert, Y.; Ramakrishna, S. N.; Benetti, E. M., Mixing Poly(ethylene glycol) and Poly(2-alkyl-2-oxazoline)s Enhances Hydration and Viscoelasticity of Polymer Brushes and Determines Their Nanotribological and Antifouling Properties. *ACS Appl. Mater. Interfaces* **2018,** *10* (48), 41839-41848, Copyright 2018 American Chemical Society.

Besides studying the properties of grafts presenting two or more components mixed on the same substrate, the immiscibility between chemically diverse homopolymer brushes grafted from different surfaces allowed de Beer et al. to substantially hinder brush interpenetration when these two assemblies are sheared one against each other.[36] The consequent reduction of dissipative forces between opposing grafts sliding in opposite directions[17-18, 37] generated a substantial reduction in the coefficient of friction (μ) if compared to that measured by shearing identical, interpenetrating brushes.

It is also important to emphasize that a comparable suppression of brush interdigitation, with a concurrent improvement in lubricity, could be potentially accomplished by substituting one of the two countersurfaces with a responsive brush capable of varying its swelling and conformation in response to a physical stimulus, such as a shift in pH or temperature.[37, 86]

An alternative approach for broadening the functional character of polymer brushes and expand their physicochemical properties has encompassed the application of (multi)block copolymer grafts, typically synthesized by sequential SI-CRP methods.[2]

Especially in the designing of biointerfaces, hierarchical brush structures including a substrate-bound, biopassive block, and functional/bioactive interfacial segments have been applied for

regulating the adhesion of cells and bacteria. This general design enabled the fabrication of coatings capable of repelling bacteria, as well as displaying bactericidal properties.[87-88] Similar block copolymer brushes have been applied to functionalize the surface of biosensors, where just one brush block can selectively bind analytes from solution.[89-92]

Alternatively, functional block copolymer brushes have been exploited to trigger the adhesion of cells and simultaneously modulate their response.[93-97] Generally, within these brush formulations one or more brush segments feature a biopassive character, although their tunable physical properties are exploited to regulate the behavior of cells, whose attachment to the surface is stimulated by the presence of functional cues on the other blocks.

Block copolymer brushes characterized by an alternation of biopassive and cell-adhesive blocks were applied to modulate the surface exposure of covalently bound peptides, which were "buried" by interfacial brush segments of different molecular weights,[93-94] and whose presentation at the interface could be altered when the bioinert segments feature temperature-dependent swelling properties.[98]

Following this strategy, the morphology of adhering cells and their attachment on the brush interface could be precisely adjusted, suggesting possible strategies to influence cell's behavior (proliferation and/or differentiation) on biomaterials previously modified with different brush architectures.

The influence of the physicochemical properties of cell-adhesive brush films on the adhesion of different cell types could be dissected by designing block copolymer brushes including a substrate-bound brush block with variable degree of crosslinking and an interfacial linear brush decorated with cell-adhesive cues.[99] In particular, Schönherr et al. demonstrated how the nanomechanical properties of polyacrylamide (PAAm) brushes could be precisely varied by tuning of the relative concentration of acrylamide/bisacrylamide during SI-ATRP (Figure 9a). Simultaneously, an interfacial brush based on PAA functionalized with arginine-glycine-

aspartic acid (RGD)-containing peptides guaranteed a comparable cell-adhesive character to the exposed surface. In this way, the effect of underlying brush' stiffness on the behavior of both fibroblasts and cancer cells could be addressed independently of the morphology and composition of the interface (Figure 9b and 9c).

In addition to the fabrication of protein- or cell-responsive surfaces, block copolymer brushes including a hydrophobic, substrate-bound block and hydrophilic interfacial segments were applied in order to increase the long-term stability of polymer brush coatings within particularly aggressive media, such as cell culture solutions or salty waters, and to preserve their distinctive interfacial properties, otherwise undergoing a progressive alteration during brush degradation.

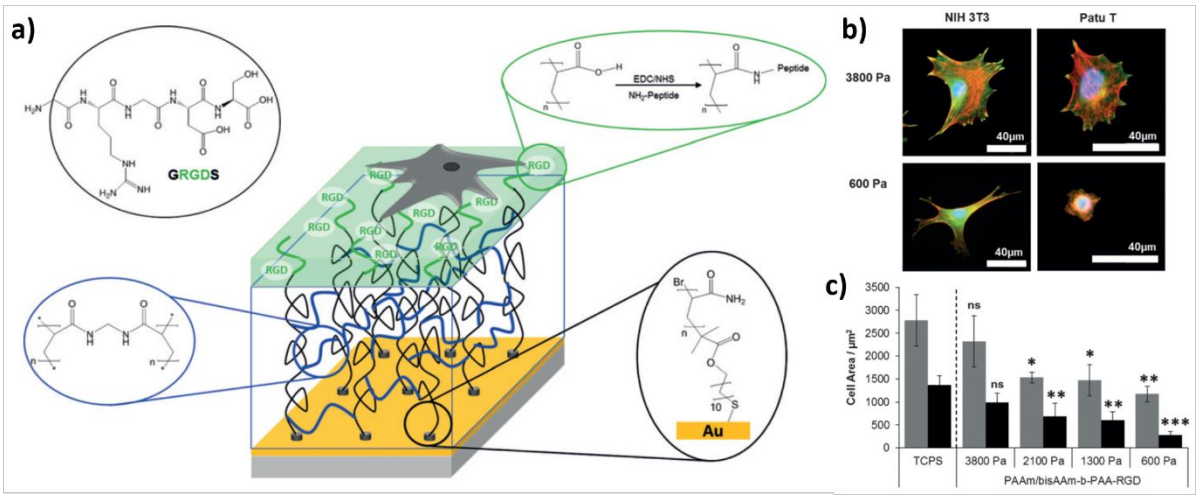

Figure 9. (a) Block copolymer brushes featuring a substrate bound, crosslinked PAAm brush hydrogel with variable stiffness, and an interfacial PAA brush functionalized with peptide-based cues were applied to study the attachment of different cell types and their cytoskeleton organization (b,c). (Reproduced from Ref. 99, Copyright 2016 John Wiley and Sons).

For instance, the resistance of poly(sulfobetaine methacrylamide) (PSBMAm)[100] and poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) brushes[101] towards hydrolytic degradation and degrafting could be significantly improved by including hydrophobic brush blocks as protective layers bound to the underlying substrates. The presence of either PMMA, polystyrene (PS) or poly(glycidyl methacrylate) (PGMA) segments, all of which formed a

collapsed, substrate-bound layer, preserved the structural integrity of the highly swollen PSBMAm and PMPC grafts at the interface, maintaining their attractive biopassive and lubrication properties (Figure 10).[101]

In a similar way, the stability of PMAA[102] and poly[(oligoethylene glycol)methacrylate] (POEGMA)[103] brushes was significantly improved by the presence of substrate-bound PMMA blocks, which protected the underlying initiator functions from hydrolysis. Especially POEGMA-b-PMMA block copolymer brushes showed comparable biopassive properties and lubricity with respect to POEGMA homopolymer analogues, whereas the hydrophobic PMMA underlayer improved the structural stability of the entire films by several days under cell culture media at 37°C.[103]

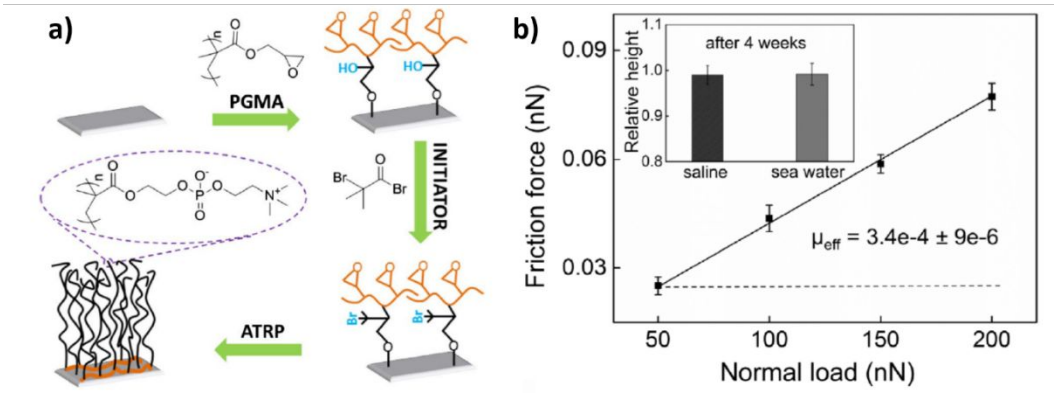

Figure 10. PMPC brushes grafted by SI-ATRP from initiator-bearing PGMA underlayers (a) preserve their structural properties even after 4 weeks of incubation in salty waters, and maintain their lubricious character, as evidenced by LFM measurements (b). Reproduced from Ref. 101, Copyright 2017 Elsevier Ltd..

Branched and Crosslinked Polymer Brushes

Polymer adsorbates featuring a branched architecture were applied to generate biopassive, brush-like assemblies on a variety of inorganic and organic substrates. The most prominent examples included hyperbranched polyglycerol (hPG)[104-105] and PEG adsorbates.[106-108]

Assemblies featuring hPG dendrons and dendrimers showed excellent resistance towards the unspecific surface contamination by proteins, cells and bacteria, often surpassing the antifouling properties displayed by linear polyglycerol brushes, and in several cases matching those showed by densely grafted PEG analogues.[109-112]

Dendronized PEG adsorbates assembled on TiO_2 surfaces via catechol-based anchors formed brushes that were less hydrated and more rigid (less viscoelastic) with respect to their linear PEG counterparts (Figure 11).[107] However, dendronized PEG brushes showed a resistance towards the adsorption of undiluted full human serum (FHS) comparable to that showed by highly swollen linear PEG assemblies. These results suggested that hydration might not represent a strict determinant for biopassivity in the case of brushes presenting an hyperbranched structure, which could thus compensate their reduced swelling with a concomitant increment in surface passivation.

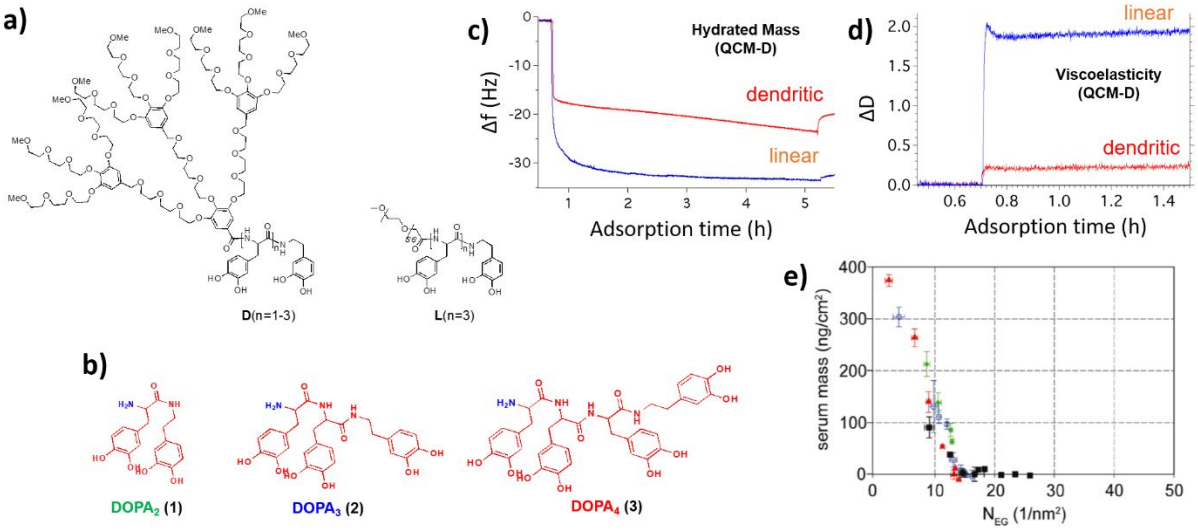

Figure 11. Dendronized PEG adsorbates (a) presenting multi-catechol anchors (b) formed brushes on TiO_2 surfaces that featured lower swelling compared to linear PEG analogues (c) and higher rigidity (d), as measured by monitoring frequency (Δf) and dissipation (ΔD) shifts with quartz crystal microbalance with dissipation (QCM-D). However, both linear and dendronized PEG brushes showed a comparable biopassivity when exposed to FHS (e), as recorded by variable angle spectroscopic ellipsometry (VASE) on assemblies featuring different polymer surface coverages (expressed as number of ethylene glycol units, N_{EG}, per nm^2). Reproduced from Gillich, T.; Benetti, E. M.; Rakhmatullina, E.; Konradi, R.; Li, W.; Zhang, A.; Schluter, A. D.; Textor, M., Self-Assembly of Focal Point Oligo-catechol Ethylene

Glycol Dendrons on Titanium Oxide Surfaces: Adsorption Kinetics, Surface Characterization, and Nonfouling Properties. *J. Am. Chem. Soc.* **2011,** *133* (28), 10940-10950, Copyright 2011 American Chemical Society.

The biopassive properties displayed by grafted-from polymer brushes featuring side chains with different degree of branching further highlighted the effect of brush architecture on its resistance towards unspecific biological contamination. In particular, the groups of Haag and Huck compared the antifouling properties of glycerol-containing linear polymethacrylate brushes synthesized by SI-ATRP with those displayed by analogous grafts featuring linear, first- and second-generation dendritic polyglycerol side chains.[113] From this comparative analysis, brushes including branched side chains were characterized by excellent biopassivity within FHS and undiluted blood plasma, with first-generation polygycerol-bearing brushes outperforming all the other tested coatings.

In addition to branching, an alternative approach to modulate both biopassivity and lubrication properties relied on the introduction of covalent or physical crosslinks between surface-grafted chains.

Brush-hydrogels of diverse compositions and including different concentrations of crosslinks could be easily synthesized by SI-ATRP, mixing mono and bi-functional monomers within the polymerization mixture.[114-118] Due to the intrinsic architecture of polymer brushes, which are characterized by polymer grafts immobilized by one chain end to the same substrate, the introduction of even a relatively low concentration of crosslinker, or a slight variation in its content, translated into a significant shift of the interfacial physicochemical properties of the resulting films.

For instance, crosslinking poly(hydroxyethyl methacrylate) (PHEMA) brushes with ~ 1 mol% of di(ethylene glycol) dimethacrylate (DEGDMA) reduced by nearly 20% the swelling ratio of the brushes, and significantly reduced their conformational freedom.[119] These changes in brush structure and properties eventually led to a twofold increment in the amount of proteins

physisorbed on brush-hydrogels from FHS, if compared to that recorded on the corresponding linear PHEMA brushes presenting comparable dry thickness (Figure 12a).

Interestingly, the substitution of DEGDMA with an equimolar amount of longer, tetra(ethylene glycol)dimethacrylate (TEGDMA) reduced the loss of biopassive properties observed on PHEMA-DEGDMA brush-hydrogels, presumably due to the increment in the overall content of water-associating ethylene glycol units within the films.

Irrespective of their composition, the introduction of covalent crosslinks between grafts and the simultaneous decrease in the content of fluid lubricant within the films caused a significant increase in friction. As an example, the coefficient of friction (μ) measured in water by lateral force microscopy (LFM) on PHEMA brushes increased from 0.49 to 0.67 and 0.76 when the grafted chains were crosslinked by 1 and 2 mol% of DEGDMA, respectively (Figure 12b and 12c).[120]

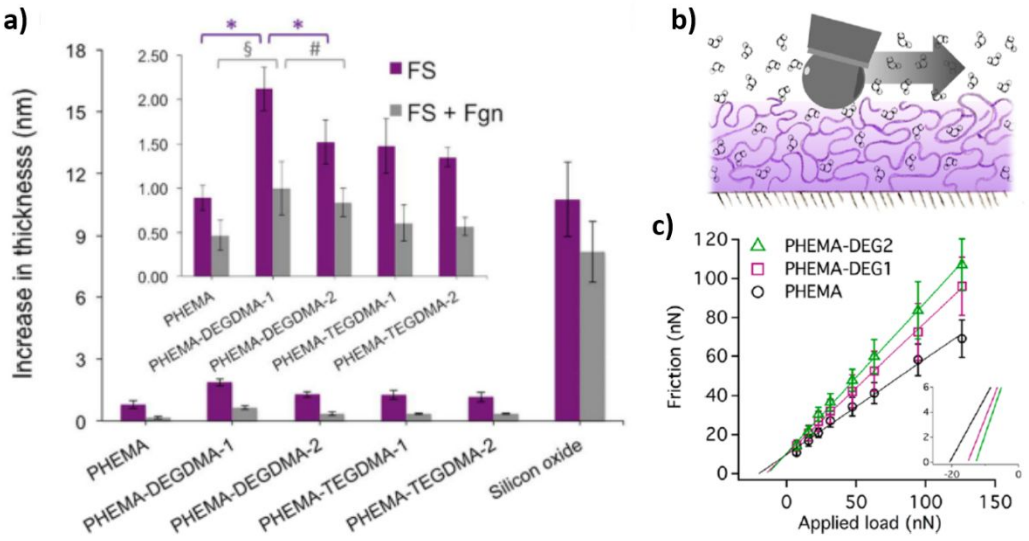

Figure 12. Adsorbed protein thickness on the different PHEMA brushes and brush-hydrogels measured by VASE following 90 minutes of incubation in FHS (violet bars) and FHS with added fibrinogen (Fgn) (gray bars). ∗ indicates a statistically significant difference analyzed by ANOVA test $P < 0.0001$, § refers to $P < 0.001$, and # indicates $P < 0.05$. Reproduced from Dehghani, E. S.; Spencer, N. D.; Ramakrishna, S. N.; Benetti, E. M., Crosslinking Polymer Brushes with Ethylene Glycol-Containing Segments: Influence on Physicochemical and Antifouling Properties. *Langmuir* **2016,** *32* (40), 10317-10327, Copyright 2016 American Chemical Society. The values of μ recorded on PHEMA brushes and brush hydrogels by LFM

(b) could be precisely modulated by varying the content of DEGDMA crosslinker between 1 and 2 mol%. Reproduced from Dehghani, E. S.; Ramakrishna, S. N.; Spencer, N. D.; Benetti, E. M., Controlled Crosslinking Is a Tool To Precisely Modulate the Nanomechanical and Nanotribological Properties of Polymer Brushes. *Macromolecules* **2017,** *50* (7), 2932-2941, Copyright 2017 American Chemical Society.

A more pronounced reduction in lubricity was observed in the case of more hydrophilic polymer grafts,[30, 121-122] such as polyacrylamide (PAAm) brushes synthesized by surface-initiated photoiniferter-mediated polymerization (SI-PIMP),[123-124] and crosslinked by 0.1-5 mol% of bisacrylamide (bisAAm).[30, 122] In particular, PAAm brush-hydrogels presenting 5 mol% of bisAAm showed a tenfold decrease in swelling properties in water, and a concomitant increment in μ by more than an order of magnitude.

Besides the fabrication of covalent brush networks, the designing of polymer brushes that could be reversibly crosslinked through the formation of organometallic complexes between linear grafts, enabled the fabrication of surfaces presenting switchable swelling and nanotribological properties.[125-127] In the chemically simplest case, linear PHEMA brushes bearing succinic acid-based side chains (PHEMA-SA) could be reversibly crosslinked by treatment with divalent metal ions, such as Zn^{II} and Ca^{II} (Figure 13a).[126] Tuning of the pH during the formation of the polymer-metal complexes enabled the synthesis of either mono- or bidentate bridges between the grafts (Figure 13b), generating brush networks with pronounced differences in swelling and lubrication properties (Figure 13c and 13d). Brush networks including Zn^{II} ions thus showed a reversible shift in μ from 0.8, when more strongly crosslinked dehydrated structures were formed via bidentate complexes, to 0.03 in the case of more compliant and swollen networks based on monodentate bridges (Figure 13d).

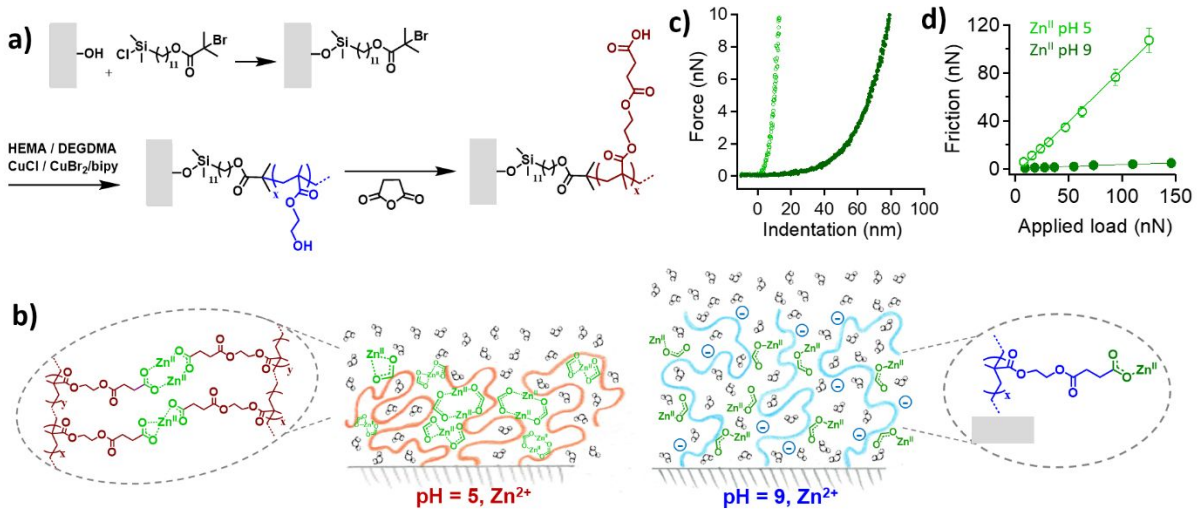

Figure 13. PHEMA-SA brushes were synthesized by SI-ATRP followed by derivatization with succinic anhydride (a). When PHEMA-SA brushes were treated with 10 mM Zn^{2+} solution at pH 5, bridging and chelating complexes were formed, while in 10 mM Zn^{2+} at pH 9 brush networks presenting monodentate conjugates were obtained (b). Force-vs-indentation (FI) and F_fL profiles recorded by AFM on PHEMA-SA-Zn^{II} brushes highlight how the swelling and lubrication properties were determined by the formation of different types of crosslinks between the PHEMA-SA grafts. Reproduced from Dehghani, E. S.; Naik, V. V.; Mandal, J.; Spencer, N. D.; Benetti, E. M., Physical Networks of Metal-Ion-Containing Polymer Brushes Show Fully Tunable Swelling, Nanomechanical and Nanotribological Properties. *Macromolecules* **2017,** *50* (6), 2495-2503, Copyright 2017 American Chemical Society.

Polymer Brushes Presenting Cyclic and Loop Topologies

Recent studies from our group have highlighted that shifting the topology of polymer brushes from simple, linear chain to their cyclic counterparts, while keeping their composition and molecular weight constant, determined a pronounced alteration of biopassivity and lubrication.[52-53, 55, 128-133]

Due to their more compact molecular dimensions,[134-137] cyclic polymer adsorbates assembling on inorganic and organic substrates tend to generate much denser brushes with respect to their linear analogues, providing an exceptional steric stabilization to the functionalized surfaces. This "topological effect" translates into films that show an enhanced resistance towards biological contamination due to the exceptional osmotic pressure rising from dense cyclic brushes, as it was demonstrated for PEOXA and PMOXA assemblies on TiO_2,[52-53, 55, 132-133] F_2O_3[140] and SiO_x surfaces.[128]

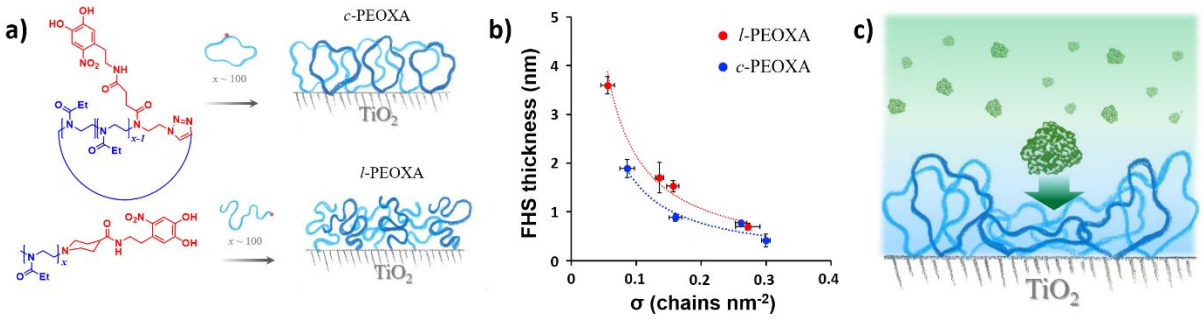

Figure 14. (a) Linear and cyclic PEOXA adsorbates featuring catechol anchors assemble on TiO_2 surfaces yielding topologically different PEOXA brushes (indicated as *c*-PEOXA and *l*-PEOXA, respectively). (b) *c*-PEOXA brushes showed an improved biopassivity towards FHS across a wide range of grafting densities with respect to *l*-PEOXA analogues. (c) The increased resistance towards unspecific protein contamination by cyclic brushes is ascribed to the additional steric barrier provided by the cyclic topology of the grafts. Reproduced from Divandari, M.; Trachsel, L.; Yan, W. Q.; Rosenboom, J. G.; Spencer, N. D.; Zenobi-Wong, M.; Morgese, G.; Ramakrishna, S. N.; Benetti, E. M., Surface Density Variation within Cyclic Polymer Brushes Reveals Topology Effects on Their Nanotribological and Biopassive Properties. *ACS Macro Lett.* **2018,** *7* (12), 1455-1460, Copyright 2018, American Chemical Society.

It is important to emphasize that the steric constraints introduced during cyclization of polymer adsorbates provide an additional barrier towards unspecific interaction with adsorbing biomolecules, determining a slight but significant improvement in biopassivity for cyclic brushes across a wide range of surface densities, when compared to structurally and chemically identical linear analogues (Figure 14).[52, 55]

The absence of interfacial chain ends, which is intrinsic in the cyclic topology, additionally hinders brush interpenetration when opposing assemblies are compressed and sheared against each other,[18-19, 138-139] providing to cyclic brushes a superlubricious character.[52, 132-133] As a result of the combined effects of suppression of dissipative forces between cyclic-brush countersurfaces, and increased steric stabilization of the underlying substrates, which leads to an improved load-bearing capacity, even amphiphilic cyclic PEOXA brushes in water provide values of μ as low as 10^{-3}, nearly reaching the lubricity typically displayed by highly hydrophilic polyzwitterionic-based linear analogues (Figure 15).[26]

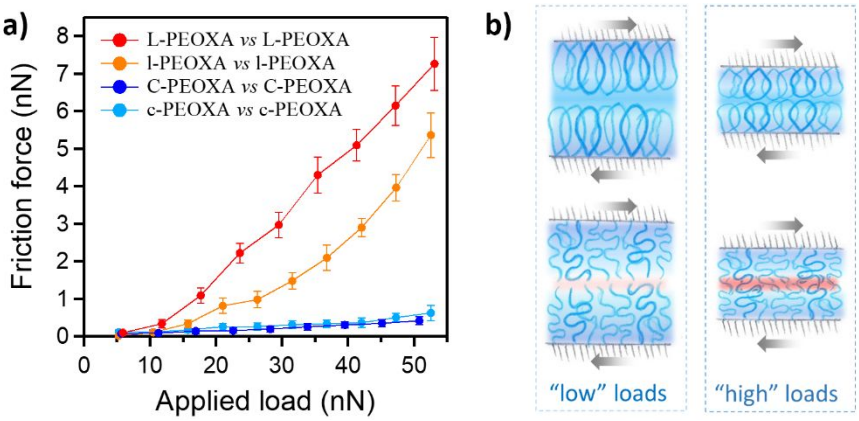

Figure 15. (a) F_fL profiles recorded by LFM while shearing PEOXA brushes against topologically identical brush-bearing countersurfaces (b). In (a), the F_fL profiles for 10 and 5 kDa linear PEOXA brushes (*L* and *l*-PEOXA, respectively) are compared to those recorded while shearing cyclic PEOXA bushes of 10 and 5 kDa (*C*- and *c*-PEOXA, respectively). Reproduced from Divandari, M.; Morgese, G.; Trachsel, L.; Romio, M.; Dehghani, E. S.; Rosenboom, J. G.; Paradisi, C.; Zenobi-Wong, M.; Ramakrishna, S. N.; Benetti, E. M., Topology Effects on the Structural and Physicochemical Properties of Polymer Brushes. *Macromolecules* **2017,** *50* (19), 7760-7769, Copyright 2017, American Chemical Society.

The unique biopassivity and lubricity of polymer brushes constituted by cyclic macromolecules triggered their application on supports where both these properties are highly required, such as in the case of the articular cartilage. Especially during degenerative syndromes that alter the content of natural biolubricants present in the synovial fluid,[140-144] as in the case of osteoarthritis (OA), tissue adhesive graft-copolymers[145] forming a cyclic brush layer on the exposed collagenous surface of cartilage were demonstrated to re-establish its lubrication properties, and protect it from the enzymatic degradation connected to OA progression.[129]

Biopassive and nanotribological characteristics similar to those displayed by cyclic brushes could be observed on "loop"-forming grafts, usually assembled on surfaces from telechelic polymer-based or multifunctional copolymer adsorbates.[53, 146-155] Interestingly, even a relatively low surface concentration of residual linear chain ends exposed at the interface was identified as a factor strongly influencing the lubricious character of loop brushes, while increasing the loops-to-linear "tails" ratio was accompanied by a progressive improvement of

both biopassivity and lubrication, gradually approximating the interfacial properties of cyclic brushes (Figure 16).[53]

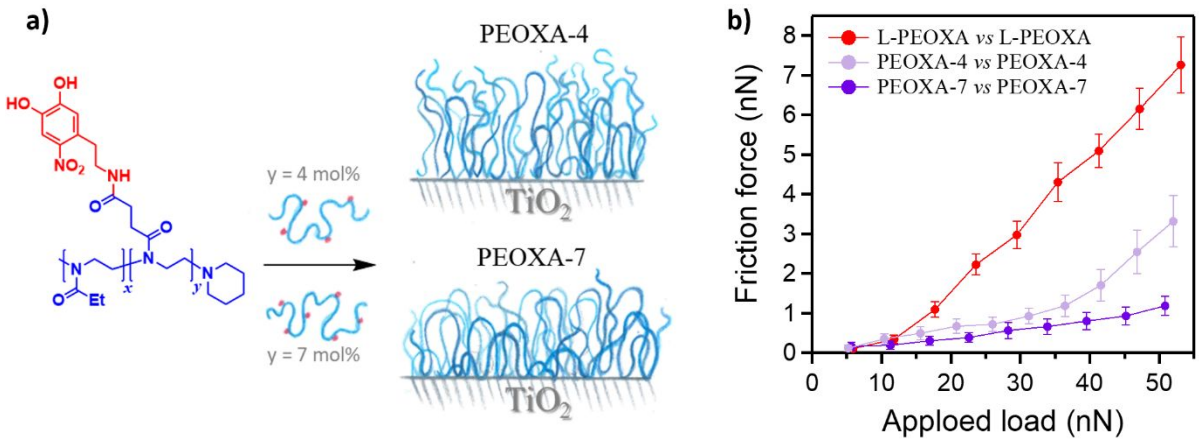

Figure 16. (a) PEOXA brushes featuring a mixture of loops and linear tails are assembled on TiO_2 surfaces from random PEOXA copolymers including 4 and 7 mol% of catechol-bearing co-monomers (indicated as PEOXA-4 and PEOXA-7, respectively). In (b) F_fL profiles for linear PEOXA brushes of 10 kDa (*L*-PEOXA) are compared to those recorded on PEOXA-4 and PEOXA-7. Reproduced from Divandari, M.; Morgese, G.; Trachsel, L.; Romio, M.; Dehghani, E. S.; Rosenboom, J. G.; Paradisi, C.; Zenobi-Wong, M.; Ramakrishna, S. N.; Benetti, E. M., Topology Effects on the Structural and Physicochemical Properties of Polymer Brushes. *Macromolecules* **2017,** *50* (19), 7760-7769, Copyright 2017, American Chemical Society.

Conclusions and Perspectives

During the last decade of research, increasing efforts have been spent in designing polymer interfaces on solid surfaces with molecular precision, in order to modulate interfacial physicochemical properties that are fundamental in the fabrication, modification and performance of devices, ranging from sensors to tissue engineering supports. The reduction of unspecific biological contamination and lubrication have represented two of the most required properties, especially when synthetic materials are expected to integrate within physiological media without altering their interfacial composition, and if a minimization of the mechanical stress towards the surrounding environment when shear is applied is sought.

In order to meet these needs, the composition of polymer brush-based coatings has been progressively optimized in order to reach full biopassivity within highly contaminating media, such as blood and serum, reduce polymer degradation even after long incubation times, and simultaneously increment lubricity. While attaining increasingly bioinert and lubricious surfaces has encompassed the application of highly hydrated polymer brushes, for instance featuring polyzwitterions,[156] the modulation of polymer-brush architecture has concomitantly emerged as an additional method to broaden the tuning potential for the above-mentioned properties.

In particular, while keeping the composition of a polymer assembly constant, the translation of topology effects under the confinement of a grafting surface has enabled to significantly alter interfacial physicochemical properties that determine the performance of polymer brushes within physiological environments.

Especially in our works we demonstrated that the application of branched or looped polymer architectures substantially altered steric stabilization and viscoelasticity of brush assemblies, providing a more efficient barrier towards unspecific contamination by biomolecules, and suggesting new approaches for suppressing mechanical energy dissipation under shear, and reduce friction.

The introduction of covalent or physical crosslinks between grafts, yielding brush gels or hydrogels, enabled to precisely tune the nanomechanical and nanotribological properties of the obtained films, and provided a tool to modulate their swelling properties.

Alternatively, the application of block copolymer and mixed brushes enlarged the tuning potential for interfacial composition, and allowed one to generate assemblies that can vary their nanomorphology in response to selective solvent environments, often improving the structural stability of the entire coating within aggressive media.

Despite the wealth of possibilities in the molecular structuring of polymer brushes, even the most sophisticated polymer architectures have been always characterized by a constant or "quenched" structure, which enabled just limited conformational transitions in response to *e.g.* a variation of temperature or solvent quality. Hence, it has become progressively evident that one of the next challenges that will involve polymer and materials chemists will deal with the realization of soft-matter interfaces characterized by a "dynamic" architecture, which can remodel itself via topological transformations of its macromolecular constituents,[157-158] in this way modulating surface interaction with the surrounding medium.

Simultaneously, a growing need for controlled SI-CRP processes, compatible with ambient conditions, and scalable to large and morphologically different substrates has emerged. Following closely the development of oxygen-tolerant reversible deactivation radical polymerization (RDRP) processes in solution,[159] several methods enabling the living growth of polymer brushes in the presence of oxygen, and which are applicable on extremely large substrates while using just microliter-volumes of reaction mixtures were proposed.[160-166]

Collectively, all these ongoing and future challenges involve experts from different fields of chemistry, physics and materials science, who are concentrating not only on defining new chemistries for the fabrication of polymeric biointerfaces, but also developing coating processes, and establishing robust analytical methods for dissecting interfacial properties.

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Competing interests

The author declares no competing interests.

References

1. Zdyrko, B.; Luzinov, I., Polymer Brushes by the "Grafting to" Method. *Macromol. Rapid Commun.* **2011,** *32* (12), 859-869.
2. Zoppe, J. O.; Ataman, N. C.; Mocny, P.; Wang, J.; Moraes, J.; Klok, H. A., Surface-Initiated Controlled Radical Polymerization: State-of-the-Art, Opportunities, and Challenges in Surface and Interface Engineering with Polymer Brushes. *Chem. Rev.* **2017,** *117* (5), 4667-4667.
3. Krishnamoorthy, M.; Hakobyan, S.; Ramstedt, M.; Gautrot, J. E., Surface-Initiated Polymer Brushes in the Biomedical Field: Applications in Membrane Science, Biosensing, Cell Culture, Regenerative Medicine and Antibacterial Coatings. *Chem. Rev.* **2014,** *114* (21), 10976-11026.
4. Banerjee, I.; Pangule, R. C.; Kane, R. S., Antifouling Coatings: Recent Developments in the Design of Surfaces That Prevent Fouling by Proteins, Bacteria, and Marine Organisms. *Adv. Mater.* **2011,** *23* (6), 690-718.
5. Raynor, J. E.; Capadona, J. R.; Collard, D. M.; Petrie, T. A.; García, A. s. J., Polymer brushes and self-assembled monolayers: Versatile platforms to control cell adhesion to biomaterials. *Biointerphases* **2009,** *4*, FA3.
6. Moroni, L.; Gunnewiek, M. K.; Benetti, E. M., Polymer brush coatings regulating cell behavior: Passive interfaces turn into active. *Acta Biomater.* **2014,** *10* (6), 2367-2378.
7. Hadjesfandiari, N.; Yu, K.; Mei, Y.; Kizhakkedathu, J. N., Polymer brush-based approaches for the development of infection-resistant surfaces. *J. Mater. Chem. B* **2014,** *2* (31), 4968-4978.
8. Yu, K.; Lo, J. C. Y.; Yan, M.; Yang, X. Q.; Brooks, D. E.; Hancock, R. E. W.; Lange, D.; Kizhakkedathu, J. N., Anti-adhesive antimicrobial peptide coating prevents catheter associated infection in a mouse urinary infection model. *Biomaterials* **2017,** *116*, 69-81.
9. Bozukova, D.; Pagnoulle, C.; De Pauw-Gillet, M. C.; Desbief, S.; Lazzaroni, R.; Ruth, N.; Jerome, R.; Jerome, C., Improved performances of intraocular lenses by poly(ethylene glycol) chemical coatings. *Biomacromolecules* **2007,** *8* (8), 2379-2387.
10. Gensheimer, W. G.; Kleinman, D. M.; Gonzalez, M. O.; Sobti, D.; Cooper, E. R.; Smits, G.; Loxley, A.; Mitchnick, M.; Aquavella, J. V., Novel Formulation of Glycerin 1% Artificial Tears Extends Tear Film Break-Up Time Compared with Systane Lubricant Eye Drops. *J. Ocul. Pharmacol. Th.* **2012,** *28* (5), 473-478.
11. Yoshikawa, C.; Goto, A.; Tsujii, Y.; Fukuda, T.; Kimura, T.; Yamamoto, K.; Kishida, A., Protein repellency of well-defined, concentrated poly(2-hydroxyethyl methacrylate) brushes by the size-exclusion effect. *Macromolecules* **2006,** *39* (6), 2284-2290.

12. Hamilton-Brown, P.; Gengebach, T.; Griesser, H. J.; Meagher, L., End Terminal, Poly(ethylene oxide) Graft Layers: Surface Forces and Protein Adsorption. *Langmuir* **2009,** *25* (16), 9149-9156.
13. Leckband, D.; Sheth, S.; Halperin, A., Grafted poly(ethylene oxide) brushes as nonfouling surface coatings. *J. Biomat. Sci. Polym. Ed.* **1999,** *10* (10), 1125-1147.
14. Halperin, A., Polymer brushes that resist adsorption of model proteins: Design parameters. *Langmuir* **1999,** *15* (7), 2525-2533.
15. Grest, G. S., Normal and shear forces between polymer brushes. *Adv. Polym. Sci.* **1999,** *138*, 149-183.
16. Grest, G. S., Interfacial sliding of polymer brushes: A molecular dynamics simulation. *Phys. Rev. Lett.* **1996,** *76* (26), 4979-4982.
17. Klein, J., Shear, friction, and lubrication forces between polymer-bearing surfaces. *Annu. Rev. Mater. Sci.* **1996,** *26*, 581-612.
18. Klein, J.; Kumacheva, E.; Mahalu, D.; Perahia, D.; Fetters, L. J., Reduction of Frictional Forces between Solid-Surfaces Bearing Polymer Brushes. *Nature* **1994,** *370* (6491), 634-636.
19. Klein, J.; Kamiyama, Y.; Yoshizawa, H.; Israelachvili, J. N.; Fredrickson, G. H.; Pincus, P.; Fetters, L. J., Lubrication Forces between Surfaces Bearing Polymer Brushes. *Macromolecules* **1993,** *26* (21), 5552-5560.
20. Benetti, E. M.; Spencer, N. D., Using Polymers to Impart Lubricity and Biopassivity to Surfaces: Are These Properties Linked? *Helv. Chim. Acta* **2019,** *102* (5).
21. Lee, S.; Spencer, N. D., Aqueous lubrication of polymers: Influence of surface modification. *Tribol. Int.* **2005,** *38* (11-12), 922-930.
22. Yan, X.; Perry, S. S.; Spencer, N. D.; Pasche, S.; De Paul, S. M.; Textor, M.; Lim, M. S., Reduction of Friction at Oxide Interfaces upon Polymer Adsorption from Aqueous Solutions. *Langmuir* **2004,** *20* (2), 423-428.
23. Lee, S.; Muller, M.; Ratoi-Salagean, M.; Voros, J.; Pasche, S.; De Paul, S. M.; Spikes, H. A.; Textor, M.; Spencer, N. D., Boundary lubrication of oxide surfaces by Poly(L-lysine)-g-poly(ethylene glycol) (PLL-g-PEG) in aqueous media. *Tribol. Lett.* **2003,** *15* (3), 231-239.
24. Ishihara, K., Highly lubricated polymer interfaces for advanced artificial hip joints through biomimetic design. *Polym. J.* **2015,** *47* (9), 585-597.
25. Kitano, K.; Inoue, Y.; Matsuno, R.; Takai, M.; Ishihara, K., Nanoscale evaluation of lubricity on well-defined polymer brush surfaces using QCM-D and AFM. *Colloid Surf. B* **2009,** *74* (1), 350-357.
26. Chen, M.; Briscoe, W. H.; Armes, S. P.; Klein, J., Lubrication at Physiological Pressures by Polyzwitterionic Brushes. *Science* **2009,** *323* (5922), 1698-1701.
27. Zhang, Z.; Chao, T.; Chen, S. F.; Jiang, S. Y., Superlow fouling sulfobetaine and carboxybetaine polymers on glass slides. *Langmuir* **2006,** *22* (24), 10072-10077.
28. Liu, Q. S.; Singh, A.; Lalani, R.; Liu, L. Y., Ultralow Fouling Polyacrylamide on Gold Surfaces via Surface-Initiated Atom Transfer Radical Polymerization. *Biomacromolecules* **2012,** *13* (4), 1086-1092.
29. Cringus-Fundeanu, I.; Luijten, J.; van der Mei, H. C.; Busscher, H. J.; Schouten, A. J., Synthesis and Characterization of Surface-Grafted Polyacrylamide Brushes and Their Inhibition of Microbial Adhesion. *Langmuir* **2007,** *23* (9), 5120-5126.
30. Li, A.; Benetti, E. M.; Tranchida, D.; Clasohm, J. N.; Schonherr, H.; Spencer, N. D., Surface-Grafted, Covalently Cross-Linked Hydrogel Brushes with Tunable Interfacial and Bulk Properties. *Macromolecules* **2011,** *44* (13), 5344-5351.
31. Rodriguez-Emmenegger, C.; Brynda, E.; Riedel, T.; Houska, M.; Subr, V.; Alles, A. B.; Hasan, E.; Gautrot, J. E.; Huck, W. T. S., Polymer Brushes Showing Non-Fouling

in Blood Plasma Challenge the Currently Accepted Design of Protein Resistant Surfaces. *Macromol. Rapid Commun.* **2011,** *32* (13), 952-957.
32. Zhao, C.; Zheng, J., Synthesis and Characterization of Poly(N-hydroxyethylacrylamide) for Long-Term Antifouling Ability. *Biomacromolecules* **2011,** *12* (11), 4071-4079.
33. Morgese, G.; Benetti, E. M., Polyoxazoline biointerfaces by surface grafting. *Eur. Polym. J.* **2017,** *88*, 470-485.
34. Tauhardt, L.; Kempe, K.; Gottschaldt, M.; Schubert, U. S., Poly(2-oxazoline) functionalized surfaces: from modification to application. *Chem. Soc. Rev.* **2013,** *42* (20), 7998-8011.
35. Morgese, G.; Verbraeken, B.; Ramakrishna, S. N.; Gombert, Y.; Cavalli, E.; Rosenboom, J. G.; Zenobi-Wong, M.; Spencer, N. D.; Hoogenboom, R.; Benetti, E. M., Chemical Design of Non-Ionic Polymer Brushes as Biointerfaces: Poly(2-oxazine)s Outperform Both Poly(2-oxazoline)s and PEG. *Angew. Chem. Int. Edit.* **2018,** *57* (36), 11667-11672.
36. de Beer, S.; Kutnyanszky, E.; Schon, P. M.; Vancso, G. J.; Muser, M. H., Solvent-induced immiscibility of polymer brushes eliminates dissipation channels. *Nat. Commun.* **2014,** *5,* 3781.
37. de Beer, S., Switchable Friction Using Contacts of Stimulus-Responsive and Nonresponding Swollen Polymer Brushes. *Langmuir* **2014,** *30* (27), 8085-8090.
38. Kreer, T.; Muser, M. H.; Binder, K.; Klein, J., Frictional drag mechanisms between polymer-bearing surfaces. *Langmuir* **2001,** *17* (25), 7804-7813.
39 Neelov, I. M.; Borisov, O. V.; Binder, K., Shear deformation of two interpenetrating polymer brushes: Stochastic dynamics simulation. *J. Chem. Phys.* **1998,** *108* (16), 6973-6988.
40 Zhulina, E. B.; Leermakers, F. A. M.; Borisov, O. V., Brushes of Cycled Macromolecules: Structure and Lubricating Properties. *Macromolecules* **2016,** *49* (22), 8758-8767.
41. Halperin, A.; Kroger, M., Theoretical considerations on mechanisms of harvesting cells cultured on thermoresponsive polymer brushes. *Biomaterials* **2012,** *33* (20), 4975-4987.
42. Halperin, A.; Kröger, M., Collapse of Thermoresponsive Brushes and the Tuning of Protein Adsorption. *Macromolecules* **2011,** *44*, 6986-7005.
43. de Gennes, P. G., Scaling Concepts in Polymer Physics. Ithaca, NY, 1979.
44. de Gennes, P. G. Polymers at an interface: a simplified view. *Adv. Colloid Interface Sci.* 1987, 27 (3-4), 189-209.
45. Takahashi, H.; Nakayama, M.; Yamato, M.; Okano, T., Controlled Chain Length and Graft Density of Thermoresponsive Polymer Brushes for Optimizing Cell Sheet Harvest. *Biomacromolecules* **2010,** *11* (8), 1991-1999.
46. Kobayashi, M.; Terayama, Y.; Hosaka, N.; Kaido, M.; Suzuki, A.; Yamada, N.; Torikai, N.; Ishihara, K.; Takahara, A., Friction behavior of high-density poly(2-methacryloyloxyethyl phosphorylcholine) brush in aqueous media. *Soft Matter* **2007,** *3* (6), 740-746.
47. Zhang, Z. Y.; Moxey, M.; Alswieleh, A.; Morse, A. J.; Lewis, A. L.; Geoghegan, M.; Leggett, G. J., Effect of Salt on Phosphorylcholine-based Zwitterionic Polymer Brushes. *Langmuir* **2016,** *32* (20), 5048-5057.
48. Zhang, Z. Y.; Morse, A. J.; Armes, S. P.; Lewis, A. L.; Geoghegan, M.; Leggett, G. J., Nanoscale Contact Mechanics of Biocompatible Polyzwitterionic Brushes. *Langmuir* **2013,** *29* (34), 10684-10692.
49. Zhang, Z. Y.; Morse, A. J.; Armes, S. P.; Lewis, A. L.; Geoghegan, M.; Leggett, G. J., Effect of Brush Thickness and Solvent Composition on the Friction Force Response of

Poly(2-(methacryloyloxy)ethylphosphorylcholine) Brushes. *Langmuir* **2011,** *27* (6), 2514-2521.
50. Gunnewiek, M. K.; Ramakrishna, S. N.; di Luca, A.; Vancso, G. J.; Moroni, L.; Benetti, E. M., Stem-Cell Clinging by a Thread: AFM Measure of Polymer-Brush Lateral Deformation. *Adv. Mater. Interfaces* **2016,** *3* (3), 1500456.
51. Ramakrishna, S. N.; Cirelli, M.; Divandari, M.; Benetti, E. M., Effects of Lateral Deformation by Thermoresponsive Polymer Brushes on the Measured Friction Forces. *Langmuir* **2017,** *33* (17), 4164-4171.
52. Divandari, M.; Trachsel, L.; Yan, W. Q.; Rosenboom, J. G.; Spencer, N. D.; Zenobi-Wong, M.; Morgese, G.; Ramakrishna, S. N.; Benetti, E. M., Surface Density Variation within Cyclic Polymer Brushes Reveals Topology Effects on Their Nanotribological and Biopassive Properties. *ACS Macro Lett.* **2018,** *7* (12), 1455-1460.
53. Divandari, M.; Morgese, G.; Trachsel, L.; Romio, M.; Dehghani, E. S.; Rosenboom, J. G.; Paradisi, C.; Zenobi-Wong, M.; Ramakrishna, S. N.; Benetti, E. M., Topology Effects on the Structural and Physicochemical Properties of Polymer Brushes. *Macromolecules* **2017,** *50* (19), 7760-7769.
54. Nomura, A.; Okayasu, K.; Ohno, K.; Fukuda, T.; Tsujii, Y., Lubrication Mechanism of Concentrated Polymer Brushes in Solvents: Effect of Solvent Quality and Thereby Swelling State. *Macromolecules* **2011,** *44* (12), 5013-5019.
55. Divandari, M.; Morgese, G.; Ramakrishna, S. N.; Benetti, E. M., Surface-grafted assemblies of cyclic polymers: Shifting between high friction and extreme lubricity. *Eur. Polym. J.* **2019,** *110*, 301-306.
56. Perry, S. S.; Yan, X. P.; Limpoco, F. T.; Lee, S.; Muller, M.; Spencer, N. D., Tribological Properties of Poly(L-lysine)-graft-poly(ethylene glycol) Films: Influence of Polymer Architecture and Adsorbed Conformation. *ACS Appl. Mater. Interfaces* **2009,** *1* (6), 1224-1230.
57. Motornov, M.; Sheparovych, R.; Katz, E.; Minko, S., Chemical gating with nanostructured responsive polymer brushes: Mixed brush versus homopolymer brush. *ACS Nano* **2008,** *2* (1), 41-52.
58. Usov, D.; Gruzdev, V.; Nitschke, M.; Stamm, M.; Hoy, O.; Luzinov, I.; Tokarev, I.; Minko, S., Three-dimensional analysis of switching mechanism of mixed polymer brushes. *Macromolecules* **2007,** *40* (24), 8774-8783.
59. Santer, S.; Kopyshev, A.; Yang, H. K.; Ruhe, J., Local composition of nanophase-separated mixed polymer brushes. *Macromolecules* **2006,** *39* (8), 3056-3064.
60. Ionov, L.; Houbenov, N.; Sidorenko, A.; Stamm, M.; Luzinov, I.; Minko, S., Inverse and reversible switching gradient surfaces from mixed polyelectrolyte brushes. *Langmuir* **2004,** *20* (23), 9916-9919.
61. Houbenov, N.; Minko, S.; Stamm, M., Mixed polyelectrolyte brush from oppositely charged polymers for switching of surface charge and composition in aqueous environment. *Macromolecules* **2003,** *36* (16), 5897-5901.
62. Minko, S.; Muller, M.; Usov, D.; Scholl, A.; Froeck, C.; Stamm, M., Lateral versus perpendicular segregation in mixed polymer brushes. *Phys. Rev. Lett.* **2002,** *88* (3).
63. Li, D. J.; Sheng, X.; Zhao, B., Environmentally responsive "Hairy" nanoparticles: Mixed homopolymer brushes on silica nanoparticles synthesized by living radical polymerization techniques. *J. Am. Chem. Soc.* **2005,** *127* (17), 6248-6256.
64. Zhao, B.; He, T., Synthesis of well-defined mixed poly(methyl methacrylate)/polystyrene brushes from an asymmetric difunctional initiator-terminated self-assembled monolayer. *Macromolecules* **2003,** *36* (23), 8599-8602.

65. Bao, C. H.; Tang, S. D.; Wright, R. A. E.; Tang, P.; Qiu, F.; Zhu, L.; Zhao, B., Effect of Molecular Weight on Lateral Microphase Separation of Mixed Homopolymer Brushes Grafted on Silica Particles. *Macromolecules* **2014,** *47* (19), 6824-6835.
66. Calabrese, D. R.; Ditter, D.; Liedel, C.; Blumfield, A.; Zentel, R.; Ober, C. K., Design, Synthesis, and Use of Y-Shaped ATRP/NMP Surface Tethered Initiator. *ACS Macro Lett.* **2015,** *4* (6), 606-610.
67. Julthongpiput, D.; Lin, Y. H.; Teng, J.; Zubarev, E. R.; Tsukruk, V. V., Y-shaped polymer brushes: Nanoscale switchable surfaces. *Langmuir* **2003,** *19* (19), 7832-7836.
68. Sui, X. F.; Zapotoczny, S.; Benetti, E. M.; Memesa, M.; Hempenius, M. A.; Vancso, G. J., Grafting mixed responsive brushes of poly(N-isopropylacrylamide) and poly(methacrylic acid) from gold by selective initiation. *Polym. Chem.* **2011,** *2* (4), 879-884.
69. Zhang, S. X.; Liu, W. Y.; Dong, Y. S.; Wei, T.; Wu, Z. Q.; Chen, H., Design, Synthesis, and Application of a Difunctional Y-Shaped Surface-Tethered Photoinitiator. *Langmuir* **2019,** *35* (9), 3470-3478.
70. Ionov, L.; Minko, S., Mixed Polymer Brushes with Locking Switching. *ACS Appl. Mater. Interfaces* **2012,** *4* (1), 483-489.
71. Delcroix, M. F.; Laurent, S.; Huet, G. L.; Dupont-Gillain, C. C., Protein adsorption can be reversibly switched on and off on mixed PEO/PAA brushes. *Acta Biomater.* **2015,** *11*, 68-79.
72. Bratek-Skicki, A.; Eloy, P.; Morga, M.; Dupont-Gillain, C., Reversible Protein Adsorption on Mixed PEO/PAA Polymer Brushes: Role of Ionic Strength and PEO Content. *Langmuir* **2018,** *34* (9), 3037-3048.
73. Mumtaz, F.; Chen, C. S.; Zhu, H. K.; Pan, C.; Wang, Y. M., Controlled protein adsorption on PMOXA/PAA based coatings by thermally induced immobilization. *Appl. Surf. Sci.* **2018,** *439*, 148-159.
74. Pan, C.; Liu, X. R.; Gong, K.; Mumtaz, F.; Wang, Y. M., Dopamine assisted PMOXA/PAA brushes for their switchable protein adsorption/desorption. *J. Mater. Chem. B* **2018,** *6* (4), 556-567.
75. Bratek-Skicki, A.; Cristaudo, V.; Savocco, J.; Nootens, S.; Morsomme, P.; Delcorte, A.; Dupont-Gillain, C., Mixed Polymer Brushes for the Selective Capture and Release of Proteins. *Biomacromolecules* **2019,** *20* (2), 778-789.
76. Psarra, E.; Konig, U.; Ueda, Y.; Bellmann, C.; Janke, A.; Bittrich, E.; Eichhorn, K. J.; Uhlmann, P., Nanostructured Biointerfaces: Nanoarchitectonics of Thermoresponsive Polymer Brushes Impact Protein Adsorption and Cell Adhesion. *ACS Appl. Mater. Interfaces* **2015,** *7* (23), 12516-12529.
77. Nagase, K.; Hatakeyama, Y.; Shimizu, T.; Matsuura, K.; Yamato, M.; Takeda, N.; Okano, T., Thermoresponsive Cationic Copolymer Brushes for Mesenchymal Stem Cell Separation. *Biomacromolecules* **2015,** *16* (2), 532-540.
78. Nagase, K.; Hatakeyama, Y.; Shimizu, T.; Matsuura, K.; Yamato, M.; Takeda, N.; Okano, T., Hydrophobized Thermoresponsive Copolymer Brushes for Cell Separation by Multistep Temperature Change. *Biomacromolecules* **2013,** *14* (10), 3423-3433.
79. Arisaka, Y.; Kobayashi, J.; Yamato, M.; Akiyama, Y.; Okano, T., Switching of cell growth/detachment on heparin-functionalized thermoresponsive surface for rapid cell sheet fabrication and manipulation. *Biomaterials* **2013,** *34* (17), 4214-4222.
80. Nagase, K.; Mukae, N.; Kikuchi, A.; Okano, T., Thermally Modulated Retention of Lymphoctytes on Polymer-Brush-Grafted Glass Beads. *Macromol. Biosci.* **2012,** *12* (3), 333-340.

81. Nagase, K.; Kimura, A.; Shimizu, T.; Matsuura, K.; Yamato, M.; Takeda, N.; Okano, T., Dynamically cell separating thermo-functional biointerfaces with densely packed polymer brushes. *J. Mater. Chem.* **2012,** *22* (37), 19514-19522.
82. Takahashi, H.; Nakayama, M.; Itoga, K.; Yamato, M.; Okano, T., Micropatterned Thermoresponsive Polymer Brush Surfaces for Fabricating Cell Sheets with Well-Controlled Orientational Structures. *Biomacromolecules* **2011,** *12* (5), 1414-1418.
83. Nagase, K.; Watanabe, M.; Kikuchi, A.; Yamato, M.; Okano, T., Thermo-Responsive Polymer Brushes as Intelligent Biointerfaces: Preparation via ATRP and Characterization. *Macromol. Biosci.* **2011,** *11* (3), 400-409.
84. Vyas, M. K.; Schneider, K.; Nandan, B.; Stamm, M., Switching of friction by binary polymer brushes. *Soft Matter* **2008,** *4* (5), 1024-1032.
85. Morgese, G.; Gombert, Y.; Ramakrishna, S. N.; Benetti, E. M., Mixing Poly(ethylene glycol) and Poly(2-alkyl-2-oxazoline)s Enhances Hydration and Viscoelasticity of Polymer Brushes and Determines Their Nanotribological and Antifouling Properties. *ACS Appl. Mater. Interfaces* **2018,** *10* (48), 41839-41848.
86. Nordgren, N.; Rutland, M. W., Tunable Nanolubrication between Dual-Responsive Polyionic Grafts. *Nano Lett.* **2009,** *9* (8), 2984-2990.
87. Wang, X. H.; Yan, S. J.; Song, L. J.; Shi, H. C.; Yang, H. W.; Luan, S. F.; Huang, Y. B.; Yin, J. H.; Khan, A. F.; Zhao, J., Temperature-Responsive Hierarchical Polymer Brushes Switching from Bactericidal to Cell Repellency. *ACS Appl. Mater. Interfaces* **2017,** *9* (46), 40930-40939.
88. Ye, G.; Lee, J. H.; Perreault, F.; Elimelech, M., Controlled Architecture of Dual-Functional Block Copolymer Brushes on Thin-Film Composite Membranes for Integrated "Defending" and "Attacking" Strategies against Biofouling. *ACS Appl. Mater. Interfaces* **2015,** *7* (41), 23069-23079.
89. de los Santos Pereira, A.; Kostina, N. Y.; Bruns, M.; Rodriguez-Emmenegger, C.; Barner-Kowollik, C., Phototriggered Functionalization of Hierarchically Structured Polymer Brushes. *Langmuir* **2015,** *31* (21), 5899-5907.
90. de los Santos Pereira, A.; Riedel, T.; Brynda, E.; Rodriguez-Emmenegger, C., Hierarchical antifouling brushes for biosensing applications. *Sens. Actuator B-Chem.* **2014,** *202*, 1313-1321.
91. Fortin, N.; Klok, H. A., Glucose Monitoring Using a Polymer Brush Modified Polypropylene Hollow Fiber-based Hydraulic Flow Sensor. *ACS Appl. Mater. Interfaces* **2015,** *7* (8), 4631-4640.
92. Badoux, M.; Billing, M.; Klok, H. A., Polymer brush interfaces for protein biosensing prepared by surface-initiated controlled radical polymerization. *Polym. Chem.* **2019**.
93. Navarro, M.; Benetti, E. M.; Zapotoczny, S.; Planell, J. A.; Vancso, G. J., Buried, covalently attached RGD peptide motifs in poly(methacrylic acid) brush layers: The effect of brush structure on cell adhesion. *Langmuir* **2008,** *24* (19), 10996-11002.
94. Desseaux, S.; Klok, H. A., Fibroblast adhesion on ECM-derived peptide modified poly(2-hydroxyethyl methacrylate) brushes: Ligand co-presentation and 3D-localization. *Biomaterials* **2015,** *44*, 24-35.
95. Desseaux, S.; Klok, H.-A., Temperature-controlled masking/unmasking of cell-adhesive cues with poly(ethylene glycol) methacrylate based brushes. *Biomacromolecules* **2014,** *15*, 3859-65.
96. Paripovic, D.; Hall-Bozic, H.; Klok, H. A., Osteoconductive surfaces generated from peptide functionalized poly(2-hydroxyethyl methacrylate-co-2-(methacryloyloxy)ethyl phosphate) brushes. *J. Mater. Chem.* **2012,** *22* (37), 19570-19578.

97. Dou, X. Q.; Li, P.; Jiang, S. Y.; Bayat, H.; Schonherr, H., Bioinspired Hierarchically Structured Surfaces for Efficient Capture and Release of Circulating Tumor Cells. *ACS Appl. Mater. Interfaces* **2017,** *9* (10), 8508-8518.
98. Desseaux, S.; Klok, H. A., Temperature-Controlled Masking/Unmasking of Cell-Adhesive Cues with Poly(ethylene glycol) Methacrylate Based Brushes. *Biomacromolecules* **2014,** *15* (10), 3859-3865.
99. Lilge, I.; Schonherr, H., Block Copolymer Brushes for Completely Decoupled Control of Determinants of Cell-Surface Interactions. *Angew. Chem. Int. Edit.* **2016,** *55* (42), 13114-13117.
100. Quintana, R.; Gosa, M.; Janczewski, D.; Kutnyanszky, E.; Vancso, G. J., Enhanced Stability of Low Fouling Zwitterionic Polymer Brushes in Seawater with Diblock Architecture. *Langmuir* **2013,** *29* (34), 10859-10867.
101. Yu, Y. L.; Vancso, G. J.; de Beer, S., Substantially enhanced stability against degrafting of zwitterionic PMPC brushes by utilizing PGMA-linked initiators. *Eur. Polym. J.* **2017,** *89*, 221-229.
102. Paripovic, D.; Klok, H.-A., Improving the Stability in Aqueous Media of Polymer Brushes Grafted from Silicon Oxide Substrates by Surface-Initiated Atom Transfer Radical Polymerization. *Macromol. Chem. Phys.* **2011,** *212* (9), 950-958.
103. Divandari, M.; Dehghani, E. S.; Spencer, N. D.; Ramakrishna, S. N.; Benetti, E. M., Understanding the effect of hydrophobic protecting blocks on the stability and biopassivity of polymer brushes in aqueous environments: A Tiramisù for cell-culture applications. *Polymer* **2016,** *98*, 470-480.
104. Wyszogrodzka, M.; Haag, R., Synthesis and Characterization of Glycerol Dendrons, Self-Assembled Monolayers on Gold: A Detailed Study of Their Protein Resistance. *Biomacromolecules* **2009,** *10* (5), 1043-1054.
105. Wyszogrodzka, M.; Haag, R., Study of Single Protein Adsorption onto Monoamino Oligoglycerol Derivatives: A Structure-Activity Relationship. *Langmuir* **2009,** *25* (10), 5703-5712.
106. Rud, O. V.; Polotsky, A. A.; Gillich, T.; Borisov, O. V.; Leermakers, F. A. M.; Textor, M.; Birshtein, T. M., Dendritic Spherical Polymer Brushes: Theory and Self-Consistent Field Modeling. *Macromolecules* **2013,** *46* (11), 4651-4662.
107. Gillich, T.; Benetti, E. M.; Rakhmatullina, E.; Konradi, R.; Li, W.; Zhang, A.; Schluter, A. D.; Textor, M., Self-Assembly of Focal Point Oligo-catechol Ethylene Glycol Dendrons on Titanium Oxide Surfaces: Adsorption Kinetics, Surface Characterization, and Nonfouling Properties. *J. Am. Chem. Soc.* **2011,** *133* (28), 10940-10950.
108. Gillich, T.; Acikgöz, C.; Isa, L.; Schlüter, A. D.; Spencer, N. D.; Textor, M., PEG-Stabilized Core–Shell Nanoparticles: Impact of Linear versus Dendritic Polymer Shell Architecture on Colloidal Properties and the Reversibility of Temperature-Induced Aggregation. *ACS Nano* **2012,** *7* (1), 316-329.
109. Lukowiak, M. C.; Wettmarshausen, S.; Hidde, G.; Landsberger, P.; Boenke, V.; Rodenacker, K.; Braun, U.; Friedrich, J. F.; Gorbushina, A. A.; Haag, R., Polyglycerol coated polypropylene surfaces for protein and bacteria resistance. *Polym. Chem.* **2015,** *6* (8), 1350-1359.
110. Wei, Q.; Krysiak, S.; Achazi, K.; Becherer, T.; Noeske, P. L. M.; Paulus, F.; Liebe, H.; Grunwald, I.; Dernedde, J.; Hartwig, A.; Hugel, T.; Haag, R., Multivalent anchored and crosslinked hyperbranched polyglycerol monolayers as antifouling coating for titanium oxide surfaces. *Colloid Surf. B* **2014,** *122*, 684-692.
111. Weinhart, M.; Becherer, T.; Schnurbusch, N.; Schwibbert, K.; Kunte, H. J.; Haag, R., Linear and Hyperbranched Polyglycerol Derivatives as Excellent Bioinert Glass Coating Materials. *Adv. Eng. Mater.* **2011,** *13* (12), B501-B510.

112. Calderon, M.; Quadir, M. A.; Sharma, S. K.; Haag, R., Dendritic Polyglycerols for Biomedical Applications. *Adv. Mater.* **2010,** *22* (2), 190-218.
113. Gunkel, G.; Weinhart, M.; Becherer, T.; Haag, R.; Huck, W. T. S., Effect of Polymer Brush Architecture on Antibiofouling Properties. *Biomacromolecules* **2011,** *12* (11), 4169-4172.
114. Costantini, F.; Benetti, E. M.; Tiggelaar, R. M.; Gardeniers, H. J. G. E.; Reinhoudt, D. N.; Huskens, J.; Vancso, G. J.; Verboom, W., A Brush-Gel/Metal-Nanoparticle Hybrid Film as an Efficient Supported Catalyst in Glass Microreactors. *Chem. Eur. J* **2010,** *16* (41), 12406-12411.
115. Benetti, E. M.; Sui, X. F.; Zapotoczny, S.; Vancso, G. J., Surface-Grafted Gel-Brush/Metal Nanoparticle Hybrids. *Adv. Funct. Mater.* **2010,** *20* (6), 939-944.
116. Ramakrishna, S. N.; Cirelli, M.; Kooij, E. S.; Klein Gunnewiek, M.; Benetti, E. M., Amplified Responsiveness of Multilayered Polymer Grafts: Synergy between Brushes and Hydrogels. *Macromolecules* **2015,** *48*, 7106-7116.
117. Kang, C. J.; Ramakrishna, S. N.; Nelson, A.; Cremmel, C. V. M.; Stein, H. V.; Spencer, N. D.; Isa, L.; Benetti, E. M., Ultrathin, freestanding, stimuli-responsive, porous membranes from polymer hydrogel-brushes. *Nanoscale* **2015,** *7* (30), 13017-13025.
118. Benetti, E. M.; Chung, H. J.; Vancso, G. J., pH Responsive Polymeric Brush Nanostructures: Preparation and Characterization by Scanning Probe Oxidation and Surface Initiated Polymerization. *Macromol. Rapid Commun.* **2009,** *30* (6), 411-417.
119. Dehghani, E. S.; Spencer, N. D.; Ramakrishna, S. N.; Benetti, E. M., Crosslinking Polymer Brushes with Ethylene Glycol-Containing Segments: Influence on Physicochemical and Antifouling Properties. *Langmuir* **2016,** *32* (40), 10317-10327.
120. Dehghani, E. S.; Ramakrishna, S. N.; Spencer, N. D.; Benetti, E. M., Controlled Crosslinking Is a Tool To Precisely Modulate the Nanomechanical and Nanotribological Properties of Polymer Brushes. *Macromolecules* **2017,** *50* (7), 2932-2941.
121. Iuster, N.; Tairy, O.; Driver, M. J.; Armes, S. P.; Klein, J., Cross-Linking Highly Lubricious Phosphocholinated Polymer Brushes: Effect on Surface Interactions and Frictional Behavior. *Macromolecules* **2017,** *50* (18), 7361-7371.
122. Li, A.; Ramakrishna Shivaprakash, N.; Nalam Prathima, C.; Benetti Edmondo, M.; Spencer Nicholas, D., Stratified Polymer Grafts: Synthesis and Characterization of Layered 'Brush' and 'Gel' Structures. *Adv. Mater. Interfaces* **2014,** *1* (1), 1300007.
123. Benetti, E. M.; Zapotoczny, S.; Vancso, J., Tunable thermoresponsive polymeric platforms on gold by "photoiniferter"-based surface grafting. *Adv. Mater.* **2007,** *19* (2), 268-271.
124. Benetti, E. M.; Reimhult, E.; de Bruin, J.; Zapotoczny, S.; Textor, M.; Vancso, G. J., Poly(methacrylic acid) Grafts Grown from Designer Surfaces: The Effect of Initiator Coverage on Polymerization Kinetics, Morphology, and Properties. *Macromolecules* **2009,** *42* (5), 1640-1647.
125. Loveless, D. M.; Abu-Lail, N. I.; Kaholek, M.; Zauscher, S.; Craig, S. L., Reversibly cross-linked surface-grafted polymer brushes. *Angew. Chem. Int. Edit.* **2006,** *45* (46), 7812-7814.
126. Dehghani, E. S.; Naik, V. V.; Mandal, J.; Spencer, N. D.; Benetti, E. M., Physical Networks of Metal-Ion-Containing Polymer Brushes Show Fully Tunable Swelling, Nanomechanical and Nanotribological Properties. *Macromolecules* **2017,** *50* (6), 2495-2503.
127. Yu, J.; Jackson, N. E.; Xu, X.; Morgenstern, Y.; Kaufman, Y.; Ruths, M.; de Pablo, J. J.; Tirrell, M., Multivalent counterions diminish the lubricity of polyelectrolyte brushes. *Science* **2018,** *360* (6396), 1434-+.

128. Yan, W. Q.; Divandari, M.; Rosenboom, J. G.; Ramakrishna, S. N.; Trachsel, L.; Spencer, N. D.; Morgese, G.; Benetti, E. M., Design and characterization of ultrastable, biopassive and lubricious cyclic poly(2-alkyl-2-oxazoline) brushes. *Polym Chem.* **2018,** *9* (19), 2580-2589..
129. Morgese, G.; Cavalli, E.; Rosenboom, J. G.; Zenobi-Wong, M.; Benetti, E. M., Cyclic Polymer Grafts That Lubricate and Protect Damaged Cartilage. *Angew. Chem. Int. Edit.* **2018,** *57* (6), 1621-1626.
130. Morgese, G.; Shaghasemi, B. S.; Causin, V.; Zenobi-Wong, M.; Ramakrishna, S. N.; Reimhult, E.; Benetti, E. M., Next-Generation Polymer Shells for Inorganic Nanoparticles are Highly Compact, Ultra-Dense, and Long-Lasting Cyclic Brushes. *Angew. Chem. Int. Edit.* **2017,** *56* (16), 4507-4511.
131. Benetti, E. M.; Divandari, M.; Ramakrishna, S. N.; Morgese, G.; Yan, W. Q.; Trachsel, L., Loops and Cycles at Surfaces: The Unique Properties of Topological Polymer Brushes. *Chem. Eur. J.* **2017,** *23* (51), 12433-12442.
132. Morgese, G.; Trachsel, M.; Romio, M.; Divandari, M.; Ramakrishna, S. N.; Benetti, E. M., Topological Polymer Chemistry Enters Surface Science: Linear versus Cyclic Polymer Brushes. *Angew. Chem. Int. Edit.* **2016,** *55*, 15583 –15588
133. Ramakrishna, S. N.; Morgese, G.; Zenobi-Wong, M.; Benetti, E. M., Comblike Polymers with Topologically Different Side Chains for Surface Modification: Assembly Process and Interfacial Physicochemical Properties. *Macromolecules* **2019,** *52* (4), 1632-1641.
134. Yamamoto, T.; Tezuka, Y., Cyclic polymers revealing topology effects upon self-assemblies, dynamics and responses. *Soft Matter* **2015,** *11* (38), 7458-7468.
135. Satokawa, Y.; Shikata, T.; Tanaka, F.; Qiu, X. P.; Winnik, F. M., Hydration and Dynamic Behavior of a Cyclic Poly(N-isopropylacrylamide) in Aqueous Solution: Effects of the Polymer Chain Topology. *Macromolecules* **2009,** *42* (4), 1400-1403.
136. Xu, J.; Ye, J.; Liu, S. Y., Synthesis of well-defined cyclic poly(N-isopropylacrylamide) via click chemistry and its unique thermal phase transition behavior. *Macromolecules* **2007,** *40* (25), 9103-9110.
137. Hadziioannou, G.; Cotts, P. M.; Tenbrinke, G.; Han, C. C.; Lutz, P.; Strazielle, C.; Rempp, P.; Kovacs, A. J., Thermodynamic and Hydrodynamic Properties of Dilute-Solutions of Cyclic and Linear Polystyrenes. *Macromolecules* **1987,** *20* (3), 493-497.
138. Erbas, A.; Paturej, J., Friction between ring polymer brushes. *Soft Matter* **2015,** *11* (16), 3139-3148.
139. Eiser, E.; Klein, J.; Witten, T. A.; Fetters, L. J., Shear of telechelic brushes. *Phys. Rev. Lett.* **1999,** *82* (25), 5076-5079.
140. Jahn, S.; Seror, J.; Klein, J., Lubrication of Articular Cartilage. *Annu. Rev. Biomed. Eng.* **2016,** *18*, 235-258.
141. Bonnevie, E. D.; Galesso, D.; Secchieri, C.; Cohen, I.; Bonassar, L. J., Elastoviscous Transitions of Articular Cartilage Reveal a Mechanism of Synergy between Lubricin and Hyaluronic Acid. *PLoS One* **2015,** *10* (11).
142. Seror, J.; Merkher, Y.; Kampf, N.; Collinson, L.; Day, A. J.; Maroudas, A.; Klein, J., Normal and Shear Interactions between Hyaluronan-Aggrecan Complexes Mimicking Possible Boundary Lubricants in Articular Cartilage in Synovial Joints. *Biomacromolecules* **2012,** *13* (11), 3823-3832.
143. Seror, J.; Merkher, Y.; Kampf, N.; Collinson, L.; Day, A. J.; Maroudas, A.; Klein, J., Articular Cartilage Proteoglycans As Boundary Lubricants: Structure and Frictional Interaction of Surface-Attached Hyaluronan and Hyaluronan-Aggrecan Complexes. *Biomacromolecules* **2011,** *12* (10), 3432-3443.

144. Schmidt, T. A.; Gastelum, N. S.; Nguyen, Q. T.; Schumacher, B. L.; Sah, R. L., Boundary lubrication of articular cartilage - Role of synovial fluid constituents. *Arthritis Rheumathol.* **2007,** *56* (3), 882-891.
145. Morgese, G.; Cavalli, E.; Muller, M.; Zenobi-Wong, M.; Benetti, E. M., Nanoassemblies of Tissue-Reactive, Polyoxazoline Graft-Copolymers Restore the Lubrication Properties of Degraded Cartilage. *ACS Nano* **2017,** *11* (3), 2794-2804.
146. Kang, T.; Banquy, X.; Heo, J. H.; Lim, C. N.; Lynd, N. A.; Lundberg, P.; Oh, D. X.; Lee, H. K.; Hong, Y. K.; Hwang, D. S.; Waite, J. H.; Israelachvili, J. N.; Hawker, C. J., Mussel-Inspired Anchoring of Polymer Loops That Provide Superior Surface Lubrication and Antifouling Properties. *ACS Nano* **2016,** *10* (1), 930-937.
147. Li, L.; Yan, B.; Zhang, L.; Tian, Y.; Zeng, H. B., Mussel-inspired antifouling coatings bearing polymer loops. *Chem. Commun.* **2015,** *51* (87), 15780-15783.
148. Patton, D.; Knoll, W.; Advincula, R. C., Polymer Loops vs. Brushes on Surfaces: Adsorption, Kinetics, and Viscoelastic Behavior of alpha,omega-Thiol Telechelics on Gold. *Macromol. Chem. Phys.* **2011,** *212* (5), 485-497.
149. Ashcraft, E.; Ji, H. N.; Mays, J.; Dadmun, M., Grafting Polymer Loops onto Functionalized Nanotubes: Monitoring Grafting and Loop Formation. *Macromol. Chem. Phys.* **2011,** *212* (5), 465-477.
150. Haung, Z. Y.; Ji, H. N.; Mays, J.; Dadmun, M.; Smith, G.; Bedrov, D.; Zhang, Y., Polymer Loop Formation on a Functionalized Hard Surface: Quantitative Insight by Comparison of Experimental and Monte Carlo Simulation Results. *Langmuir* **2010,** *26* (1), 202-209.
151. Huang, Z.; Alonzo, J.; Liu, M.; Ji, H.; Yin, F.; Smith, G. D.; Mays, J. W.; Kilbey, S. M.; Dadmun, M. D., Impact of solvent quality on the density profiles of looped triblock copolymer brushes by neutron reflectivity measurements. *Macromolecules* **2008,** *41* (5), 1745-1752.
152. Alonzo, J.; Huang, Z. Y.; Liu, M.; Mays, J. W.; Toomey, R. G.; Dadmun, M. D.; Kilbey, S. M., Looped polymer brushes formed by self-assembly of poly(2-vinylpyridine)-polystyrene-poly(2-vinylpyridine) triblock copolymers at the solid-fluid interface. Kinetics of preferential adsorption. *Macromolecules* **2006,** *39* (24), 8434-8439.
153. Du, Y. Q.; Jin, J.; Liang, H. J.; Jiang, W., Structural and Physicochemical Properties and Biocompatibility of Linear and Looped Polymer-Capped Gold Nanoparticles. *Langmuir* **2019,** *35* (25), 8316-8324.
154. Han, Y. Y.; Ma, J. N.; Hu, Y.; Jin, J.; Jiang, W., Effect of End-Grafted Polymer Conformation on Protein Resistance. *Langmuir* **2018,** *34* (5), 2073-2080.
155. Zhou, T.; Qi, H.; Han, L.; Barbash, D.; Li, C. Y., Towards controlled polymer brushes via a self-assembly-assisted-grafting-to approach. *Nat. Commun.* **2016,** *7*, 11119.
156. Jiang, S. Y.; Cao, Z. Q., Ultralow-Fouling, Functionalizable, and Hydrolyzable Zwitterionic Materials and Their Derivatives for Biological Applications. *Adv. Mater.* **2010,** *22* (9), 920-932.
157. Sun, H.; Kabb, C. P.; Dai, Y. Q.; Hill, M. R.; Ghiviriga, I.; Bapat, A. P.; Sumerlin, B. S., Macromolecular metamorphosis via stimulus-induced transformations of polymer architecture. *Nat. Chem.* **2017,** *9* (8), 817-823.
158. Aoki, D.; Aibara, G.; Uchida, S.; Takata, T., A Rational Entry to Cyclic Polymers via Selective Cyclization by Self-Assembly and Topology Transformation of Linear Polymers. *J. Am. Chem. Soc.* **2017,** *139* (20), 6791-6794.
159. Yeow, J.; Chapman, R.; Gormley, A. J.; Boyer, C., Up in the air: oxygen tolerance in controlled/living radical polymerisation. *Chem. Soc. Rev.* **2018,** *47* (12), 4357-4387.

160. Zhang, T.; Du, Y.; Muller, F.; Amin, I.; Jordan, R., Surface-initiated Cu(0) mediated controlled radical polymerization (SI-CuCRP) using a copper plate. *Polym. Chem.* **2015,** *6* (14), 2726-2733.
161. Zhang, T.; Du, Y.; Kalbacova, J.; Schubel, R.; Rodriguez, R. D.; Chen, T.; Zahn, D. R. T.; Jordan, R., Wafer-scale synthesis of defined polymer brushes under ambient conditions. *Polym. Chem.* **2015,** *6* (47), 8176-8183.
162. Dehghani, E. S.; Du, Y.; Zhang, T.; Ramakrishna, S. N.; Spencer, N. D.; Jordan, R.; Benetti, E. M., Fabrication and Interfacial Properties of Polymer Brush Gradients by Surface-Initiated Cu(0)-Mediated Controlled Radical Polymerization. *Macromolecules* **2017,** *50* (6), 2436-2446.
163. Narupai, B.; Page, Z. A.; Treat, N. J.; McGrath, A. J.; Pester, C. W.; Discekici, E. H.; Dolinski, N. D.; Meyers, G. F.; de Alaniz, J. R.; Hawker, C. J., Simultaneous Preparation of Multiple Polymer Brushes under Ambient Conditions using Microliter Volumes. *Angew. Chem. Int. Edit.* **2018,** *57* (41), 13433-13438.
164. Fantin, M.; Ramakrishna, S. N.; Yan, J. J.; Yan, W. Q.; Divandari, M.; Spencer, N. D.; Matyjaszewski, K.; Benetti, E. M., The Role of Cu-0 in Surface-Initiated Atom Transfer Radical Polymerization: Tuning Catalyst Dissolution for Tailoring Polymer Interfaces. *Macromolecules* **2018,** *51* (17), 6825-6835.
165. Li, M.; Fromel, M.; Ranaweera, D.; Rocha, S.; Boyer, C.; Pester, C. W., SI-PET-RAFT: Surface-Initiated Photoinduced Electron Transfer-Reversible Addition–Fragmentation Chain Transfer Polymerization. *ACS Macro Lett.* **2019,** *8*, 374-380.
166. Yan, W. Q.; Fantin, M.; Spencer, N. D.; Matyjaszewski, K.; Benetti, E. M., Translating Surface-Initiated Atom Transfer Radical Polymerization into Technology: The Mechanism of Cu^0-Mediated SI-ATRP under Environmental Conditions. *ACS Macro Lett.* **2019,** *8*, 865-870.

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Bioinert and Lubricious Surfaces by Macromolecular Design

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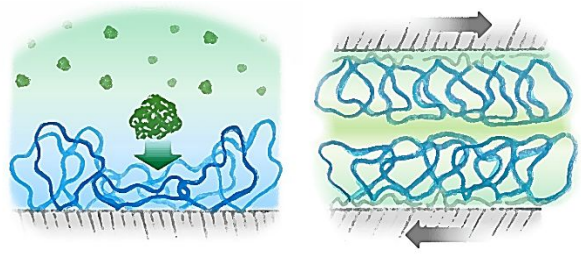

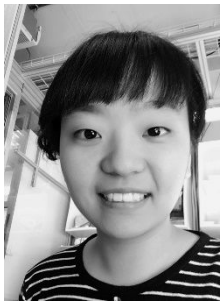

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