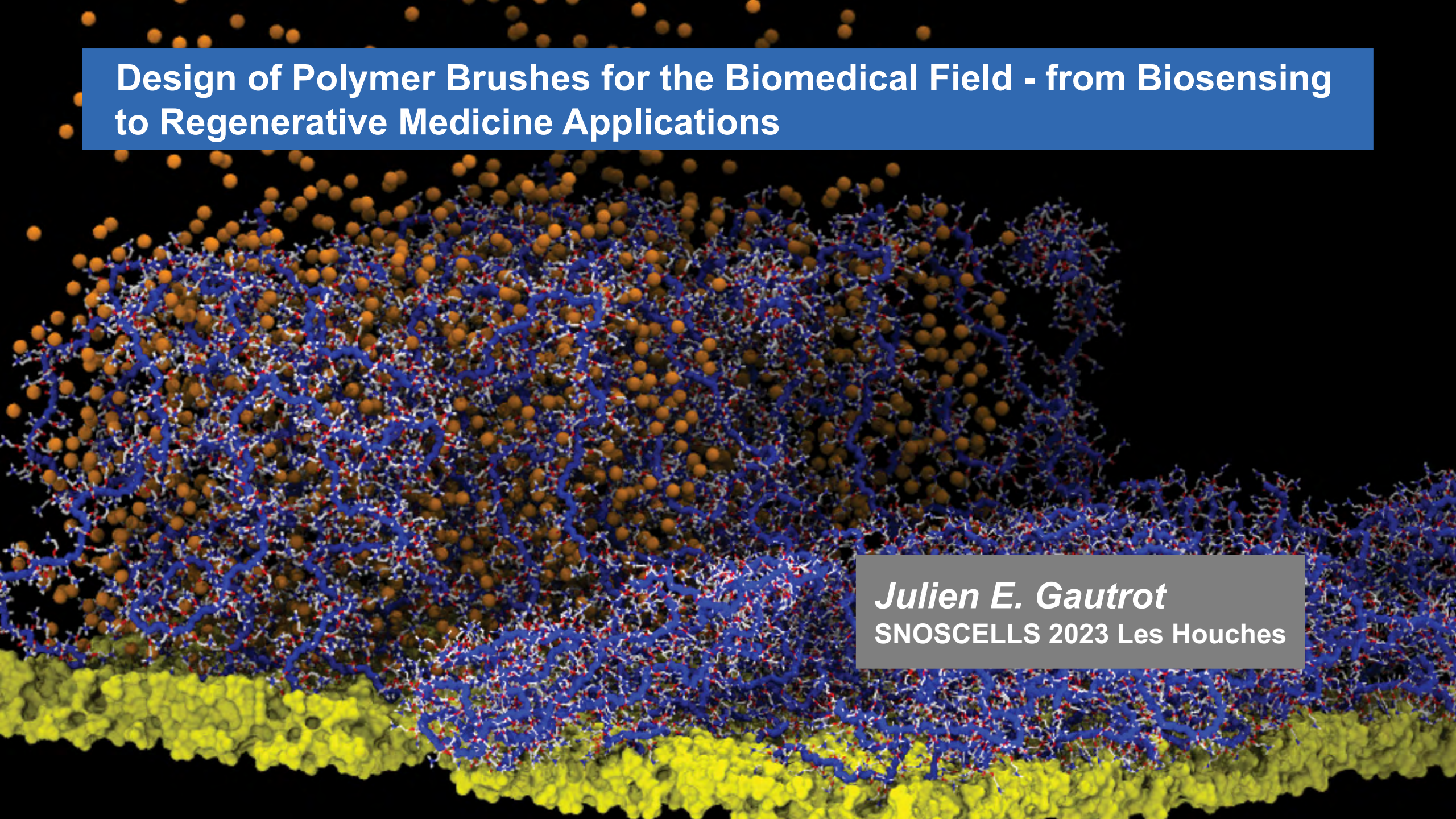
Design of Polymer Brushes for the Biomedical Field - from Biosensing to Regenerative Medicine Applications

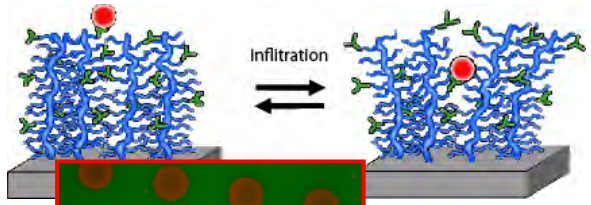


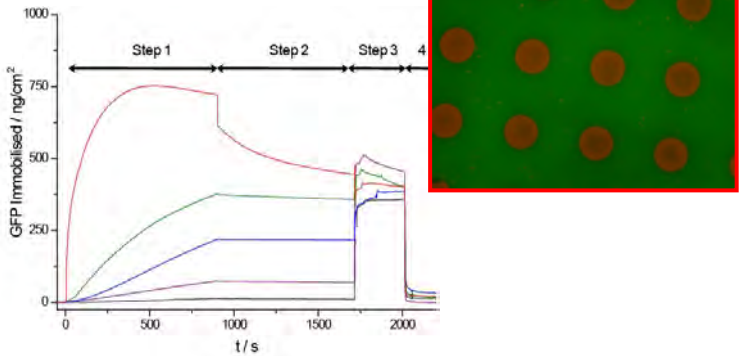
Julien E. Gautrot

SNOSCELLS 2023 Les Houches

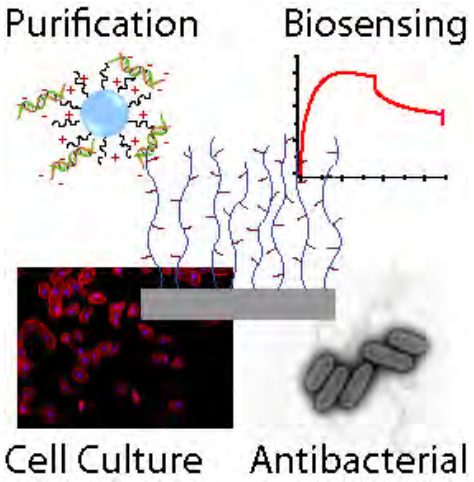
Polymer Brushes for Biomedical Applications

1. Surface functionalisation

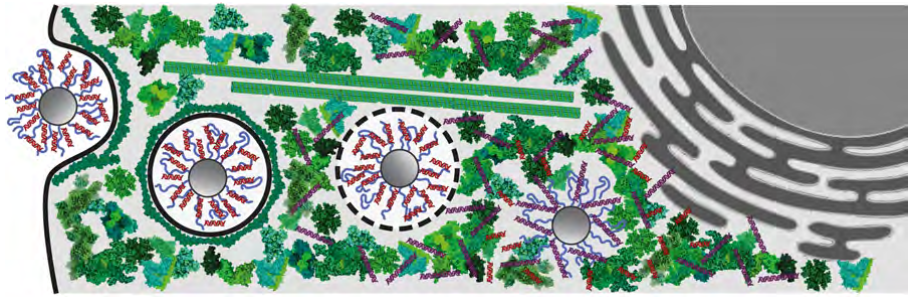




Gautrot et al. *Appl. Mater. Interfaces* 2010
Trmcic et al. *Biomacromolecules* 2009
Tan et al. *Polym. Chem.* 2016
Colak et al. *Biomacromolecules* 2018

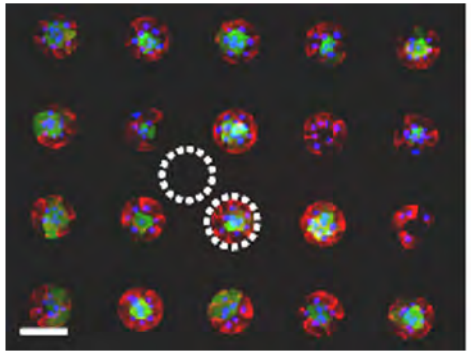


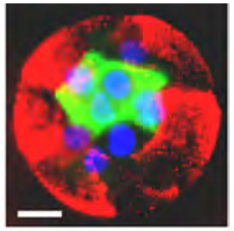
Chem. Rev. 2014

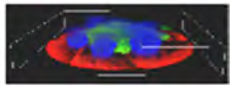


2. Design of vectors for gene delivery

Krishnamoorthy et al. *Biomacromolecules* 2017
Li et al. *Biomacromolecules* 2018
Qu et al. *Biomacromolecules* 2019
Li et al. Chem. Commun. 2019
Santos et al. *Langmuir* 2019
Chang et al. *Eur. Polym. J* 2021
Raynold et al. *Nat. Commun.* 2021
Gautrot et al. *ChemRxiv* 2022



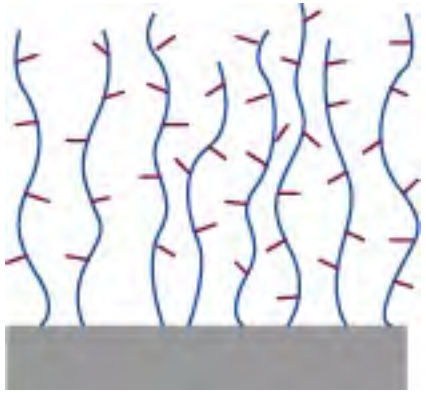




3. Cell arrays and multi-scale patterning

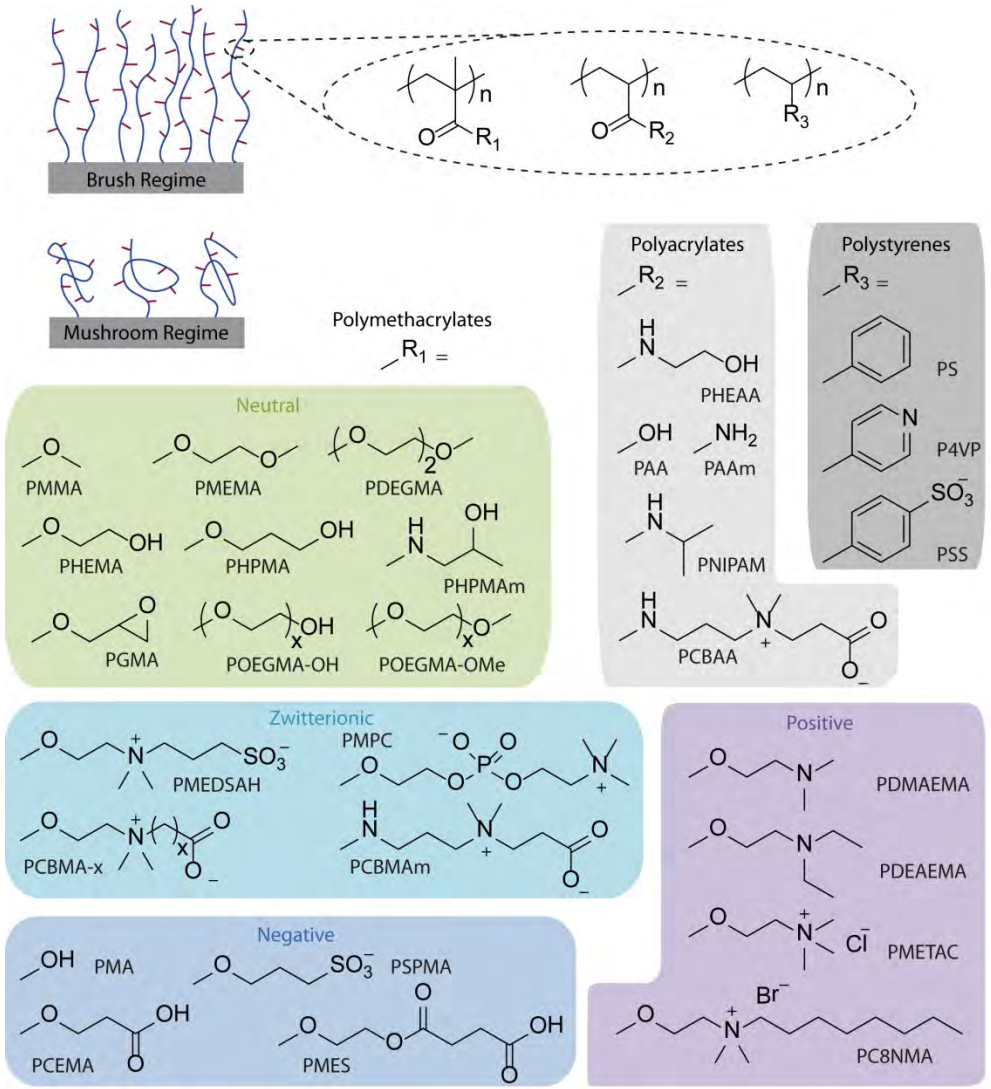
Gautrot et al. *Biomaterials* 2010
Connelly et al. *Nat. Cell Biol.* 2010
Gautrot et al. *Biomaterials* 2012
Nano Letters 2014
Di Cio et al. *Acta Biomater.* 2016
Di Cio et al. *Acta Biomater.* 2018
Colak et al. *Biomacromolecules* 2018
Di Cio et al. *Biomaterials* 2020

Design of Polymer Brushes for the Biomedical Field



1. Synthesis and physico-chemical properties.
2. Interactions with biomacromolecules.
3. Biofunctionalisation.
4. Polymer brushes for biosensing.
5. Design of cell based assays.
6. Polymer brushes for gene delivery.

1. A Wealth of Chemical Diversity

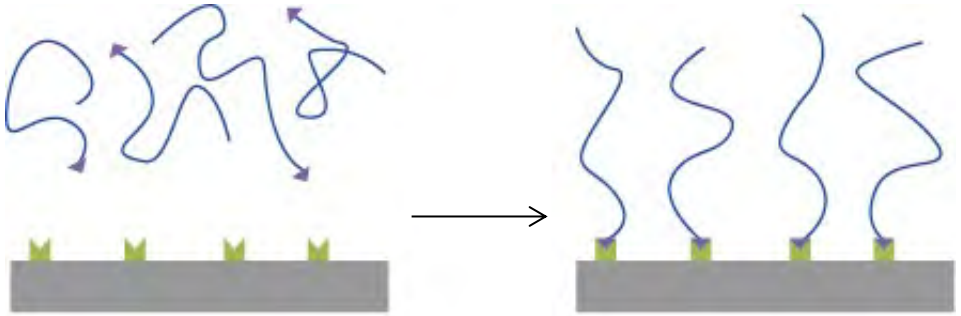


Chem Rev 2014, 114, 10976-11026

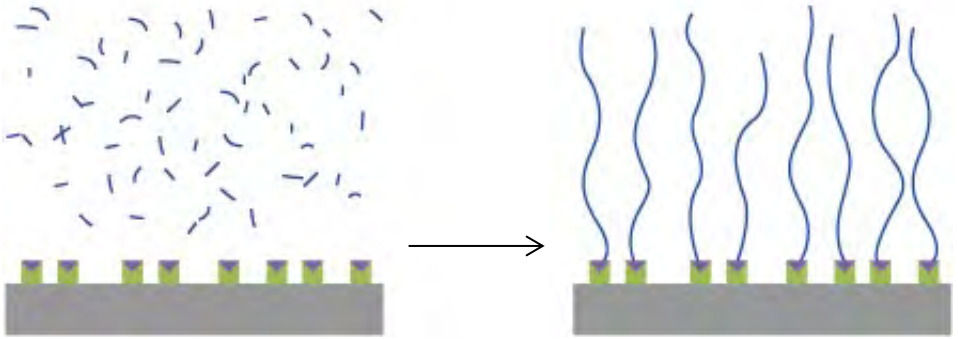
1. Different Strategies To Make Polymer Brushes

- Grafting to: potentially, control of polymer PDI and size. The chemistry of the polymer can be fully characterised. But low grafting density.
- Grafting from: high grafting density, but typically difficult to control the polydispersity of the polymer chains generated. Characterisation is limited.

Grafting To



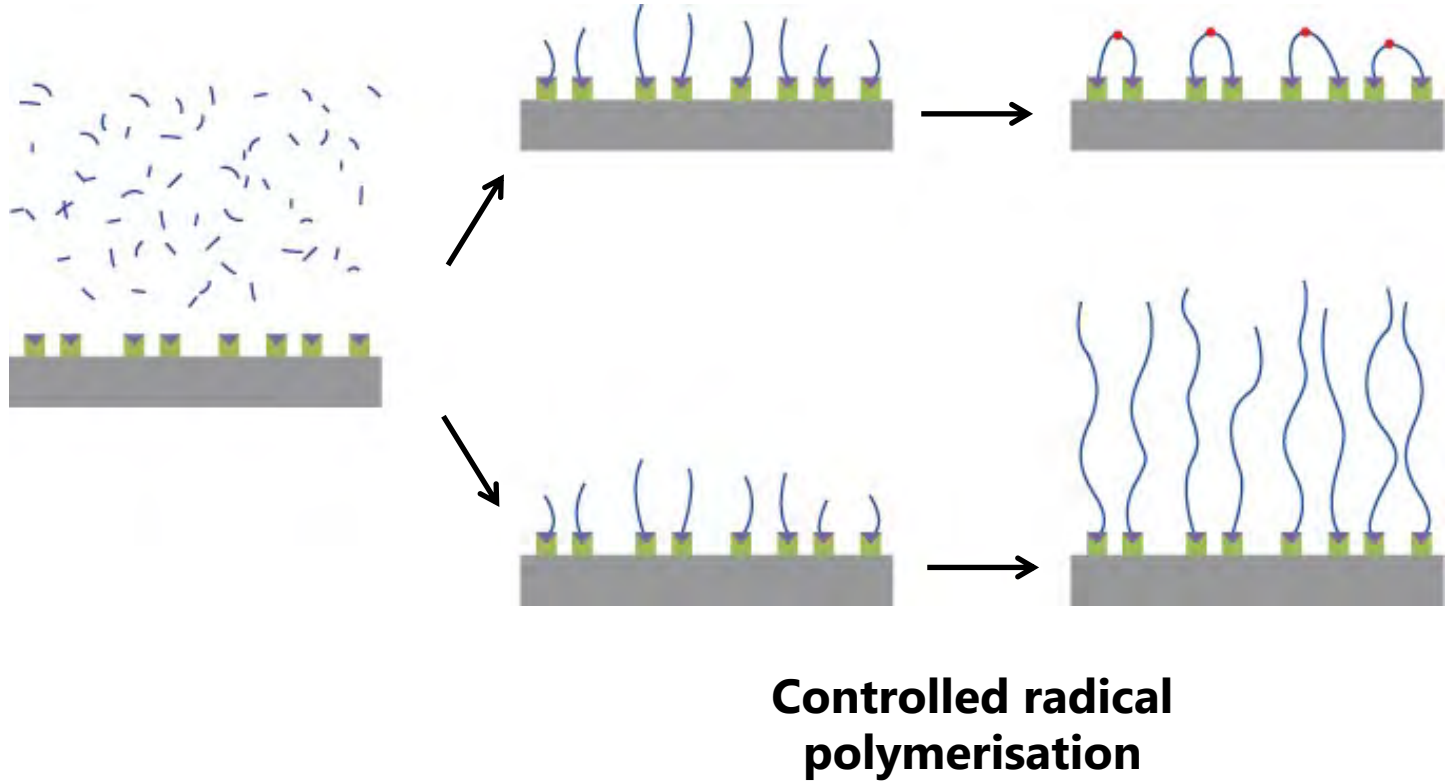
Grafting From



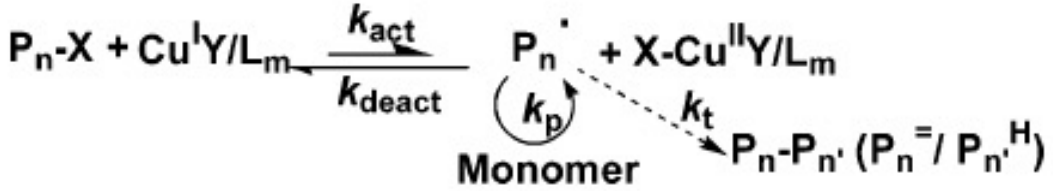
1. Grafting From: the Requirement of a Controlled Radical Polymerisation

$$R_p = k_p[M\cdot][M] \qquad R_t = 2k_t[M\cdot]^2$$

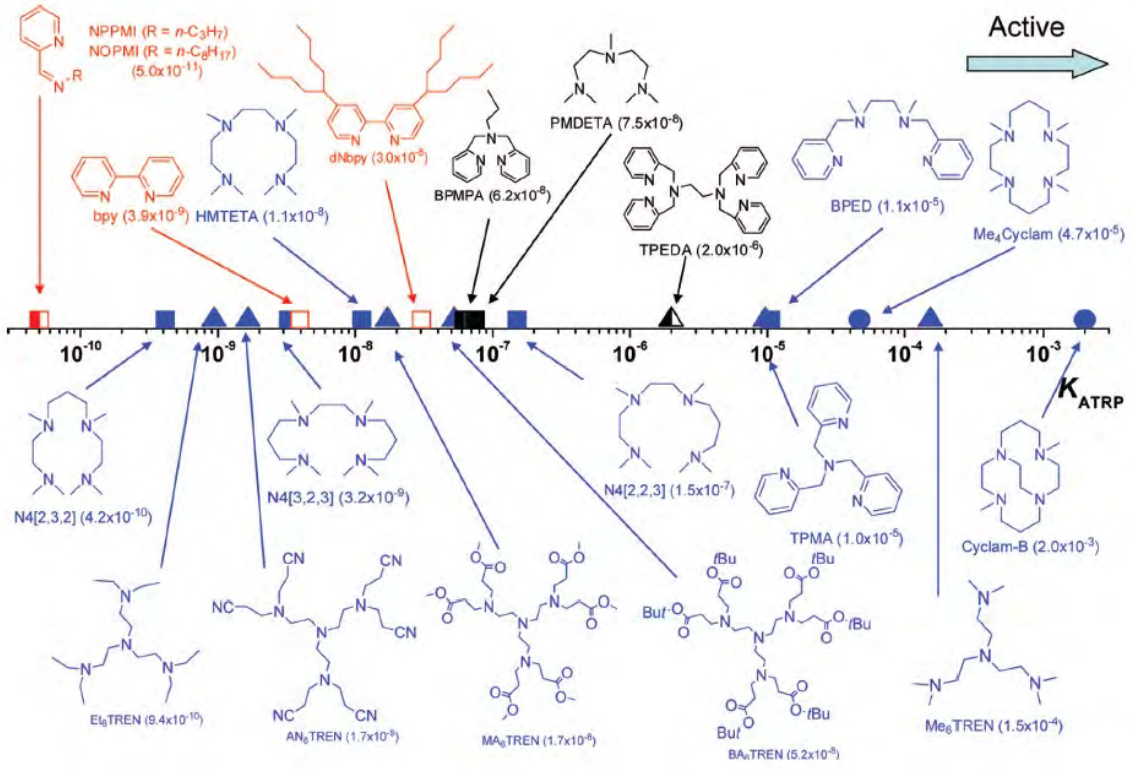
- Fast surface recombination in the case of free radical polymerisations: prevents brush growth.
- Controlled radical polymerisation techniques such as ATRP, RAFT or NMP can help reducing termination.
- Linear increase in thickness in living radical polymerisations.



1. Atom Transfer Radical Polymerisation – A Controlled Radical Polymerisation Technique



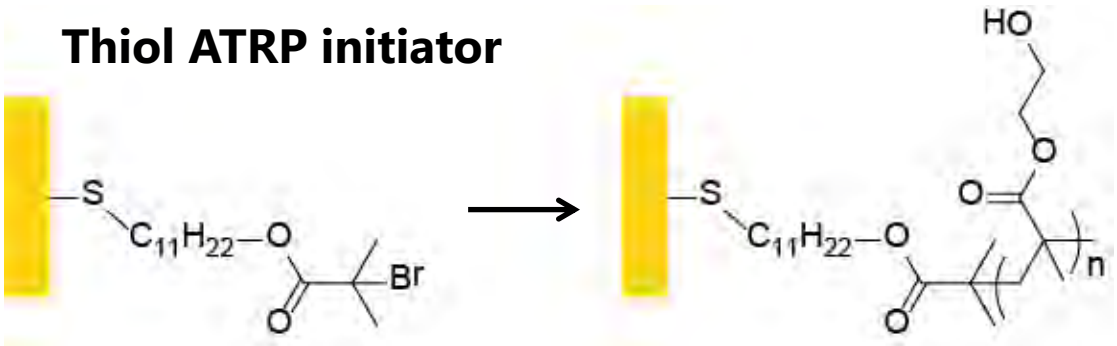
- Controlled radical polymerisations rely on the establishment of an equilibrium to reduce the instantaneous radical concentration.
- This results in a reduction in termination with a power 2 factor, essentially allowing radicals to persists throughout propagration.
- This can be used to generate a wide range of polymer architectures with multiple blocks, star shapes or brush structures.



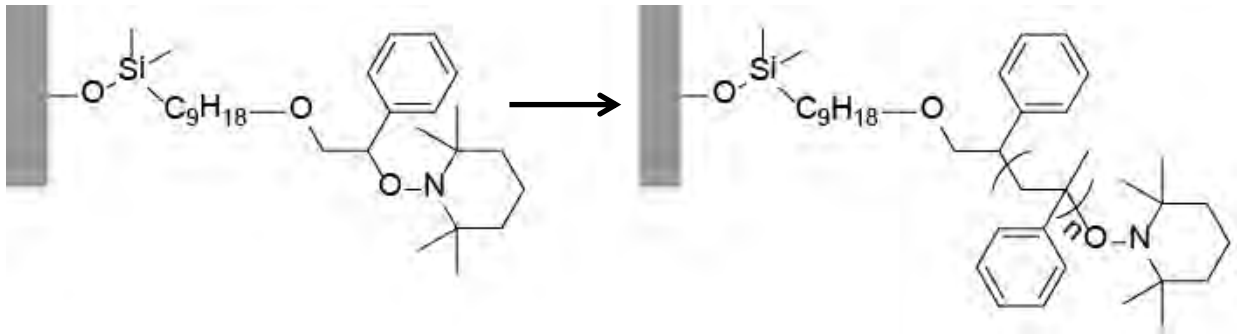
Chem. Rev. 2001, 101, 2921
J. Am. Chem. Soc. 2008, 130, 10702

1. Examples of Surface Initiating Systems

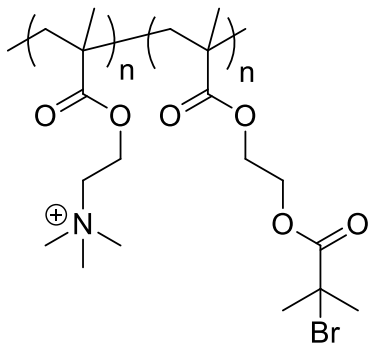
Thiol ATRP initiator

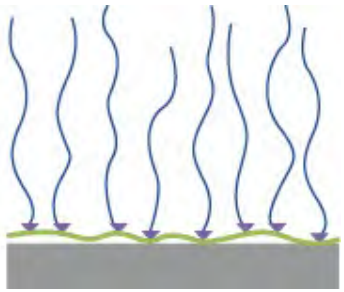


Silane NMP initiator



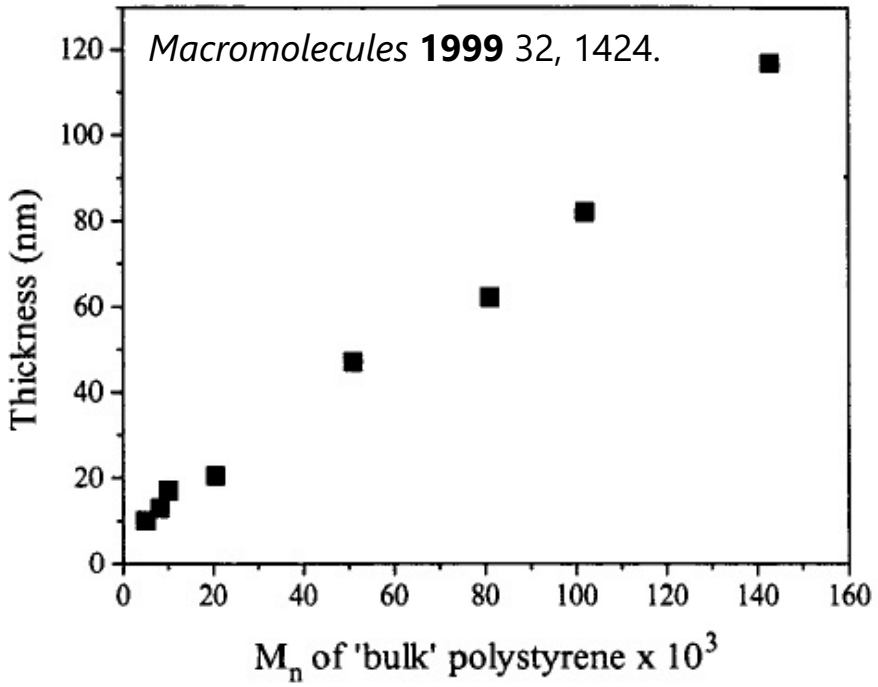
ATRP macro-initiator

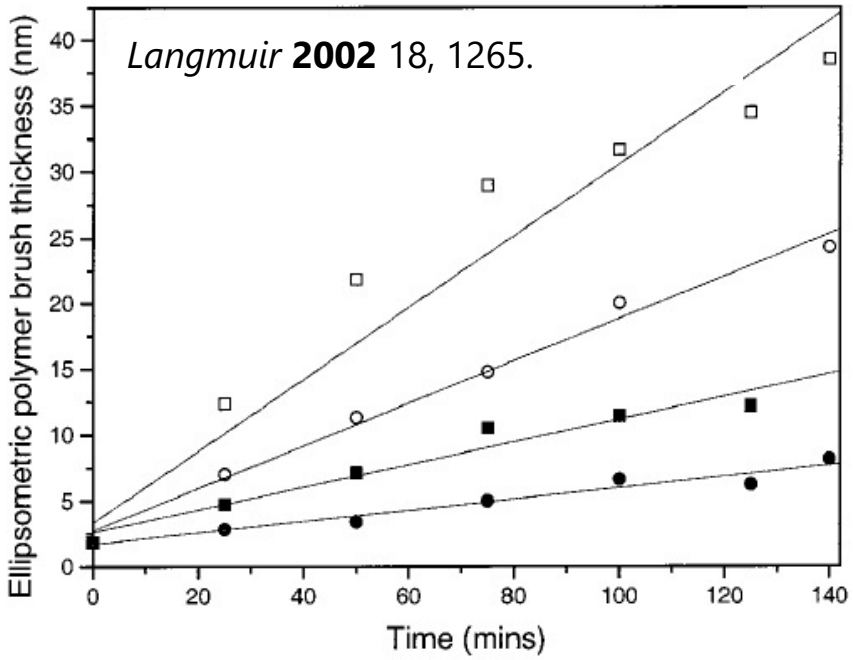




- Different initiators used for functionalising different substrates.
- The active functionality can remain the same or be tuned to the monomer type.
- Functionalisation of a wide range of surfaces (mica, silica, polymer…), providing they are charged or can be functionalised to display surface charges.
- ATRP initiator easily coupled to PHEMA backbone.

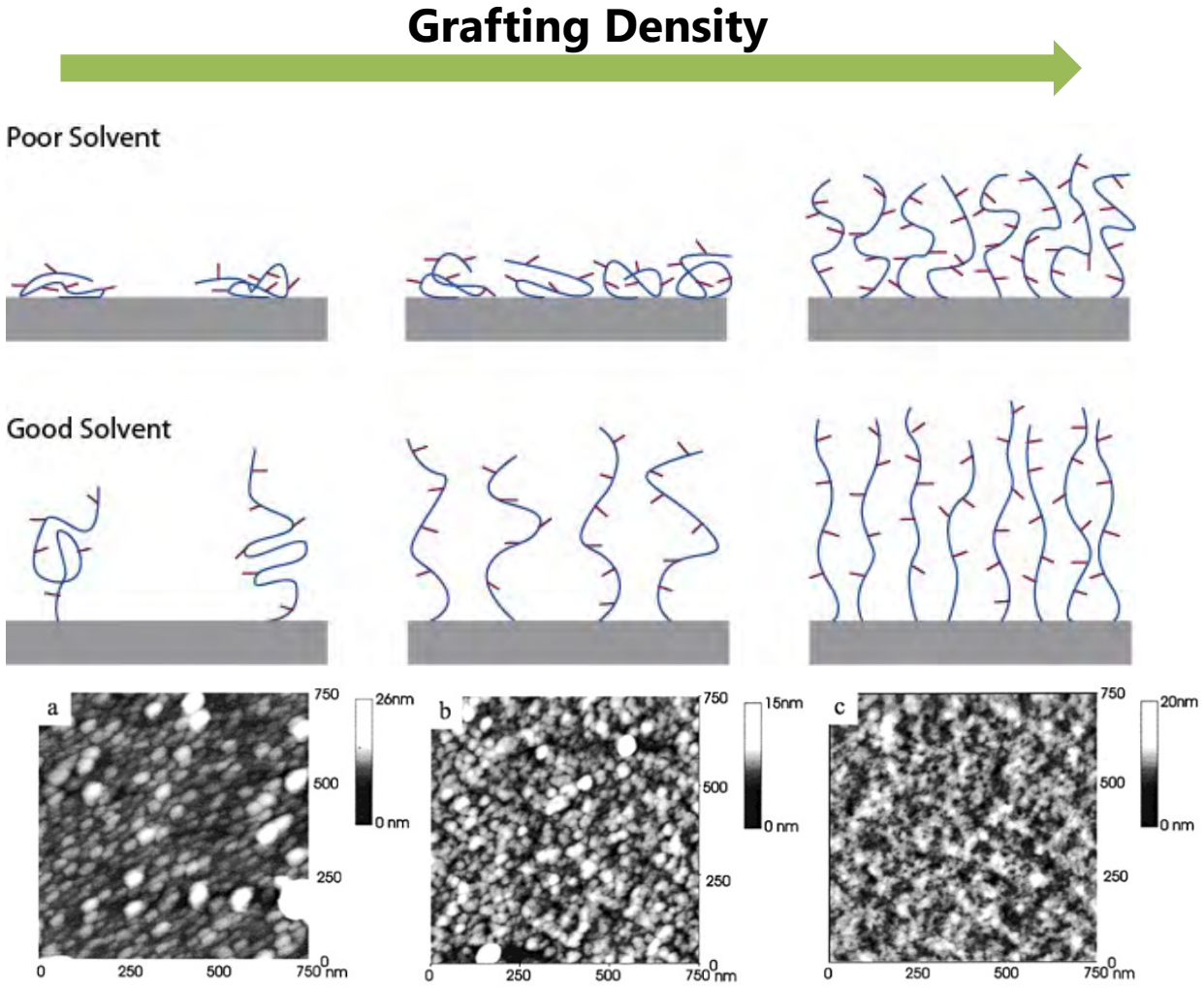
1. Typical Brush Growth Profile





- As predicted by the model of Alexander, a linear increase of thickness with increasing molecular weight of polymer chains is typically observed.
- Similar profile if plotting the increase in thickness as a function of time.
- Often the line does not cut the y axis at 0, but slightly above. Also levelling off after some time.
- Kinetics and profiles are strongly impacted by environmental parameters (solvent, pH, electrolytes, types of catalyst and ligands).

1. Impact of Density on the Morphology of Brushes

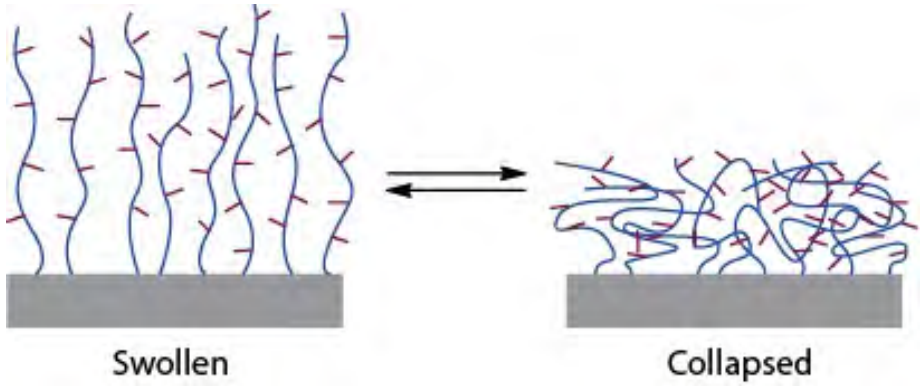


Langmuir **2002** 18, 1265.

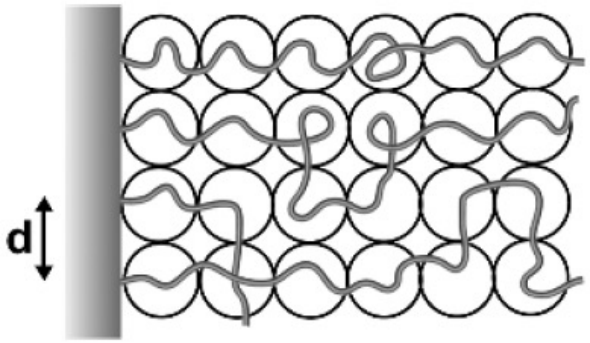
- In poor solvents, the grafting density leads to wide changes in brush height.
- In a good solvent, especially for charged polymers (polyelectrolytes), chains are more globular and even stretched to decrease osmotic pressure.
- The grafting density and interactions between brush, solvent and substrate hugely impact the surface morphology.

1. Predicting the Swelling of Brushes

- Alexander model describes the relationship between brush height, degree of polymerisation (so chain length) and the grafting density.
- Linear relationship between the brush height and the degree of polymerisation (here noted N).
- The quality of the solvent is particularly important.



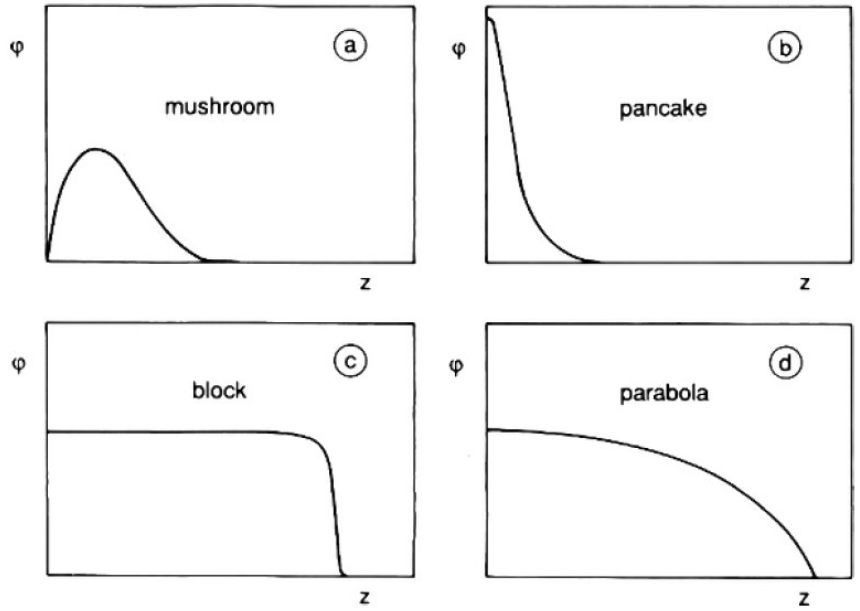
Alexander model



h, brush height.
N, degree of polymerisation.
σ, grafting density.

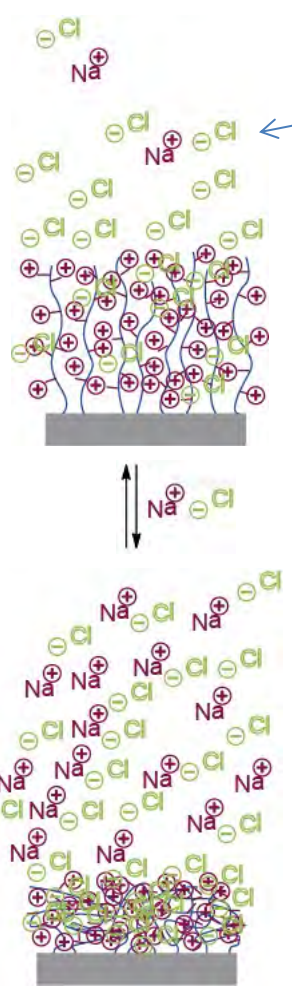
$h \sim N \times \sigma^{1/3}$

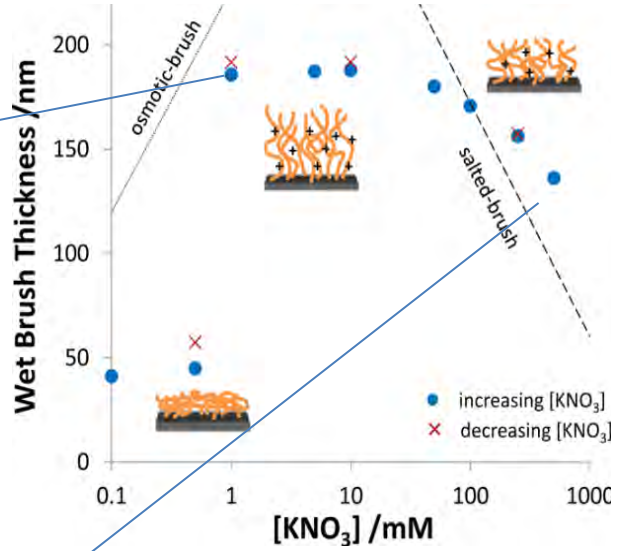
$h \sim N \times \sigma^{1/2}$



1. Responsive Brushes

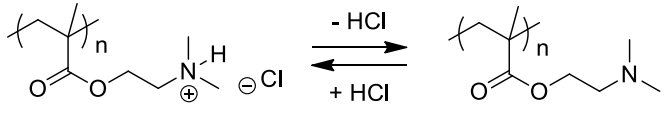
Ion Response

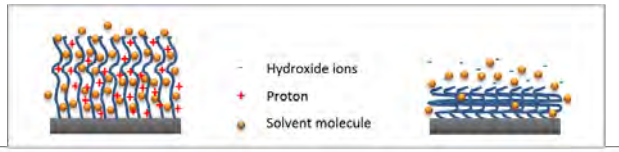


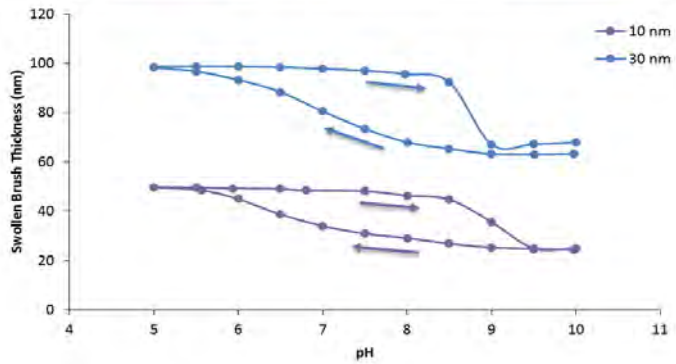


Langmuir, 30 (2014), 1827-36

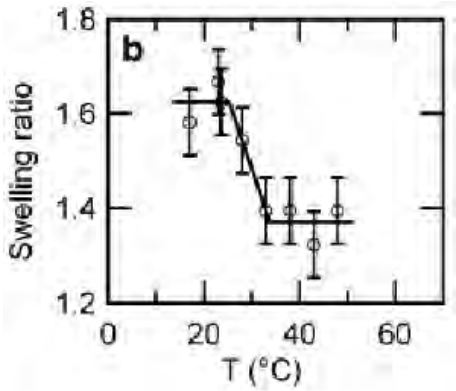
pH Response

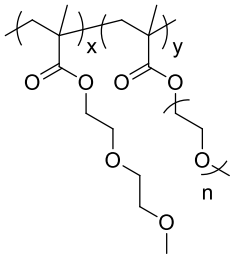






Temperature Response

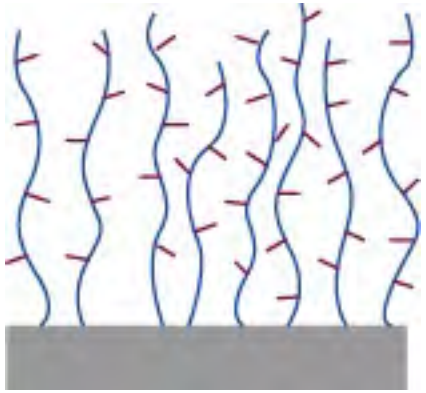




Macromolecules, 40 (2007), 4403-05

- Depending on the chemistry of brushes, their swelling and collapse can be altered by environmental parameters such as ionic strength, ion type, pH, solvent or temperature.
- Such phenomena can be used to design sensors and biosensors.
- It is also important to design and understand interfaces for other applications, in which such physico-chemical properties my impact other processes, as in cell and tissue culture platforms to generate cell sheets.

Design of Polymer Brushes for the Biomedical Field



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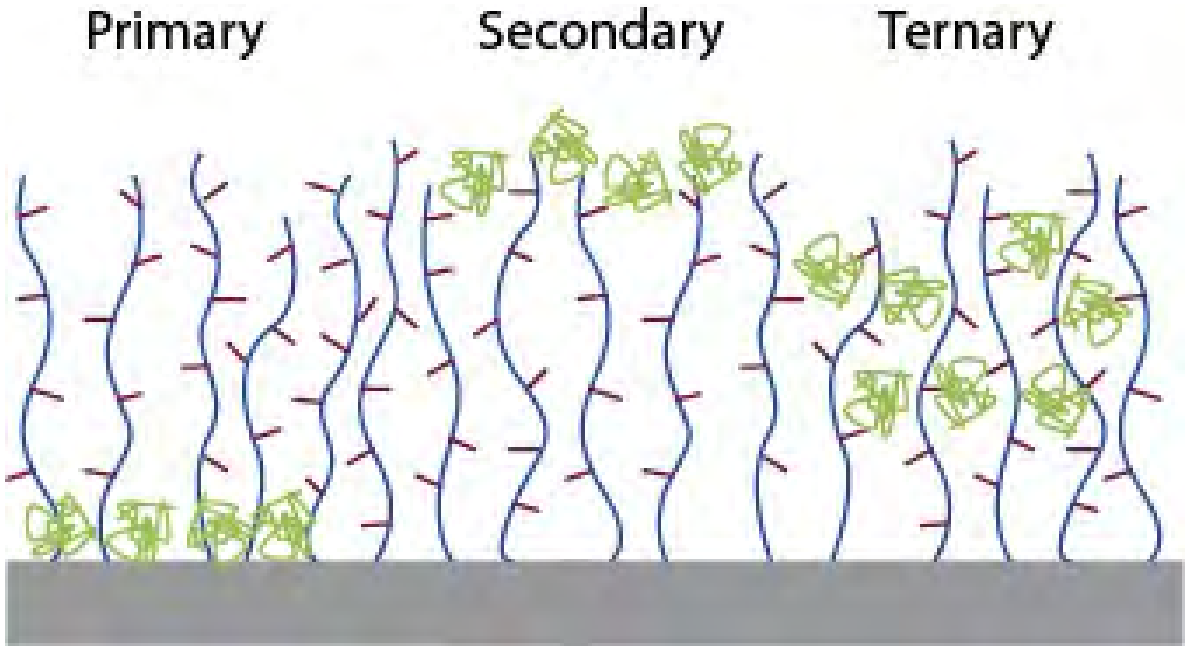
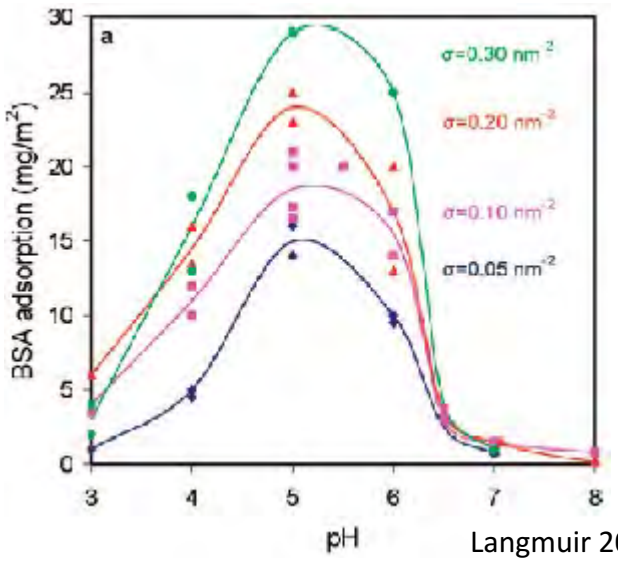
2. Biomacromolecular Interactions with Polymer Brushes



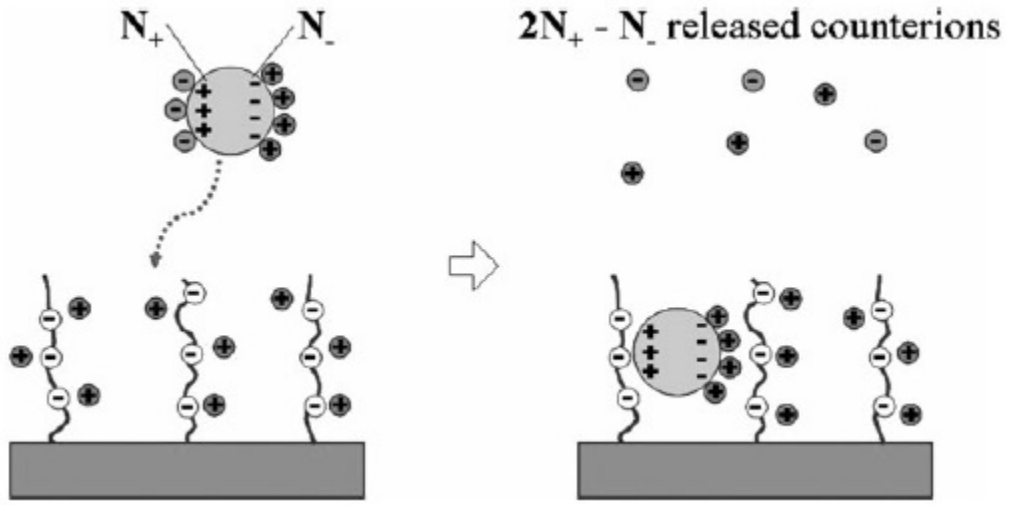
- A range of biomacromolecules may interact with polymer brushes, further impacting their (bio)physico-chemical properties and altering their performance for biomedical applications.
- Protein adsorption results from a collection of hydrophobic, electrostatic and hydrogen bonding-based forces.
- It is opposed to the brush osmotic pressure and associated restriction in diffusion through the brush thickness.

2. Protein Adsorption to Polyelectrolyte Brushes

Protein adsorption to poly(acrylic acid) brushes



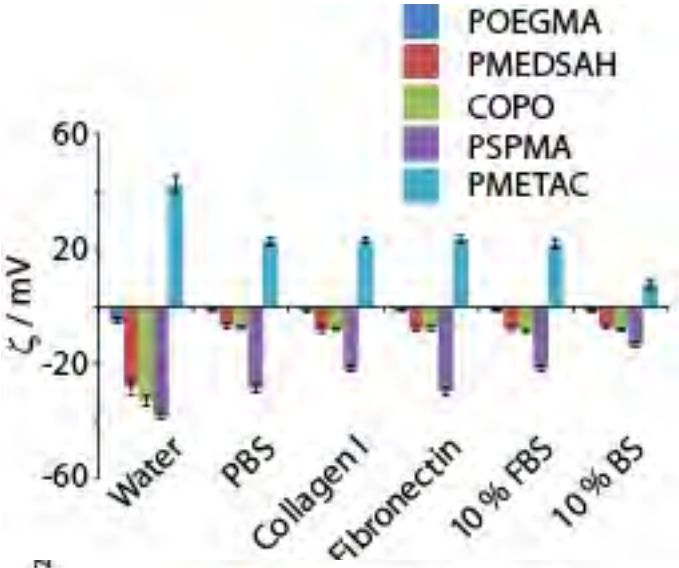
Langmuir 2008, 24, 6575

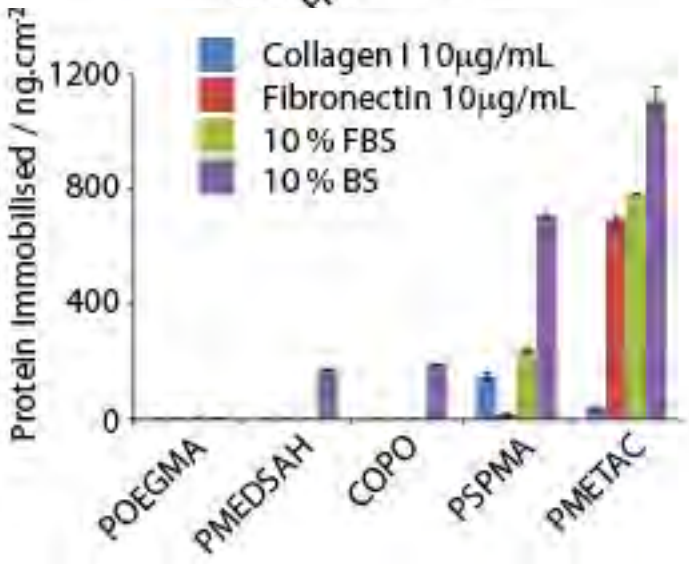


Phys. Chem. Chem. Phys. 2006, 8,5269

- Protein adsorption is driven by the brush structure and chemistry.
- Like-charged proteins can still adsorb to polymer brushes, although often more weakly.
- Entropically-driven process.
- It results in the transformation of the surface physico-chemical properties.

Impact of Brush Chemistry

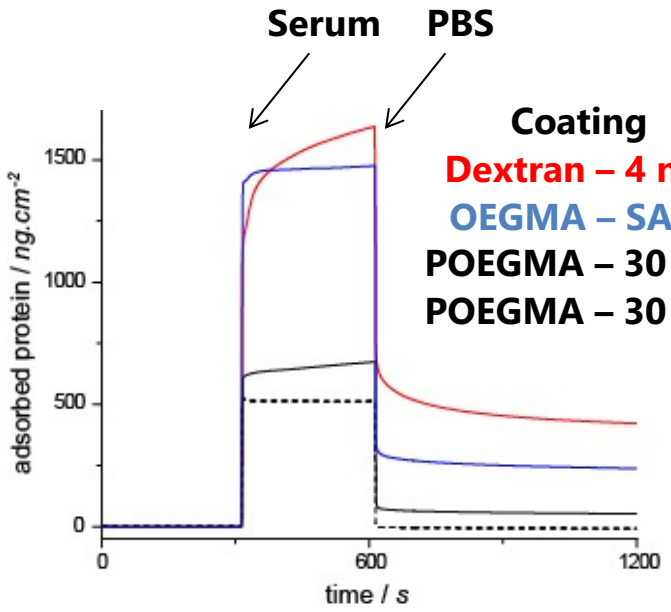




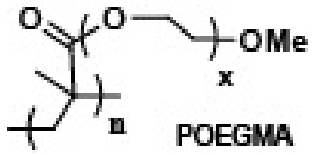
Integr. Biol. 2013, 5, 899

2. Protein Resistance

Determination of non-specific binding by SPR



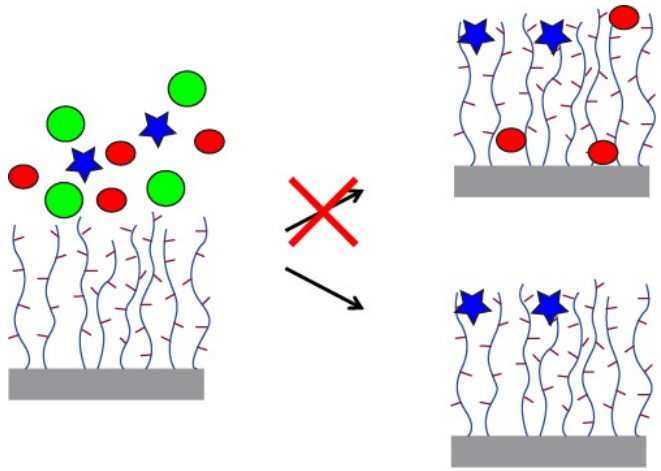
Coating	Serum	
Dextran – 4 nm	WHS	———
OEGMA – SAM	WHS	———
POEGMA – 30 nm	WHS	———
POEGMA – 30 nm	FBS	- - - - -



WHS: Whole Horse Serum

FBS: Foetal Bovine Serum

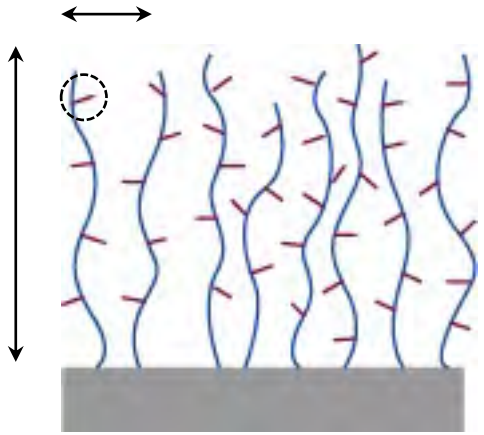
Non-specific binding

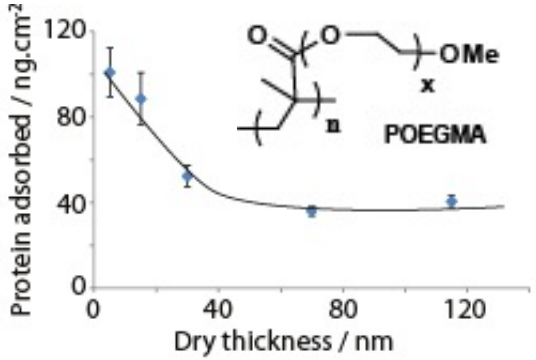


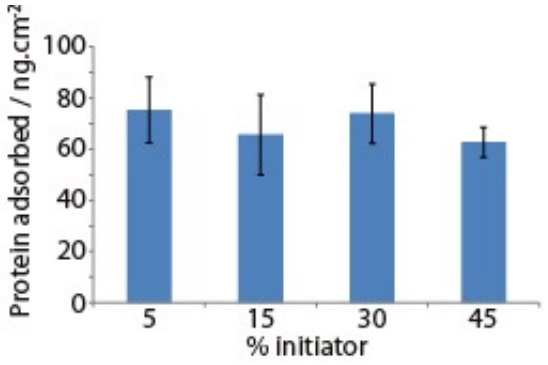
Specific recognition

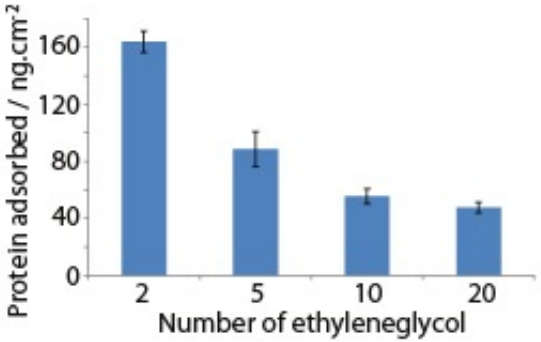
- Non-specific adsorption is key in the determination of the bioactivity of biomaterials.
- In some cases it is beneficial (for example to promote cell adhesion), but often results in poor and uncontrolled performance of biointerfaces.
- Polymer brushes are particularly good at resisting unwanted protein adsorption (proteins cannot diffuse through the dense brush easily).

2. The Role of Brush Architecture on Protein Resistance

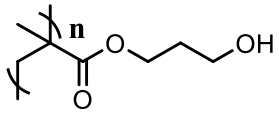






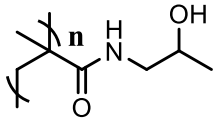


- The brush architecture (thickness, grafting density, length of side chains) plays an important role in dictating protein resistance.
- But the chemistry of the repeat units is prevalent.
- Some brushes are so protein resistant that protein adsorption is beyond the detection limit of highly sensitive techniques such as SPR or QCM.



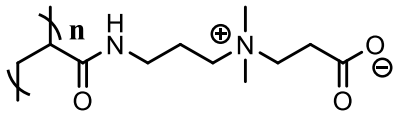
Human Serum: 24.5 ng.cm^{-2}
Human Plasma: 52.8 ng.cm^{-2}

Zheng et al. Langmuir 2010, 17375.



PHPMA
Human Plasma: < 0.03 ng.cm^{-2}

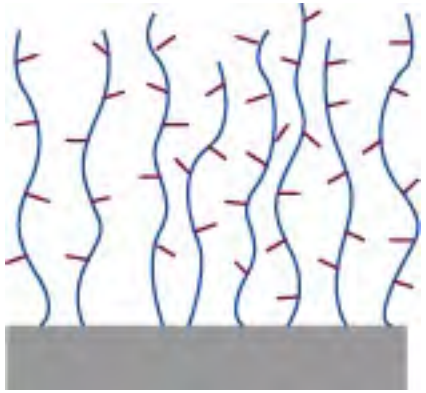
Cesar Rodriguez-Emmenegger Macromol. Rapid Comm. 2011, 952.



PCBAA
Human Plasma: < 0.03 ng.cm^{-2}

See also: Jiang et al. Langmuir 2009, 11911; Anal. Chem. 2008, 7894.

Design of Polymer Brushes for the Biomedical Field



1. Synthesis and physico-chemical properties.
2. Interactions with biomacromolecules.
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4. Polymer brushes for biosensing.
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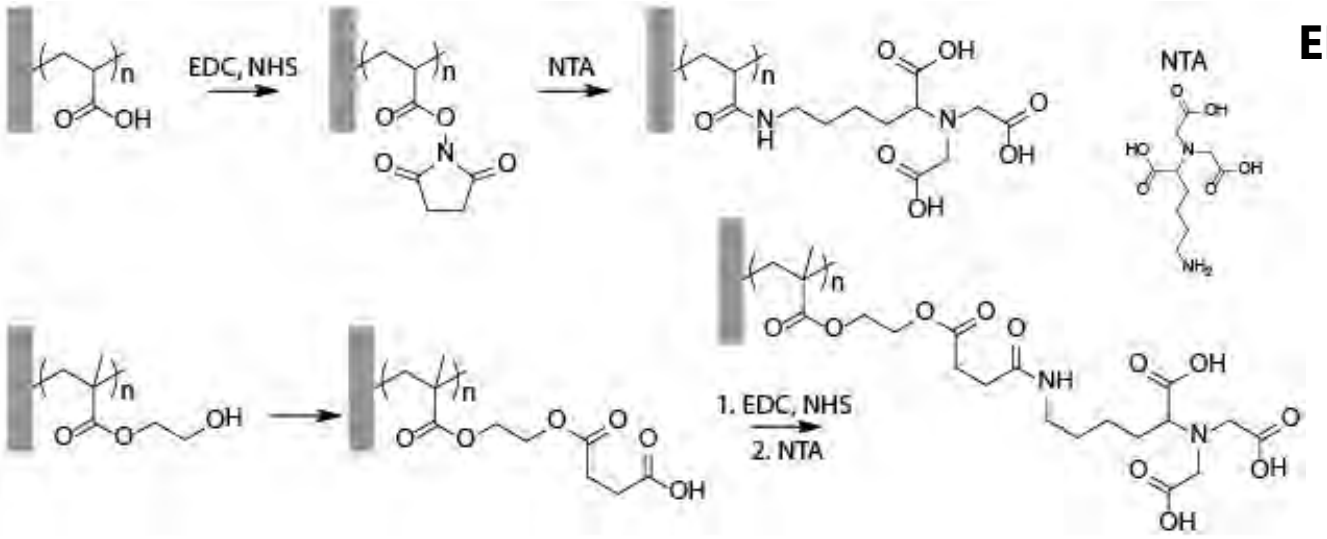
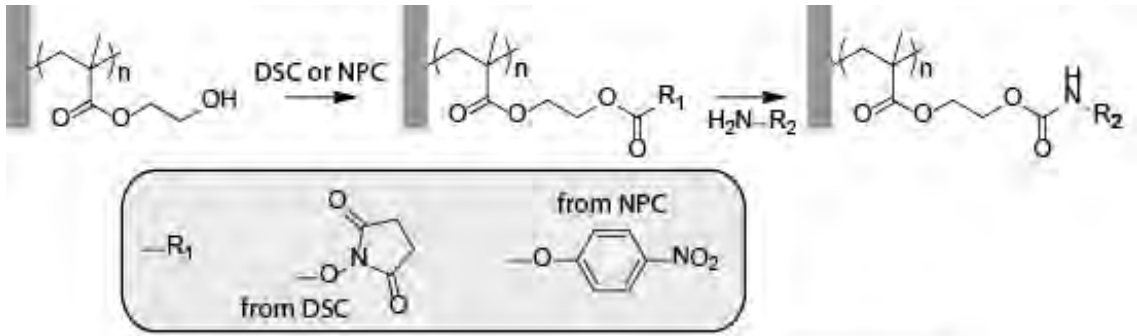
3. Coupling of Amines to Carboxylic Acids and Hydroxyls

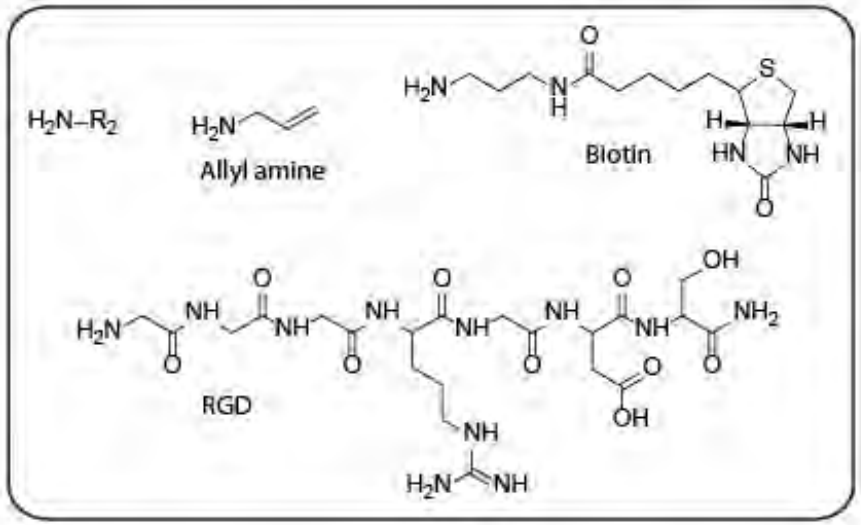


EDC/NHS Coupling to Carboxylic Acids

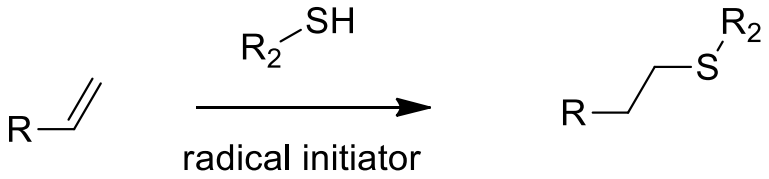
DSC or NPC Coupling to Hydroxyls

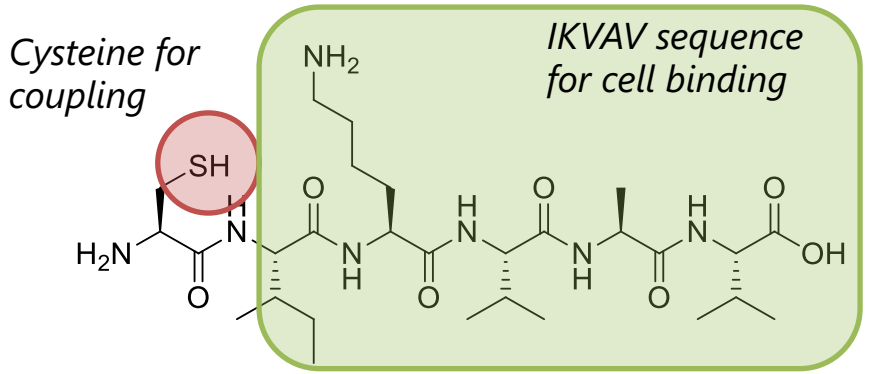


- Carboxylic acids need to be activated in order to react effectively with amines (typically primary), forming amide bonds.
- Hydroxyls can either be converted into acid functions or can be activated with carbonates (i.e. DSC) or chloroformates (i.e. NPC), prior reaction with amines to form urethane bonds.
- These reactions lack specificity and can be relatively sensitive to water (e.g. in the case of EDC/NHS coupling).

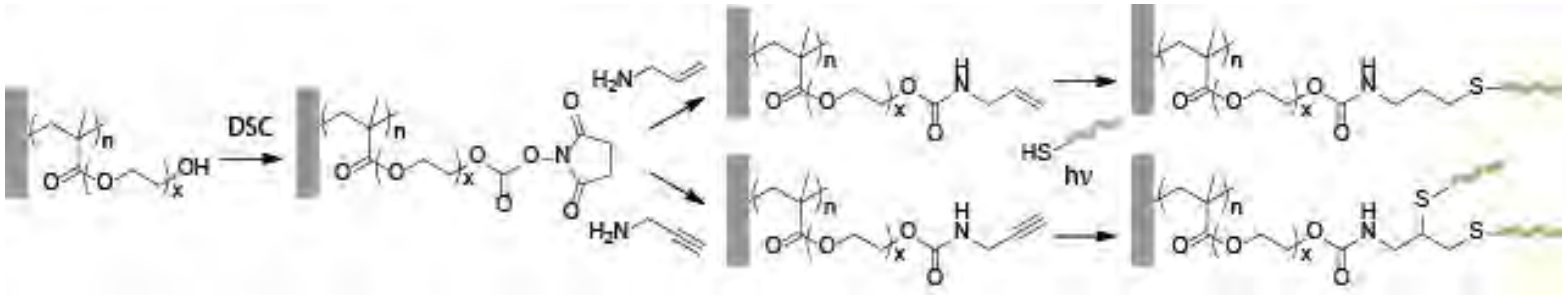


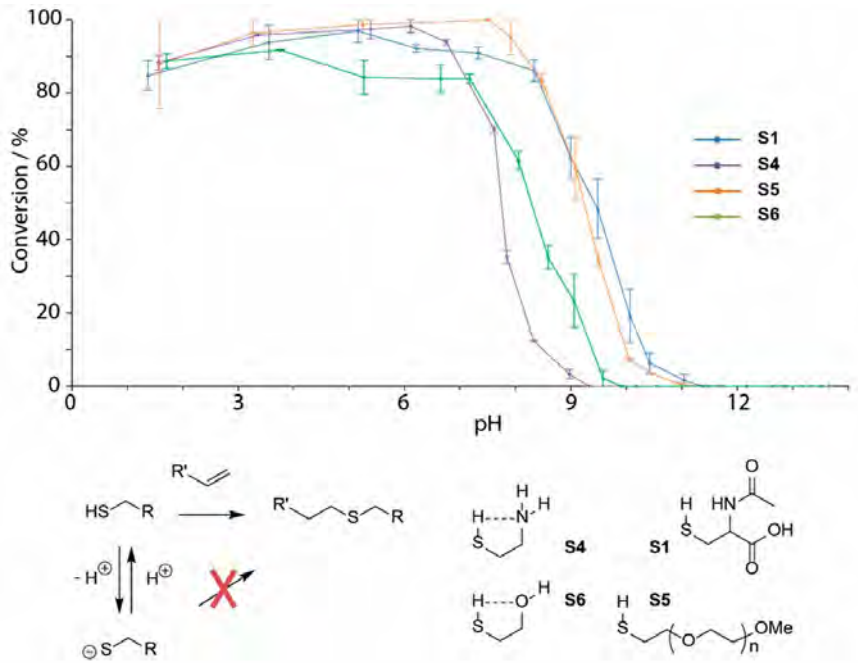
3. Coupling of Peptides via Cysteines using Thiol-Ene Chemistry





- Thiols are attractive moieties for the coupling of biomolecules such as peptides, as naturally occur, with cysteines.
- Thiol-ene coupling is very specific, especially if alkenes that are not active for Michael additions are use.
- This reaction is relatively tolerant to oxygen, although at low concentration it can be affected (not always negatively).
- The position of the cysteine is important (not N –terminal for radical thiol-ene and terminal for Michael addition).

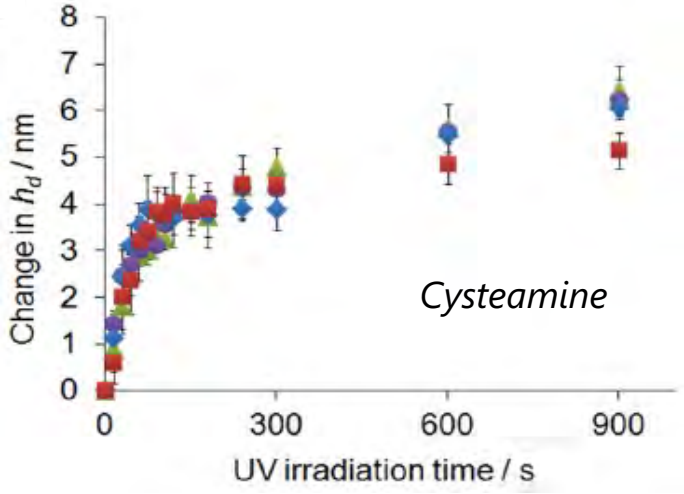


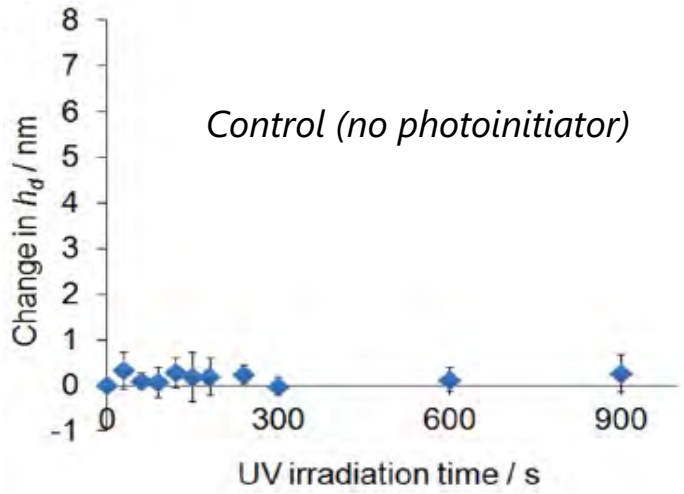


Colak et al. Bioconjugate Chem. 2016, 27, 9, 2111–2123.

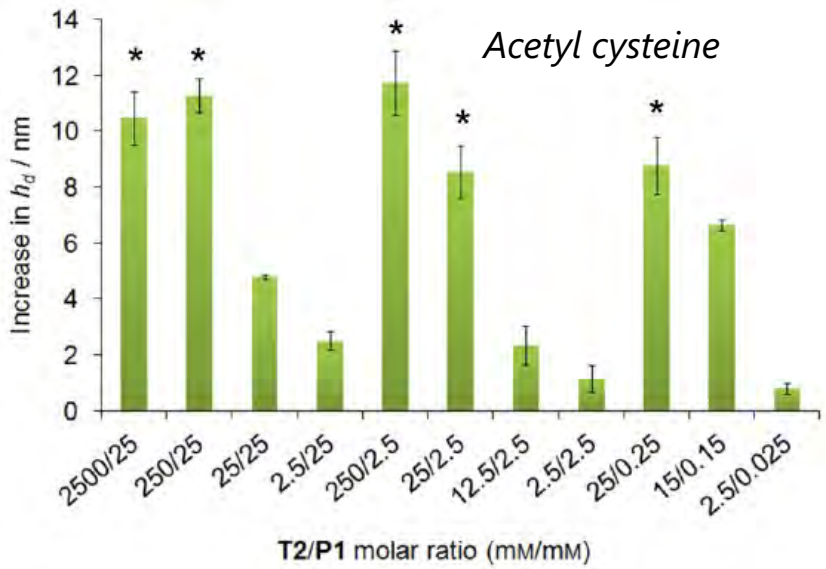
3. Optimising Thiol-Ene Reactions on Brushes and for Patterning

Following Coupling via Ellipsometry

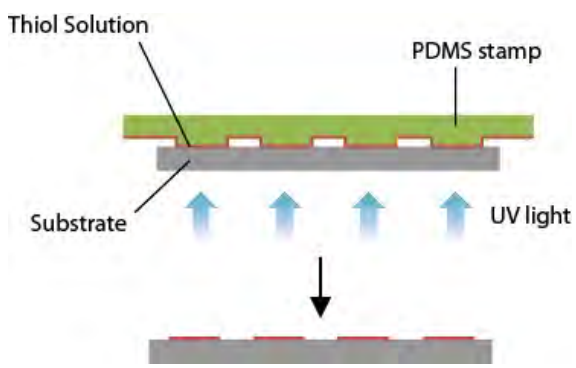


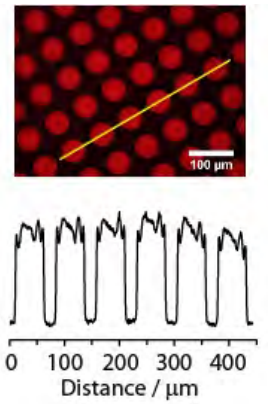


Impact of thiols/photoinitiator (T/P)



- Fast coupling to polymer interfaces, leading to slight increase in thickness associated with the mass added.
- Ratios of thiol/initiator and their concentration has a large impact on the coupling: catalytic reaction (1 radical can enable many coupling reactions).
- Sufficiently active and oxygen tolerant to enable reactive microcontact printing and patterning.

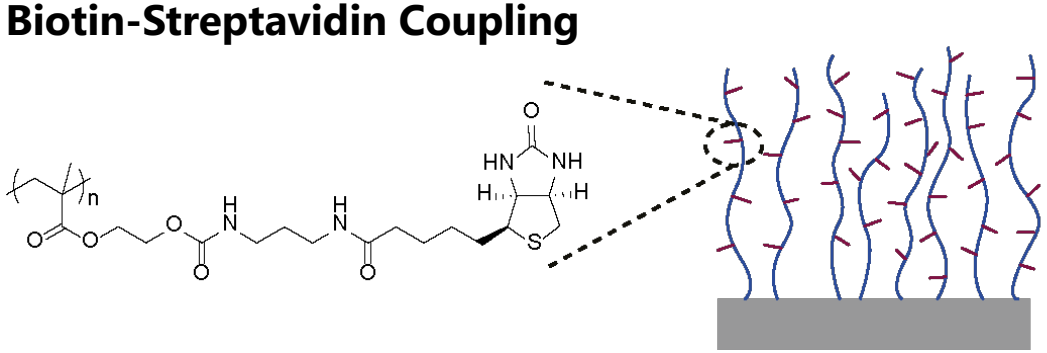


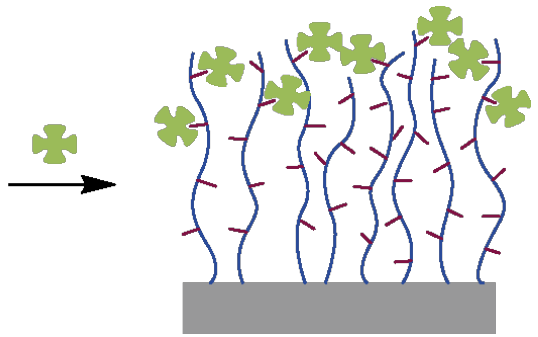


Queen Mary University of London

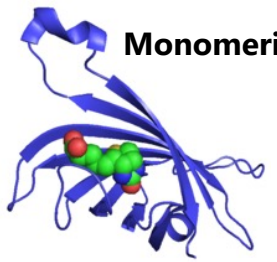
3. Coupling of Proteins using Biotin-Streptavidin Binding and Ni-NTA/His-Tags

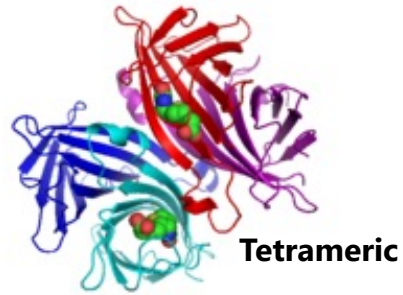
Biotin-Streptavidin Coupling



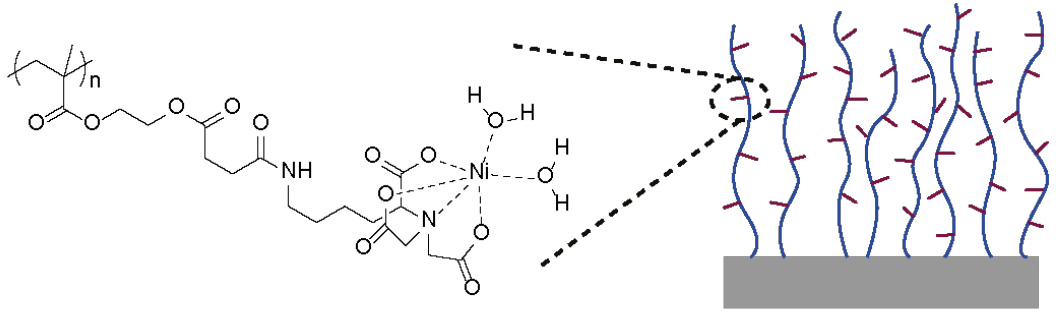


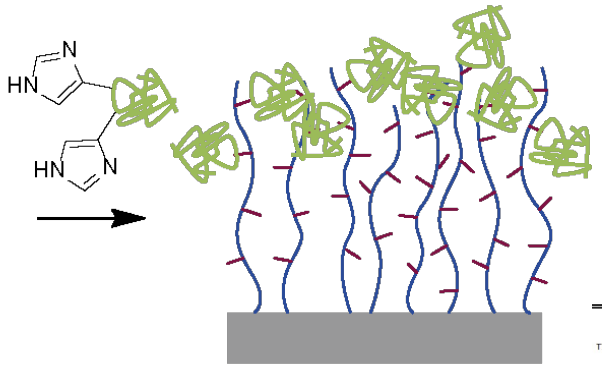
Streptavidin

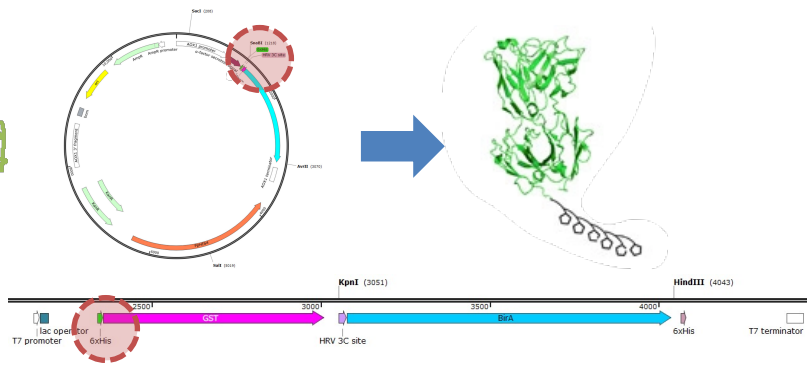




Ni-NTA/His-Tag Coupling

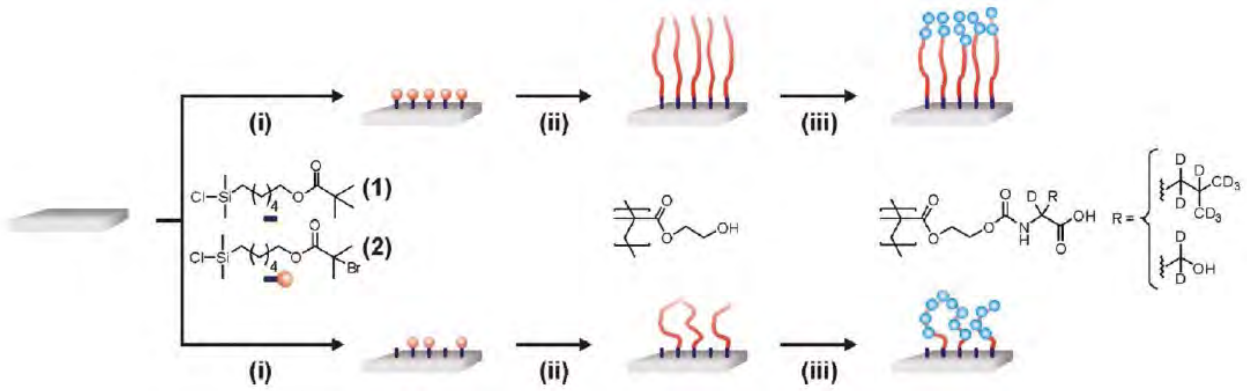


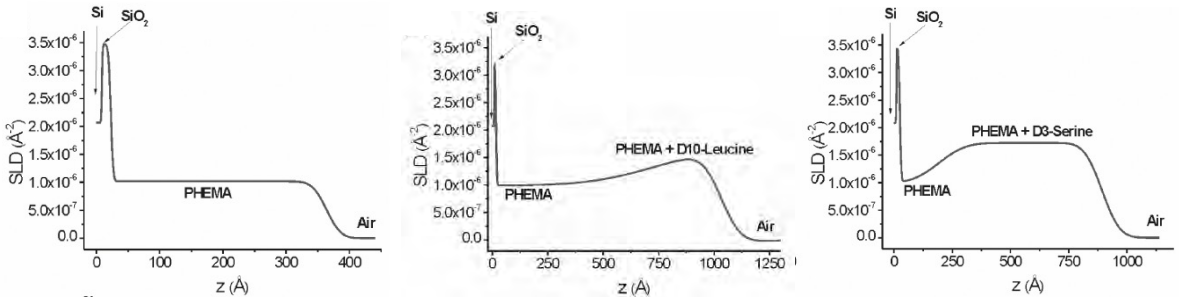




- Biotin binding to streptavidin and avidin with binding constants of 10^{14} and 10^{15} M^{-1}.
- Avidin has a higher affinity constant, but is more positively charged and tends to aggregate (harder to use).
- NTA ligands can capture histidine-tagged proteins (6-10 histidines in a row).
- Can be displaced to regenerate the surface and re-bind new proteins: often used to capture proteins for biosensors, but also for the purification of recombinant proteins.

3. Impact of the Brush Architecture on Biofunctionalisation





Macromolecules 2011, 44, 6868.

- Fast coupling to polymer interfaces, leading to slight increase in thickness associated with the mass added.
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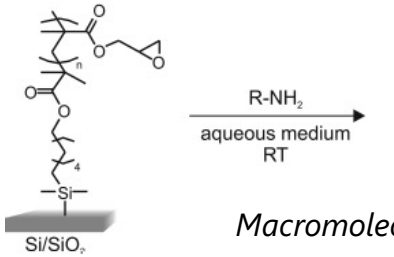
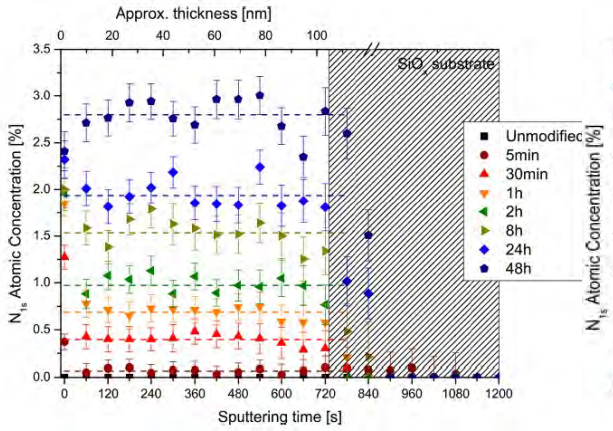
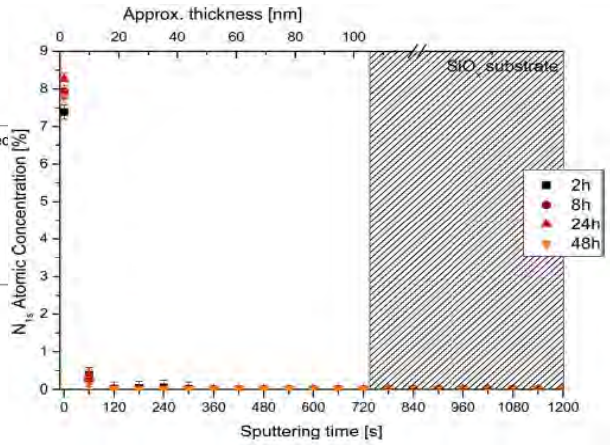


Macromolecules 2013, 46, 6151.

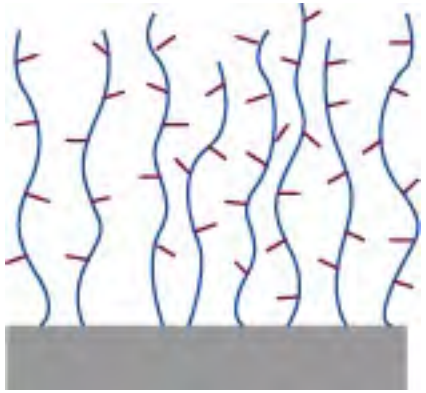
Small molecule



Protein



Design of Polymer Brushes for the Biomedical Field



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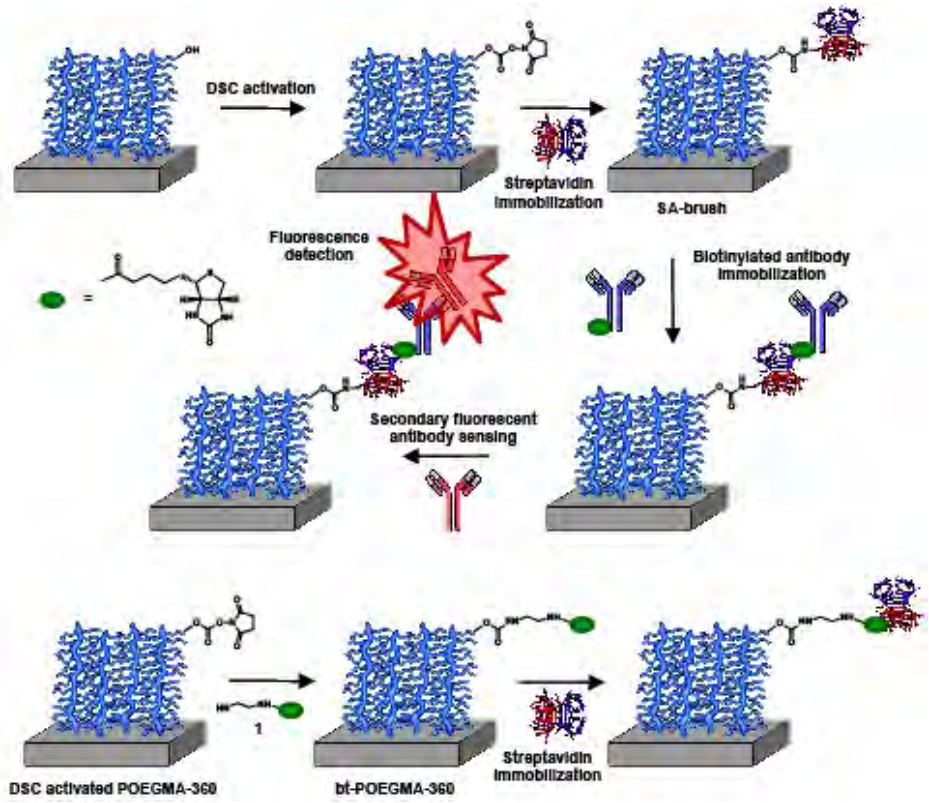
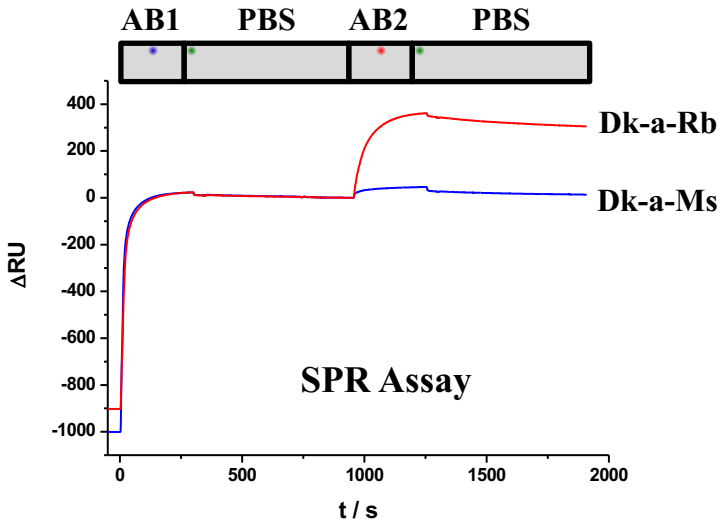
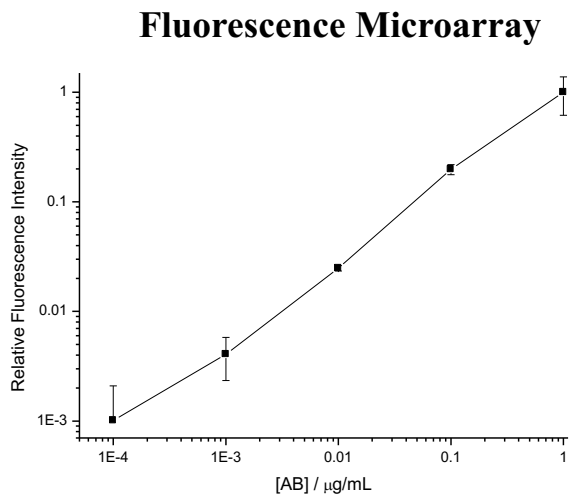
4. Biotin-Based Platforms for Biosensing



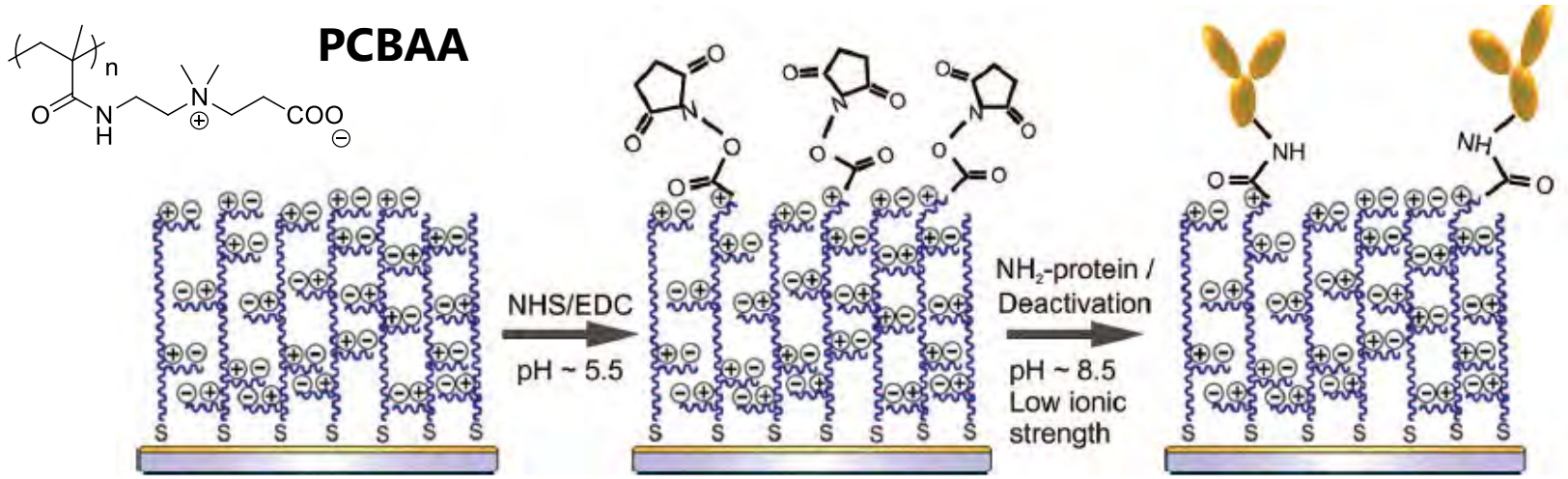
Trmcic et al. *Biomacromolecules* 2009



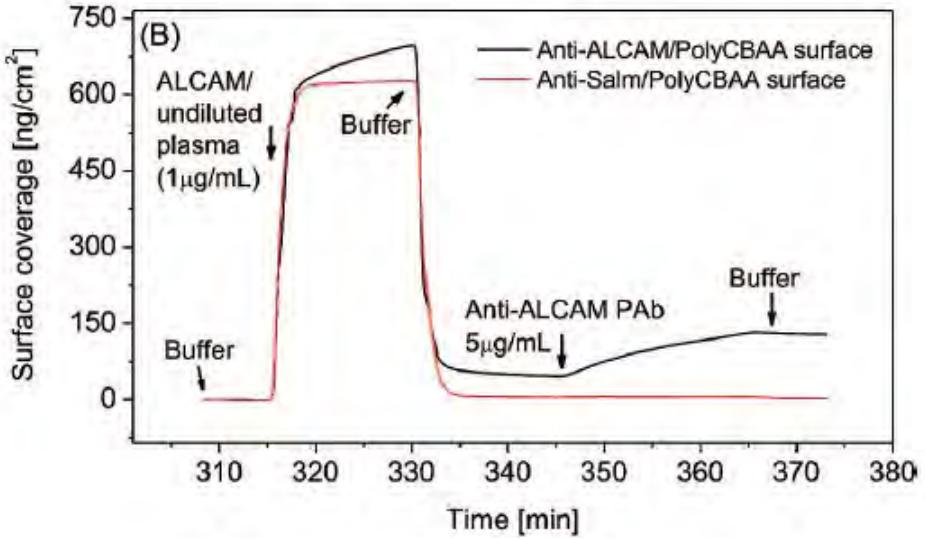


- Either direct coupling of streptavidin to the brush surface of via a biotin residue.
- Retains excellent background and protein resistance against non-specific binding.
- Detection down to the ng/mL range.

4. Zwitterionic Polymer Brushes for Biosensing in Blood or Plasma

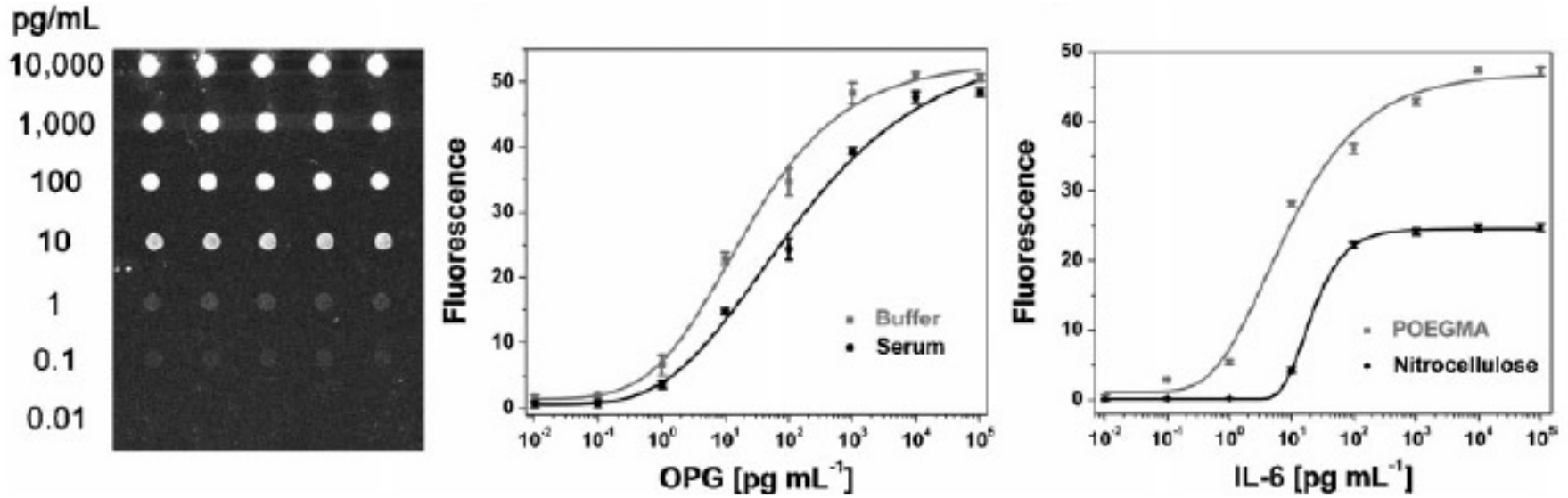


- Zwitterionic PCBAA (poly(carboxybetain acrylamide)) brushes are completely non-fouling, even in blood or plasma.
- After functionalisation with antibodies (e.g. EDC-NHS coupling), the detection of markers is enabled, even directly in plasma.
- Activated carboxylic acids can hydrolyse if not reacted, reversing to zwitterionic moieties (neutral), therefore retaining ultra-low fouling properties.



Biosensors and Bioelectronics 24 (2009) 1924
Anal. Chem. 2008, 80, 7894

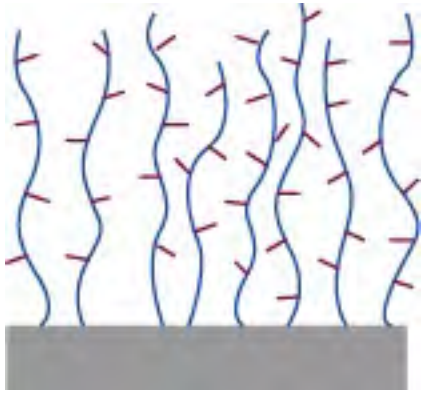
4. Antibody Micro-Arrays for Sensitive Biodetection



Adv. Mater. 2009, 21, 1–4

- No coupling of antibodies required for the infiltration of antibodies to poly(oligoethylene glycol methacrylate) (POEGMA) brushes: simple adsorption and partial drying after spotting (for printing of microarrays).
- Antibodies detect an analytes, followed by further interaction with a tagged antibody (sandwich assay analogous to many lateral flow tests).
- Excellent limit of detection in the pg/mL range.

Design of Polymer Brushes for the Biomedical Field



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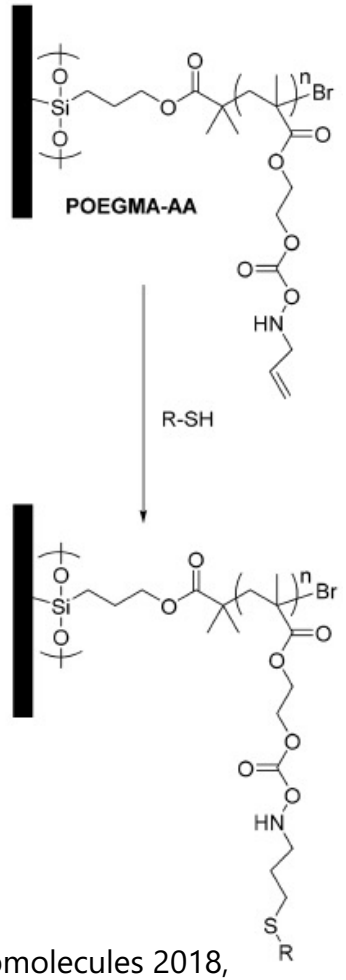
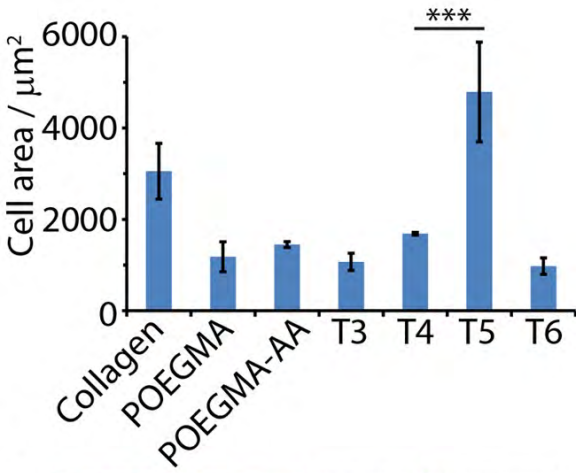
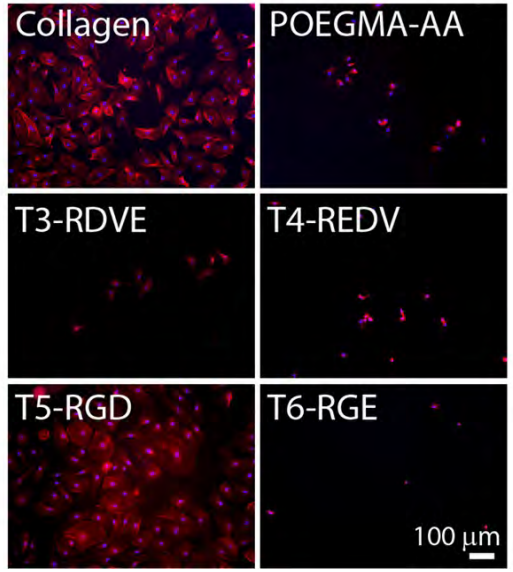
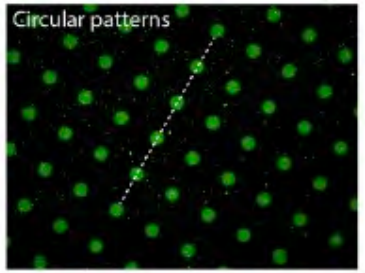
5. Peptide Micro-Patterning using Polymer Brushes

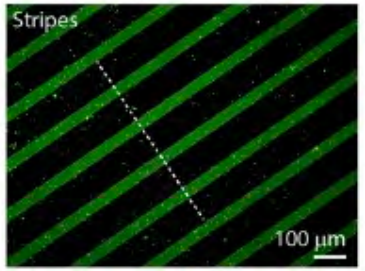


Biomacromolecules 2018, 19, 1445−1455

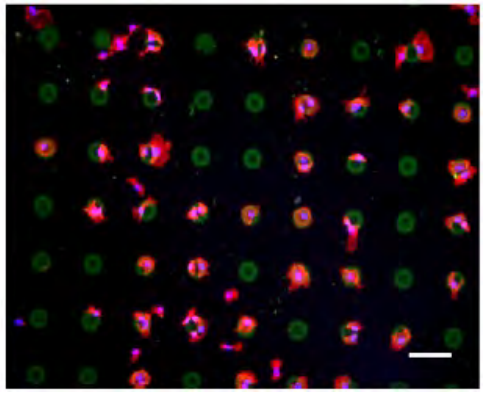






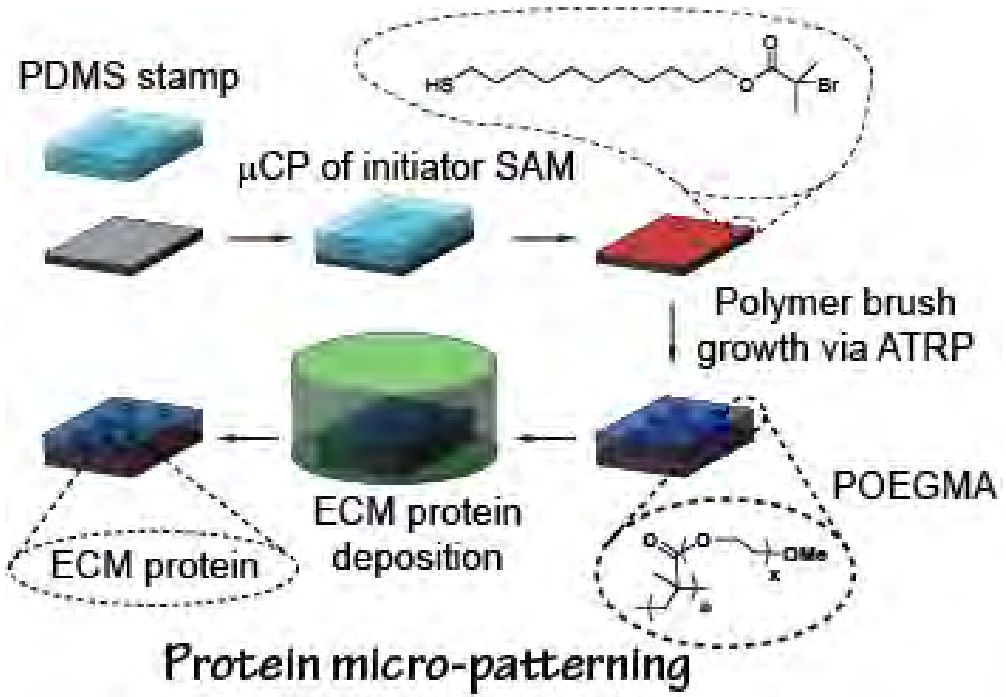


Peptide Patterning Guiding Cell Adhesion

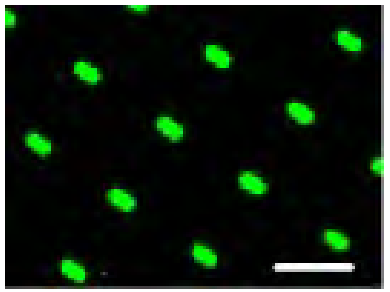


- Protein resistant POEGMA brushes can be activated for the coupling of alkene/alkyne molecules.
- Peptide functionalisation can then be mediated via thiol-ene/yne radical chemistry.
- This promotes specific and selective cell adhesion and patterning.

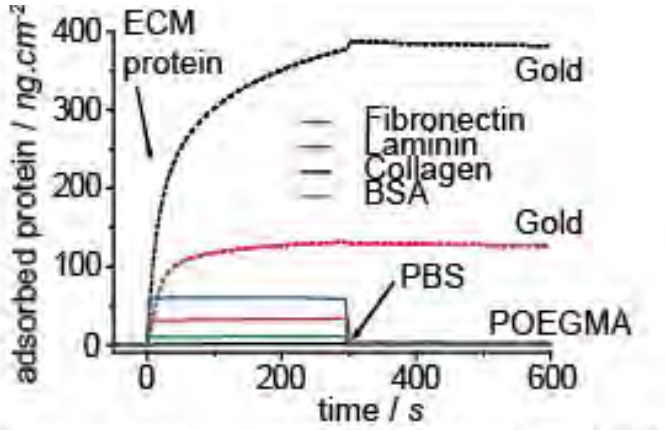
5. Protein Micro-Patterning using Polymer Brushes



Protein micro-patterning



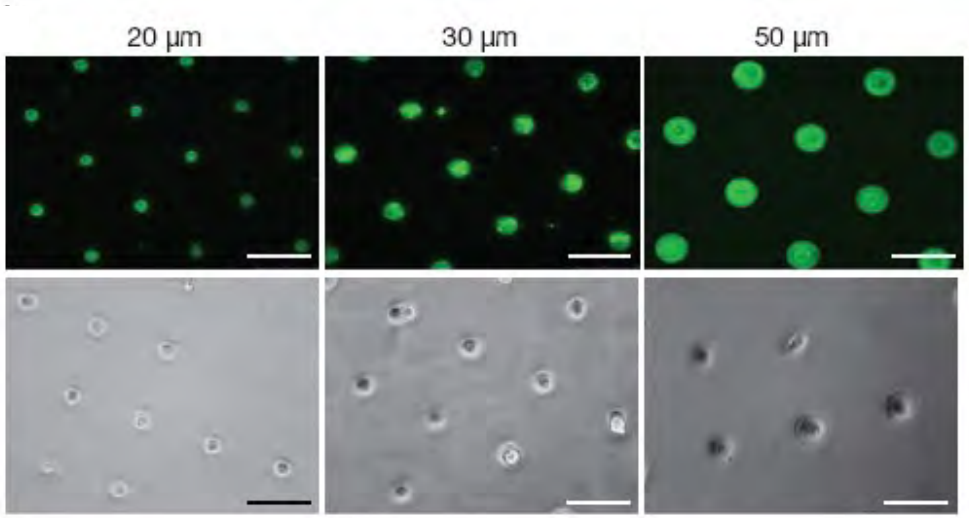
Gautrot et al.
Biomaterials 2010



Protein resistance examined by SPR

- Brushes can be patterned to restrict protein adsorption to defined areas.
- Use of ultra-low fouling protein resistant polymer brushes.
- Efficient and simple patterning of proteins with μm-resolution.

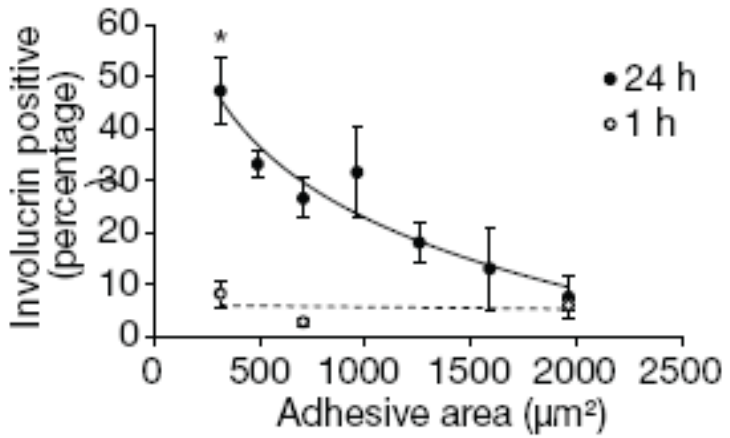
5. Shape Induced Differentiation Assay



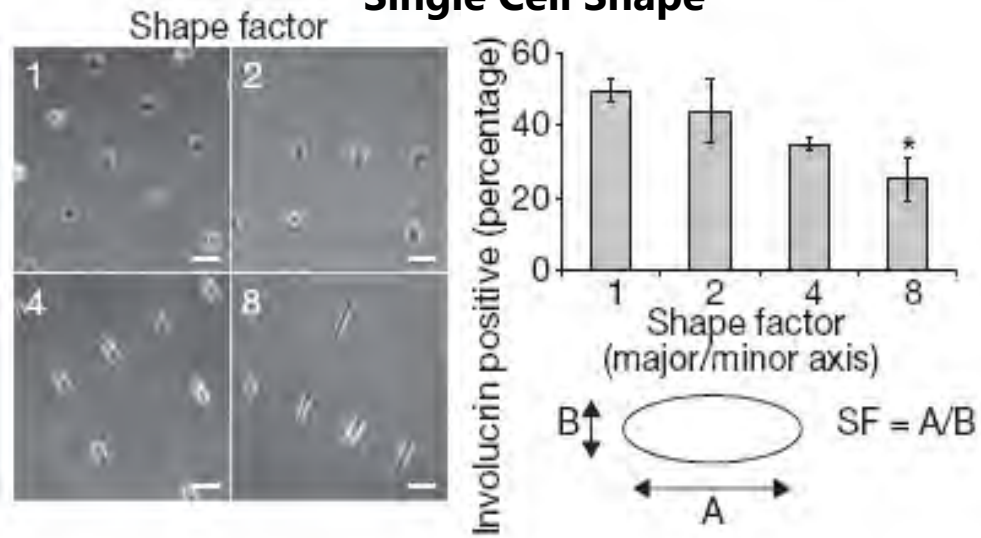
Connelly, Gautrot et al. *Nature Cell Biology* 2010

- ECM protein patterns (based on collagen or fibronectin) guide the formation of cell adhesions and control cell spreading.
- Cell adhesive islands area and shape directs cell spreading and shape.
- This in turn affects cell behaviour and differentiation.

Single Cell Spreading Area

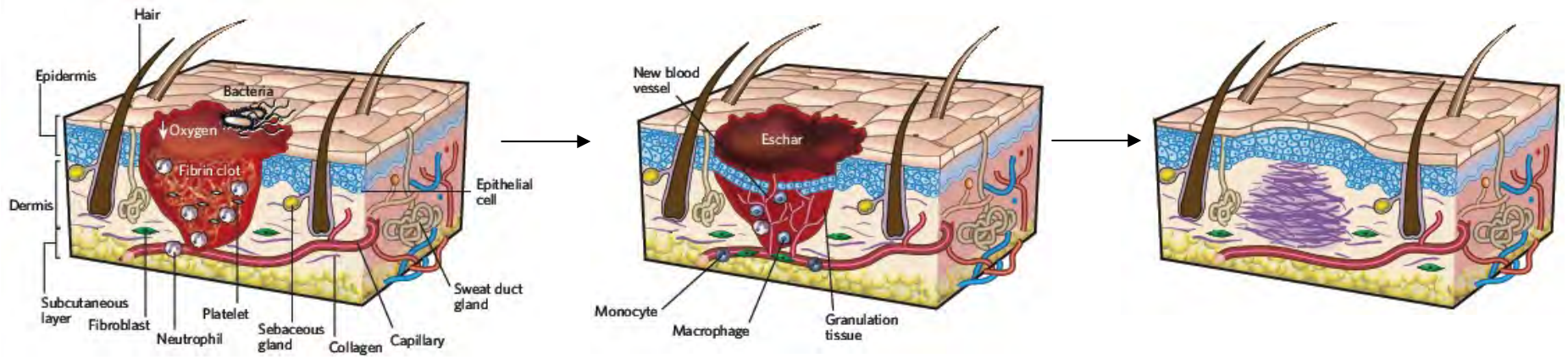


Single Cell Shape



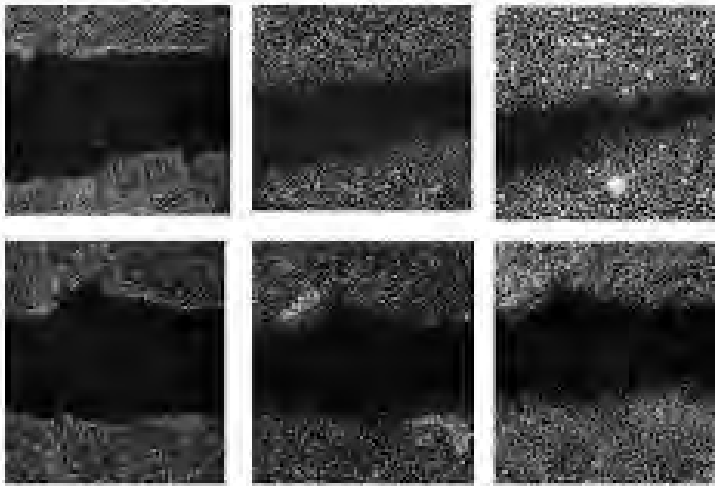
Queen Mary University of London

5. New Models for Wound Healing are Needed



Inflammatory stage **New Tissue Formation** **Remodelling**

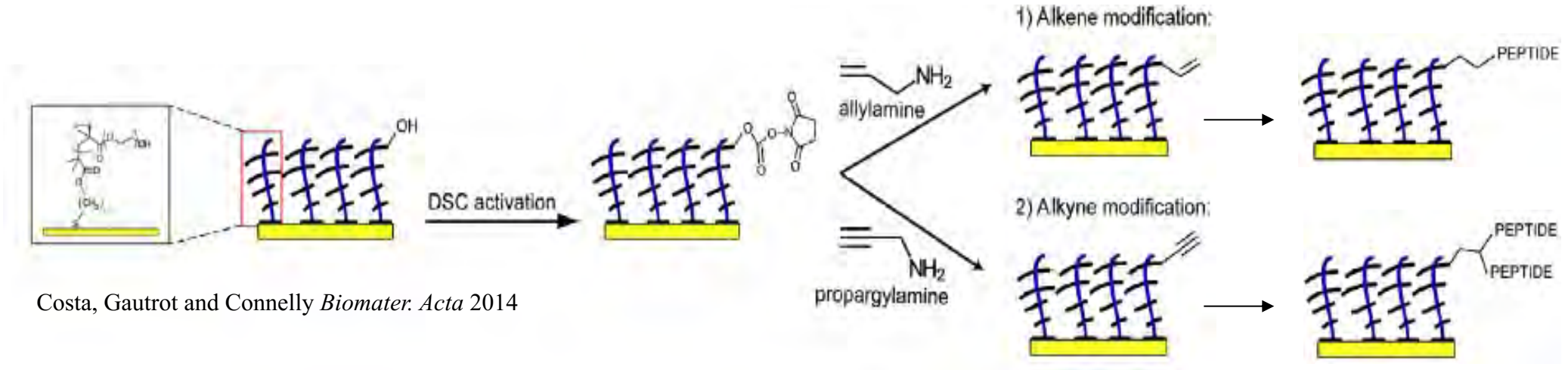
Gurtner et al. *Naure* 2008



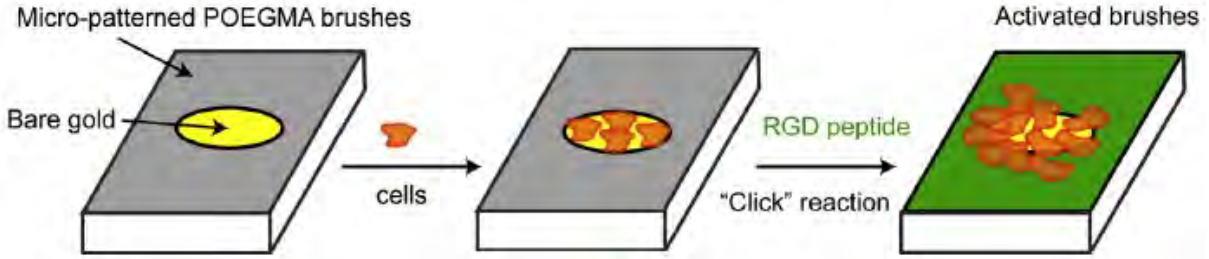
Scratch assay

- Consists in forming a cell monolayer and inducing a scratch before monitoring the closure of the “wound”.
- No real control on the wound bed geometry and the process can be difficult to automate.
- It is currently difficult to control the matrix biochemistry and mimic the microenvironment of a wound bed.

5. Polymer Brushes for the Dynamic Control of Cell Adhesion

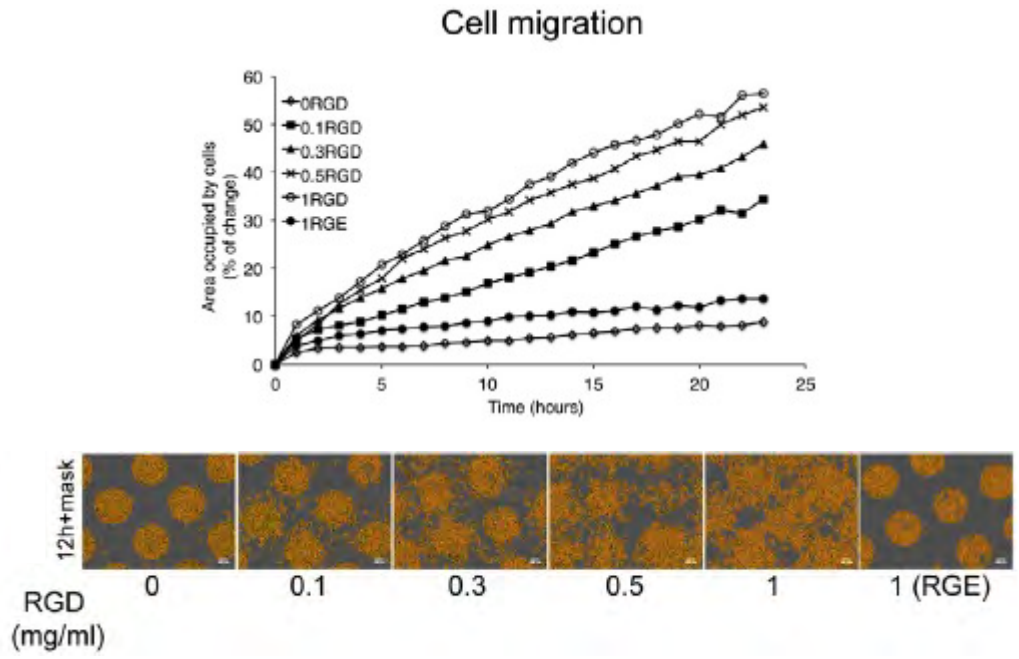


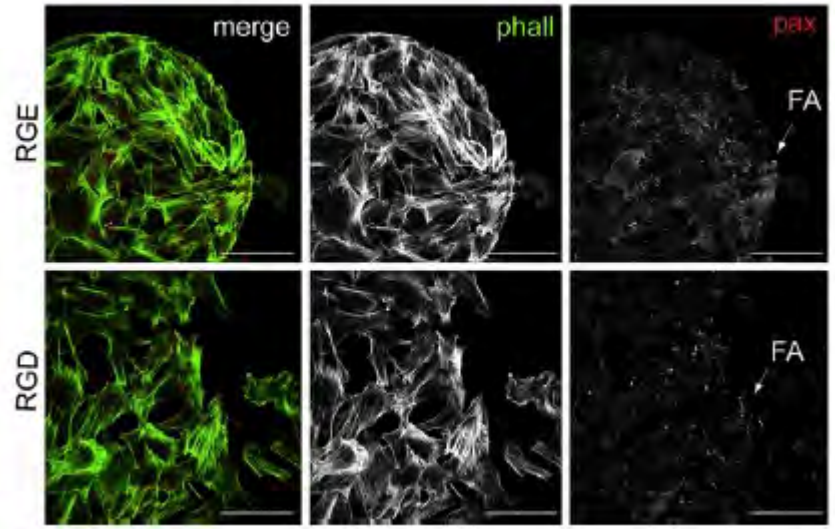
Costa, Gautrot and Connelly *Biomater. Acta* 2014



- Polymer brushes used to restrict cell adhesion initially.
- Then the brush is photo-coupled to a cell adhesive peptide that enables cell migration.
- Requires non-toxic chemistry that is compatible with physiological and/or cell culture conditions.
- Thiol-ene chemistry was used for such system as it can be photo-activated in mild conditions.

5. Dynamic Cell Adhesion for Probing Wound Healing

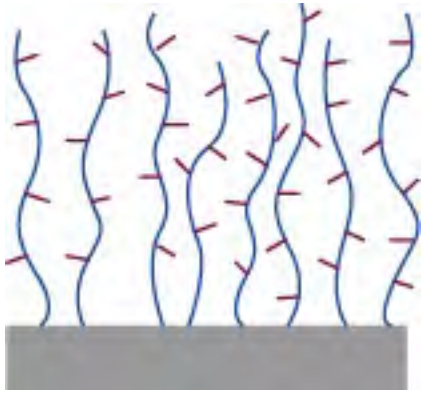




Costa, Gautrot and Connelly
Biomater. Acta 2014

- Upon photo-activation, cells start to invade the surrounding environment.
- The invasive behaviour is ligand specific and modulated by ligand density.
- This assay will allow the probing of the role of specific peptide sequences and receptor ligation during wound healing processes.

Design of Polymer Brushes for the Biomedical Field



1. Synthesis and physico-chemical properties.
2. Interactions with biomacromolecules.
3. Biofunctionalisation.
4. Polymer brushes for biosensing.
5. Design of cell based assays.
6. Polymer brushes for gene delivery.

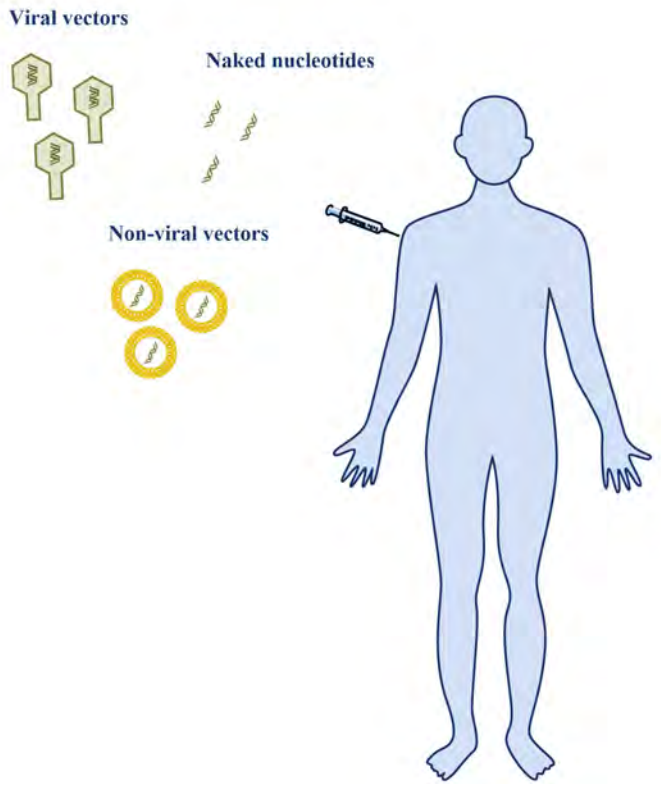
6. Opportunities and Challenges in Gene Delivery

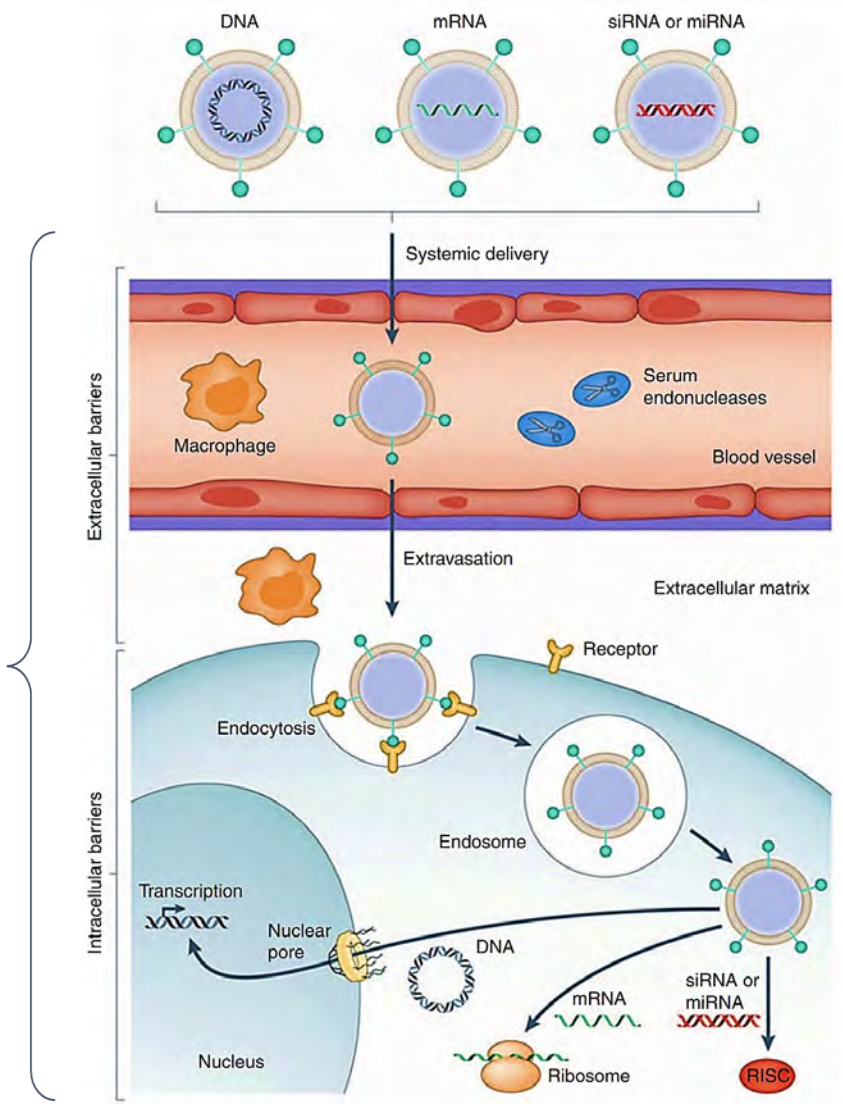
Opportunities

- Targeting a wide range of diseases and conditions from cancer to osteoarthritis and atherosclerosis.
- Development of vaccines and tissue engineering strategies.

Challenges

- Protection of genetic material and increased stability of vectors.
- Low toxicity.
- Improved targeting.
- Reduced doses.
- Prolonged efficacy.





Molecular Therapy - Methods & Clinical Development (2016) 3, 16023

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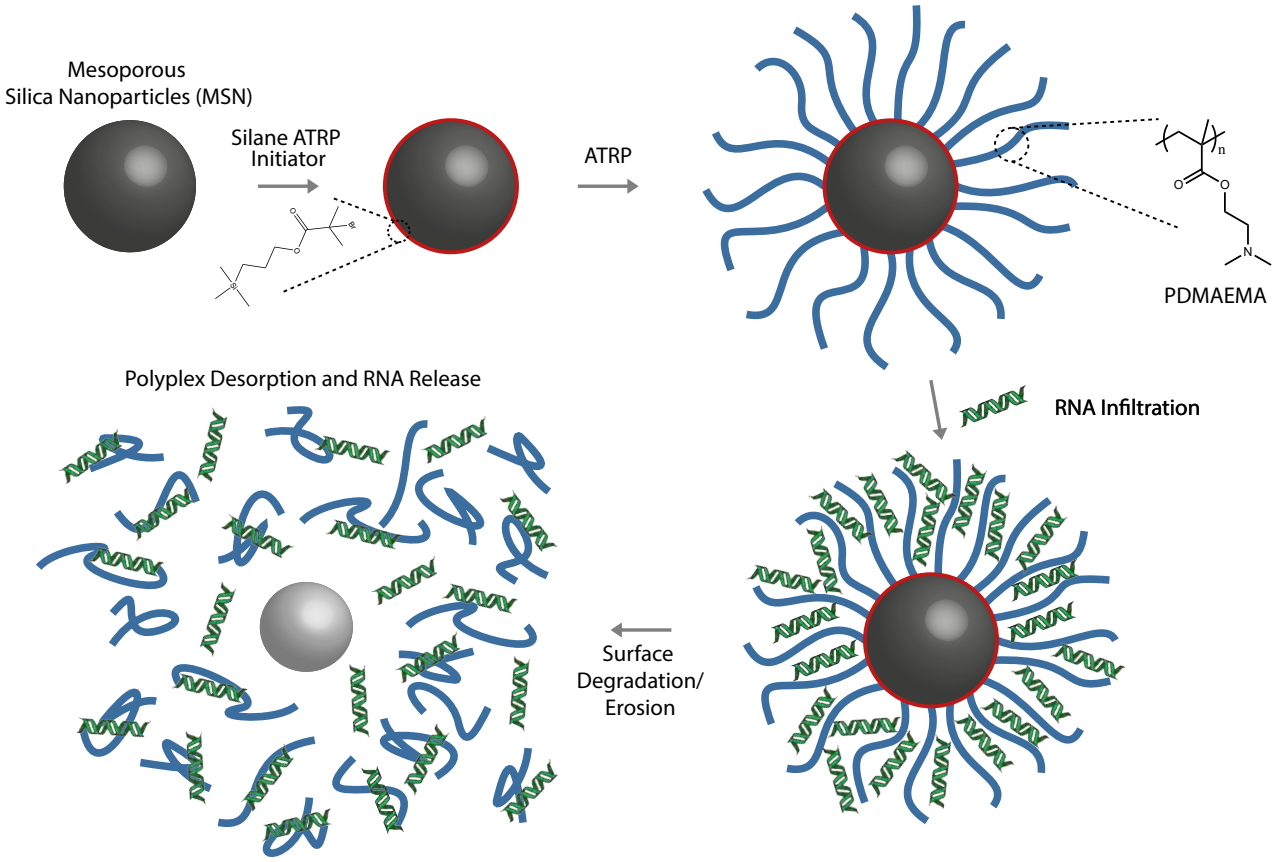
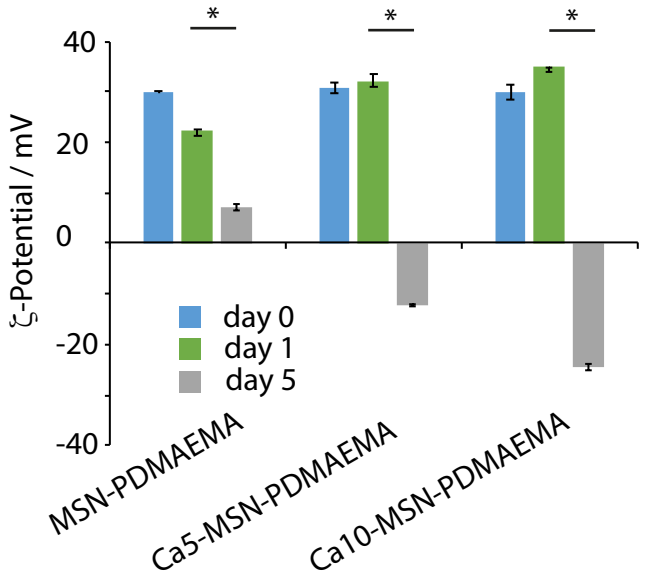
6. Growth From Mesoporous Silica Nanoparticles – Controlled Degradation

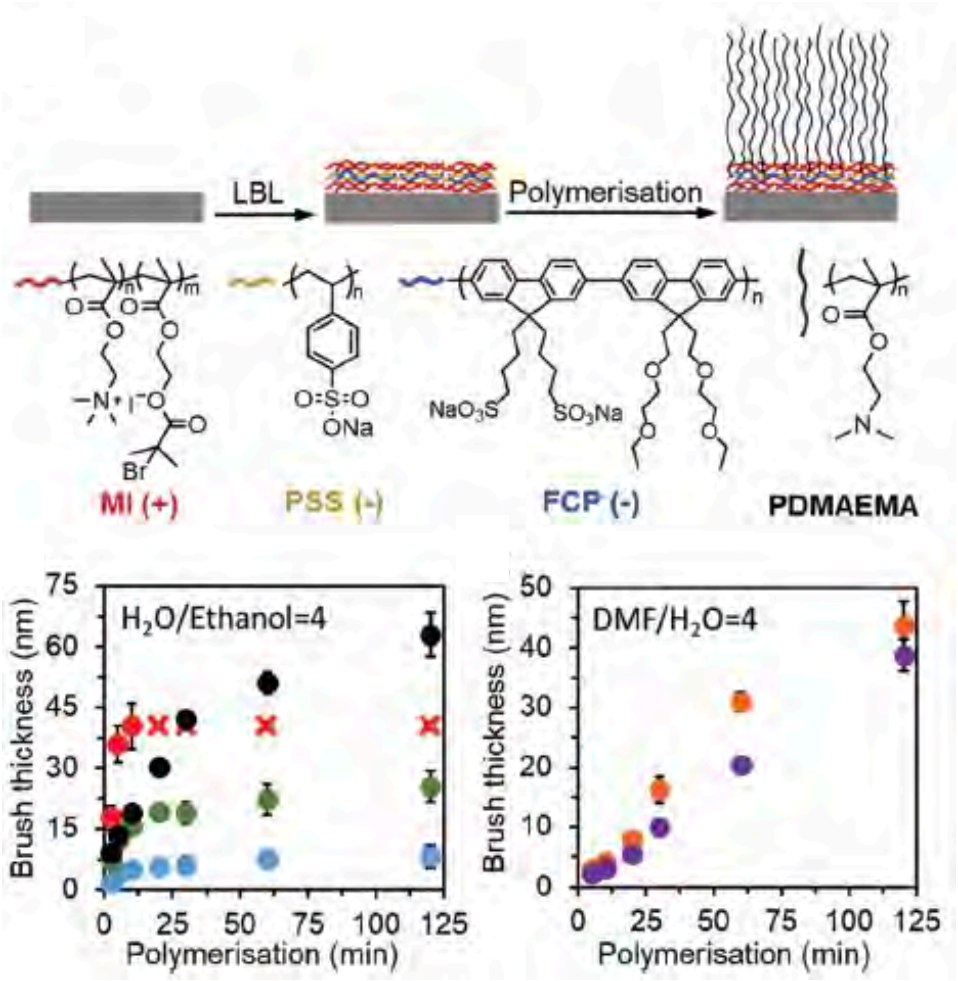


Chang et al. *European Polym. J.* 2021, 110593

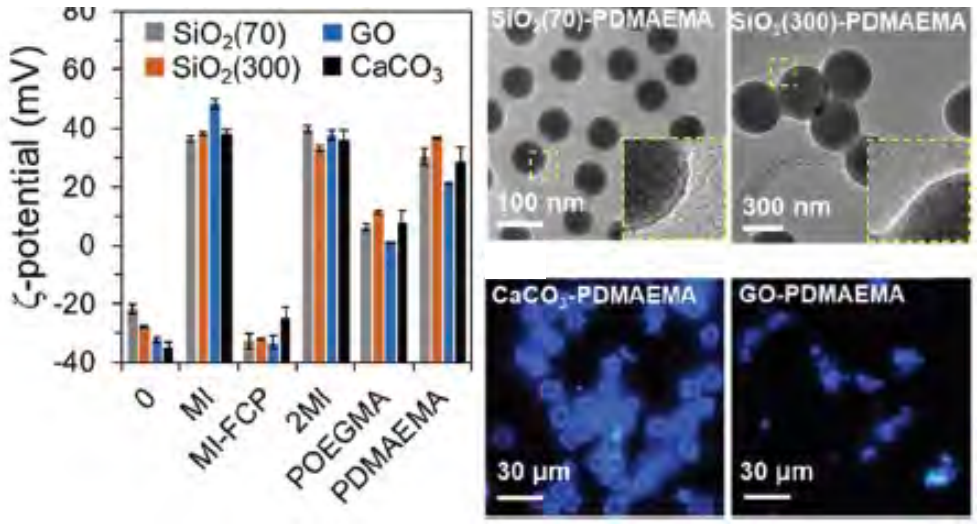


- Growth from a broader range of in organic nanoparticles.
- Independent control of core and brush shell physico-chemical properties.

6. Substrate-Independent Approach and Co-Labelling

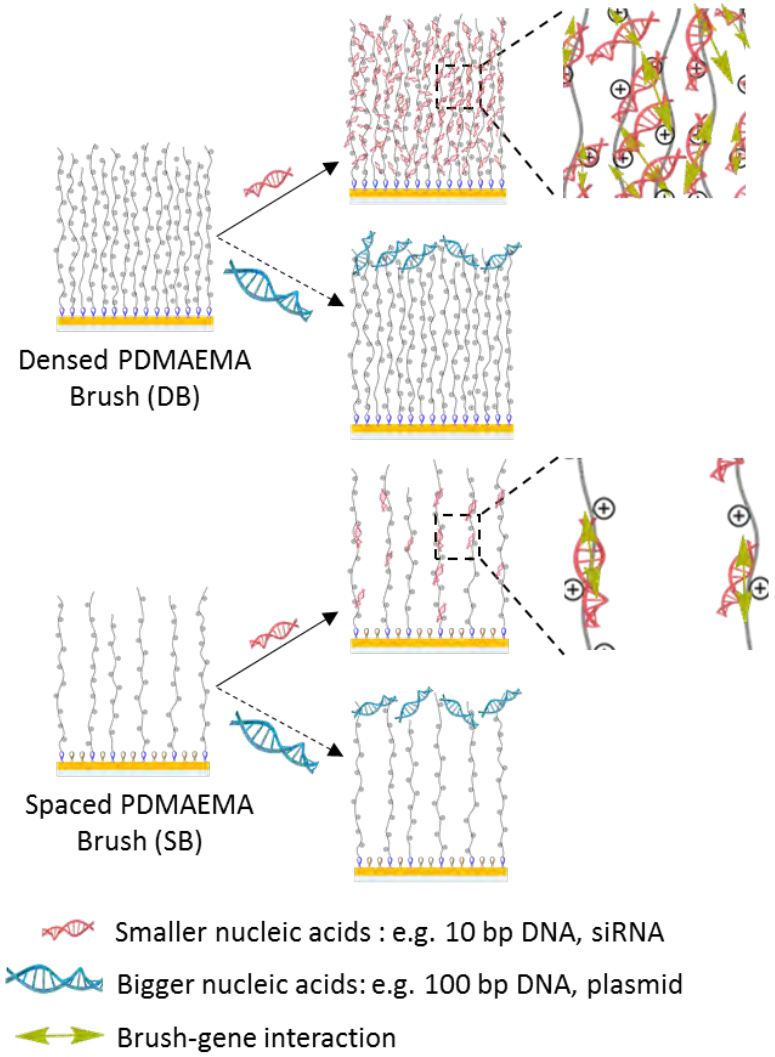


Li et al. *Chem. Commun.* 2019, 14166



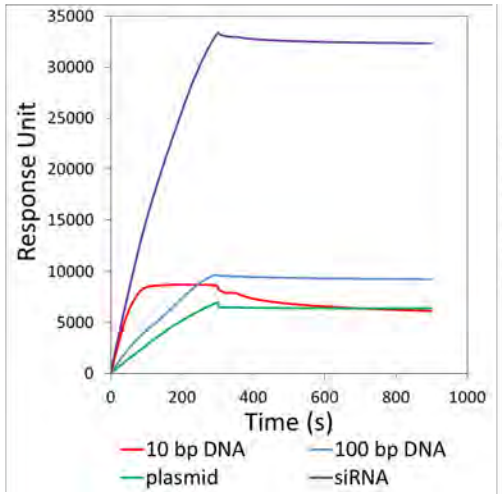
- Polyelectrolyte macroinitiator for brush growth from any charged substrate.
- Labelling within the initiator layer, without affecting brush chemistry.
- Study the impact of core size and shape independently of brush chemistry.

6. Strong Binding of Nucleic Acid Molecules to PDMAEMA Brushes

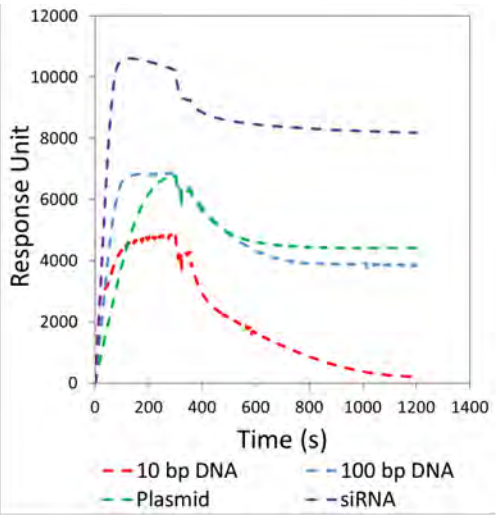


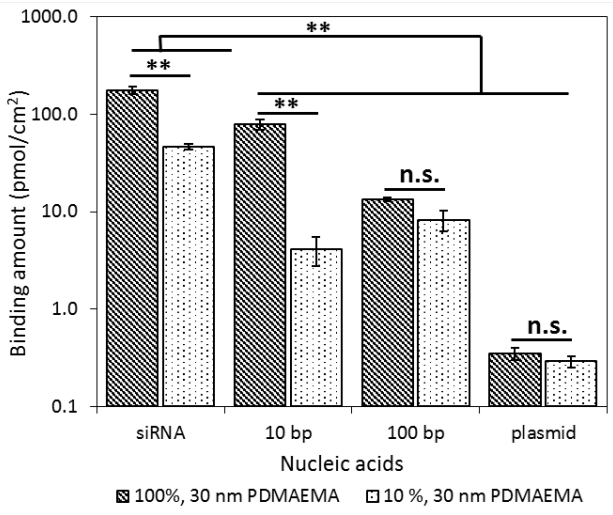
Surface Plasmon Resonance

Dense Brush (100 %)



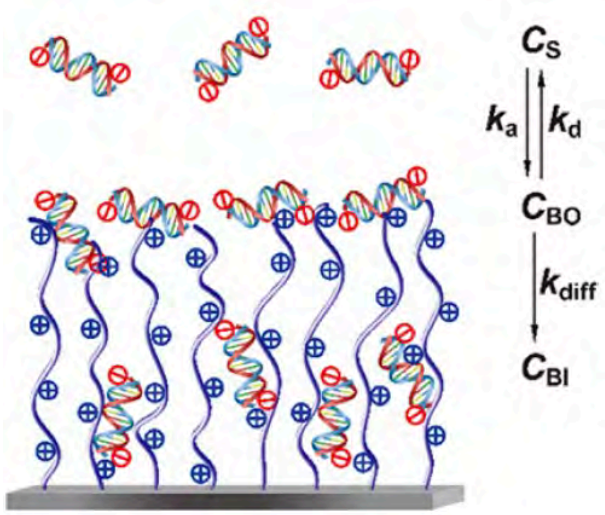
Sparse Brush (10 %)

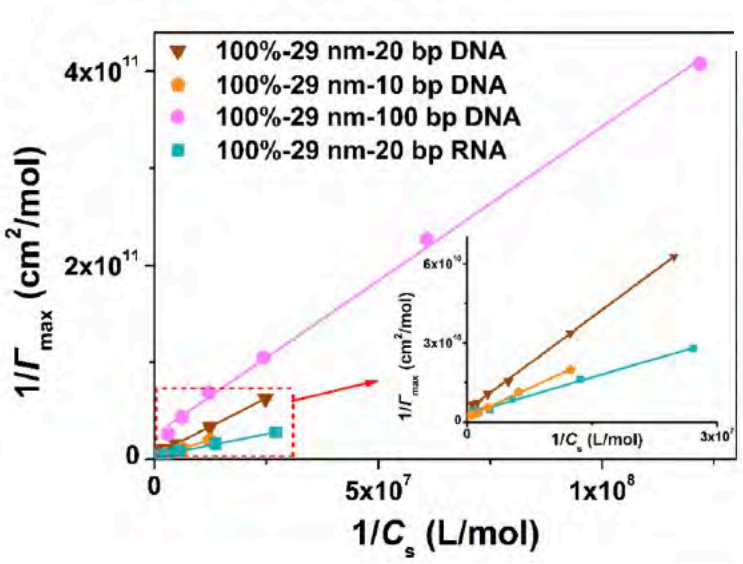


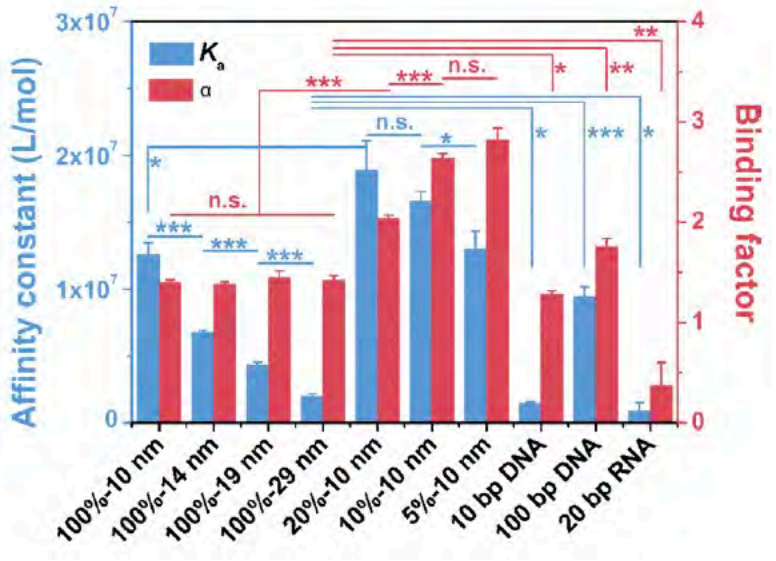


Krishnamoorthy et al. *Biomacromolecules* 2017
Li et al. *Biomacromolecules* 2018, 606

6. Model of Adsorption Kinetics





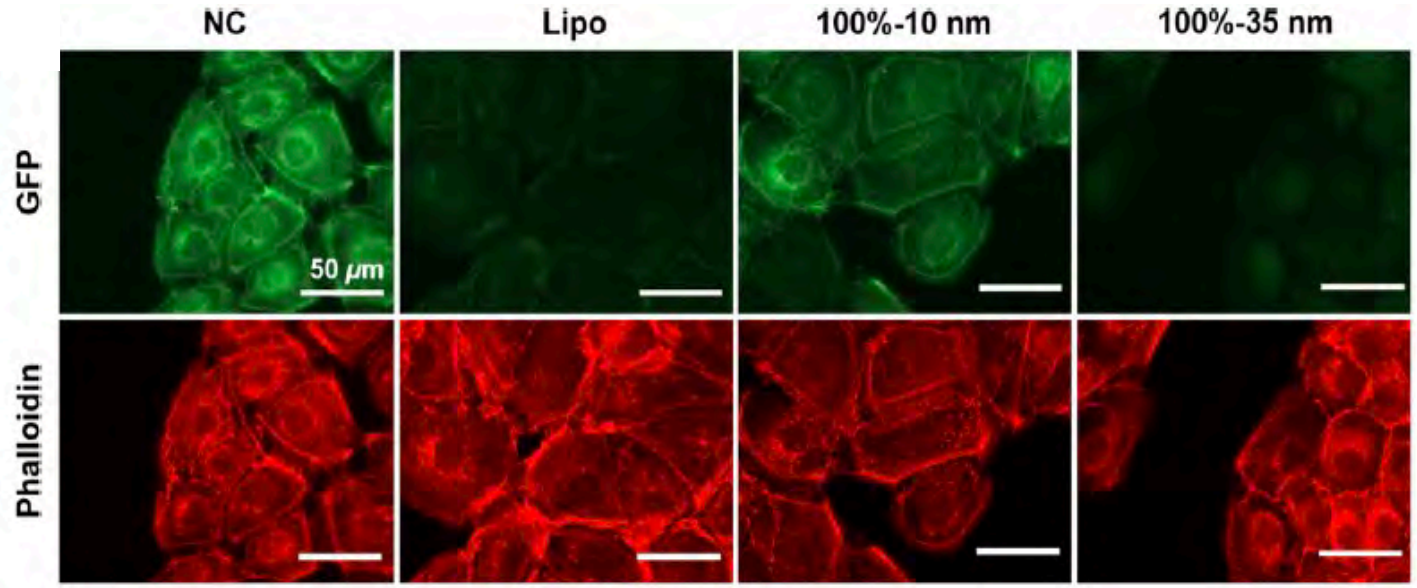


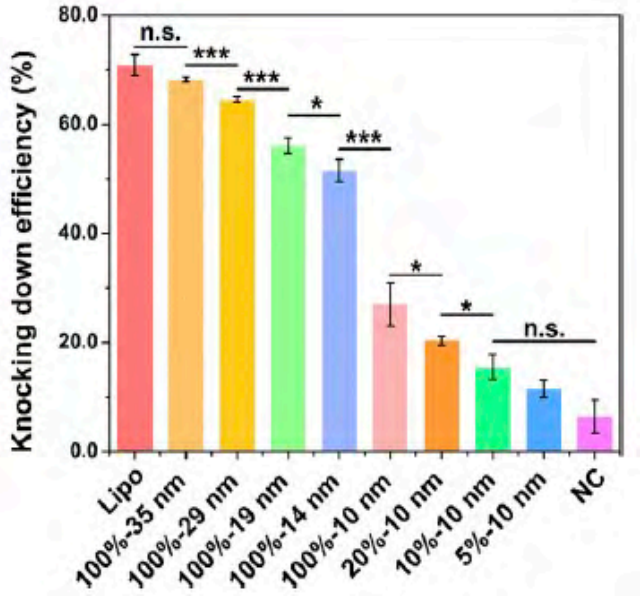
$$\frac{1}{\Gamma_{max}} = \frac{\alpha M_n^{ON}}{h\rho} + \frac{\alpha M_n^{ON}}{h\rho}\frac{1}{K_a}\frac{1}{C_S}$$

Qu et al. *Biomacromolecules* 2019, 2218

- Kinetics model of adsorption and infiltration.
- Higher brush densities improve the binding factor (inversely proportional to the maximum density of oligonucleotide per chain).
- Thicker brushes do not reduce the binding factor, but limit the affinity constant.
- RNA infiltration associated with a lower affinity constant but higher surface density (very low binding factor).

6. Knock Down Efficiency with PDMAEMA Brushes

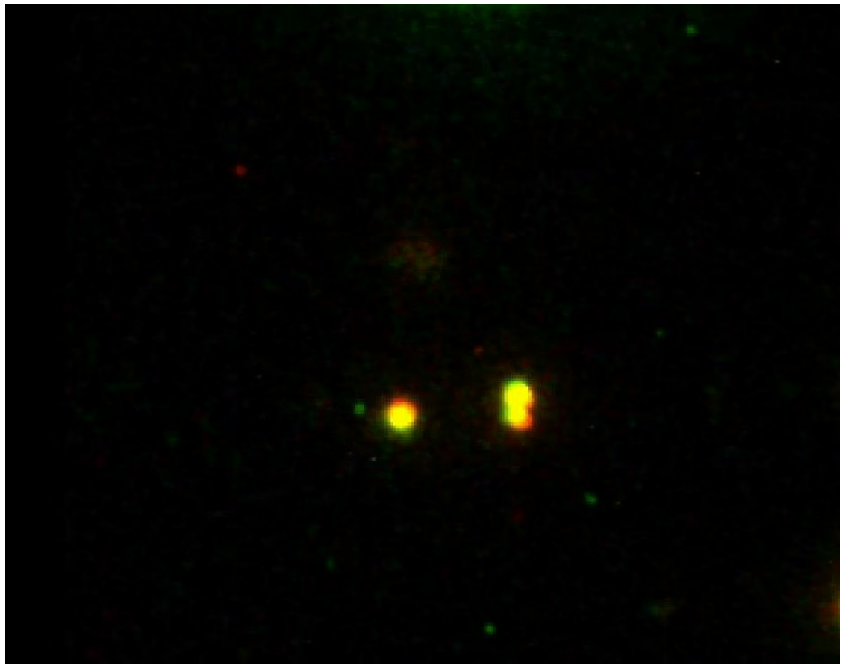




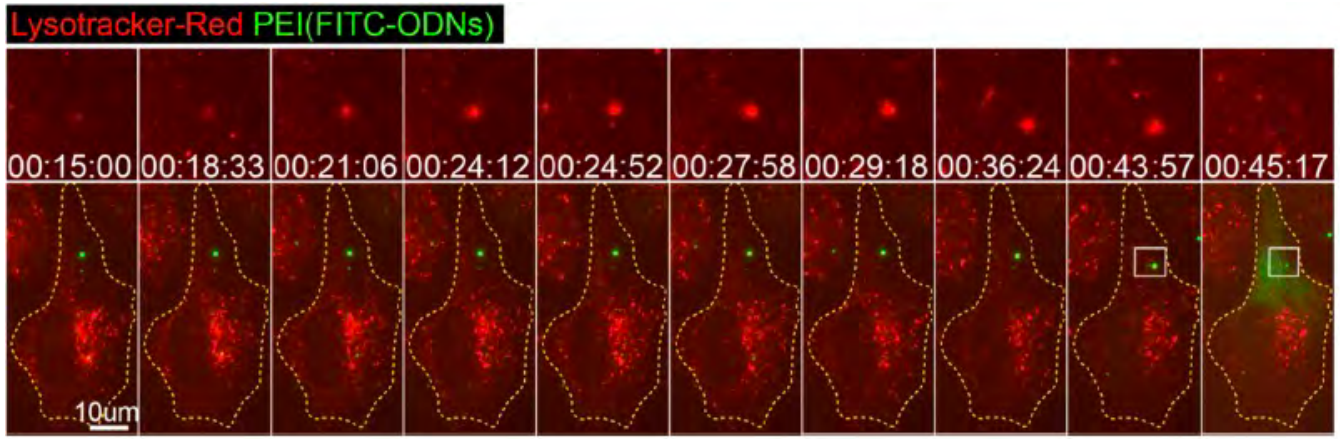
Qu et al. *Biomacromolecules* 2019, 2218

- Excellent siRNA delivery and knock down efficiency.
- Comparable to Lipofectamine control.
- Improved at high density and thicker brushes.

6. Burst Cytosolic Release from Common Cationic Polymeric Vectors

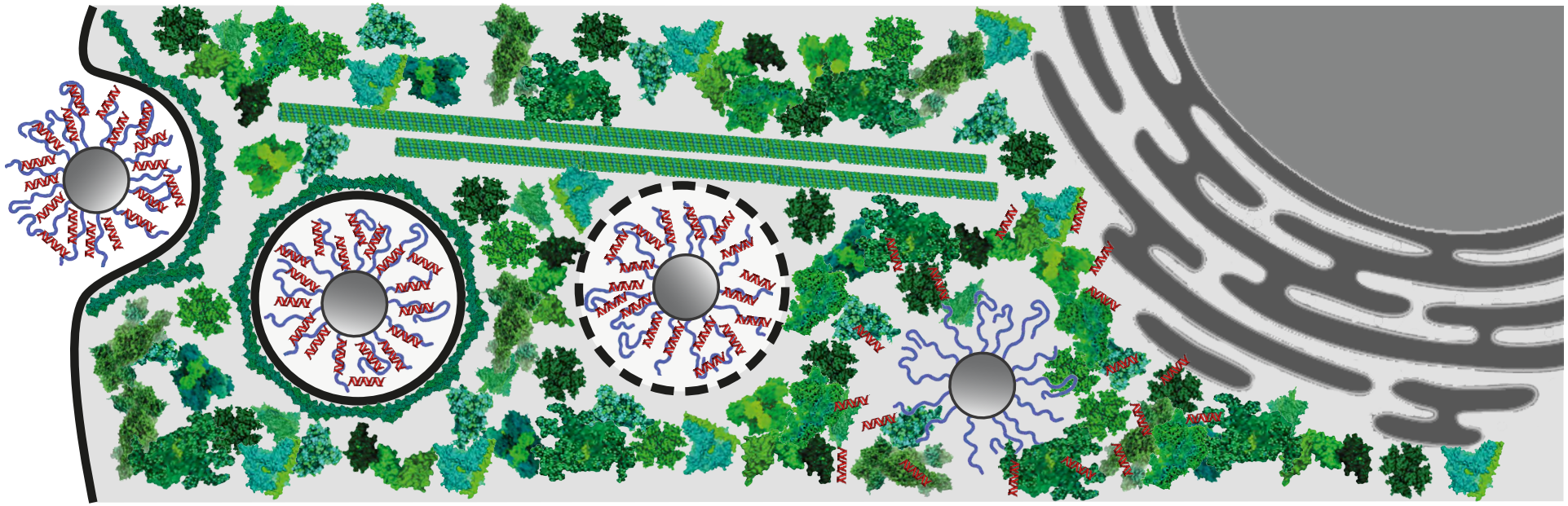


VOL. 7 ▪ NO. 5 ▪ 3767–3777 ▪ 2013 ACSNANO www.acsnano.org



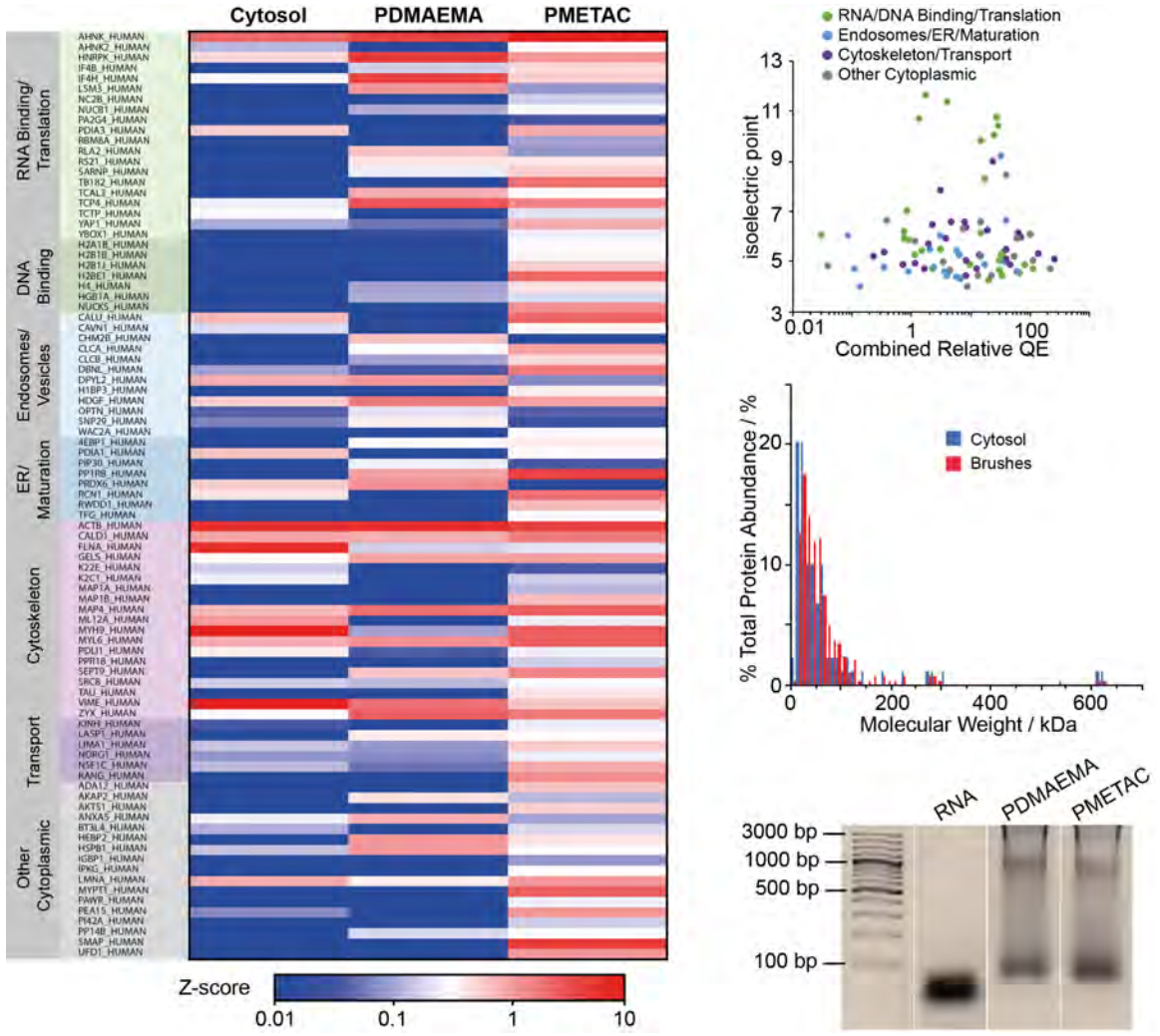
- Release of oligonucleotides from poly(ethylene imine) complexes within a few seconds.
- Apparently triggered by cytosolic entry.

6. What is the mechanism for RNA release in the cytosol?



→ How to control it?

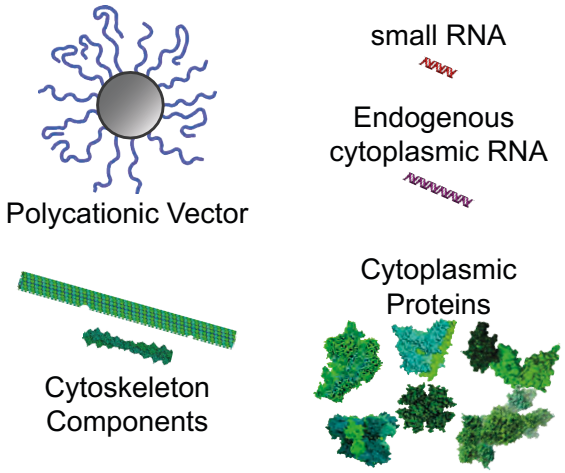
6. The Cytosolic Interactome of Polycationic Vectors

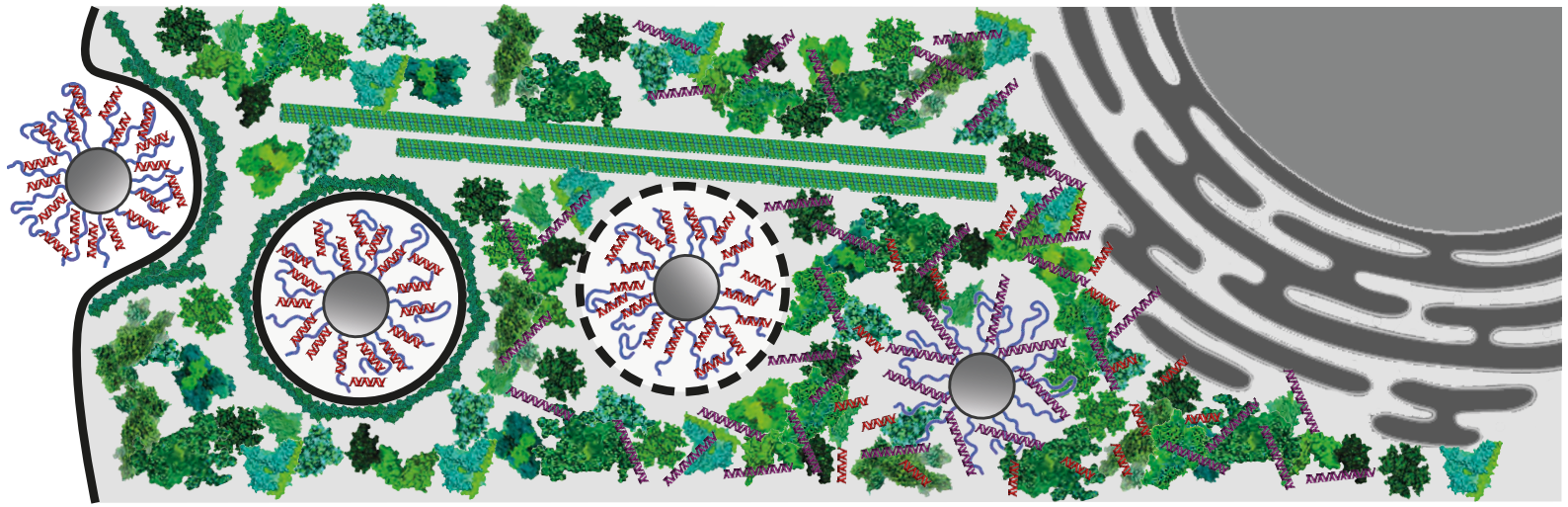


- Significant pool of proteins associated with DNA/RNA binding and translation.
- Other pool associated with endosomes, transport and proteasome
- Some proteins with very high IP.
- Significant level of RNA/DNA macromolecules adsorbed at the surface of cationic vectors.

Raynold; Li et al. *Nat. Commun.* 2021 (12) 6445

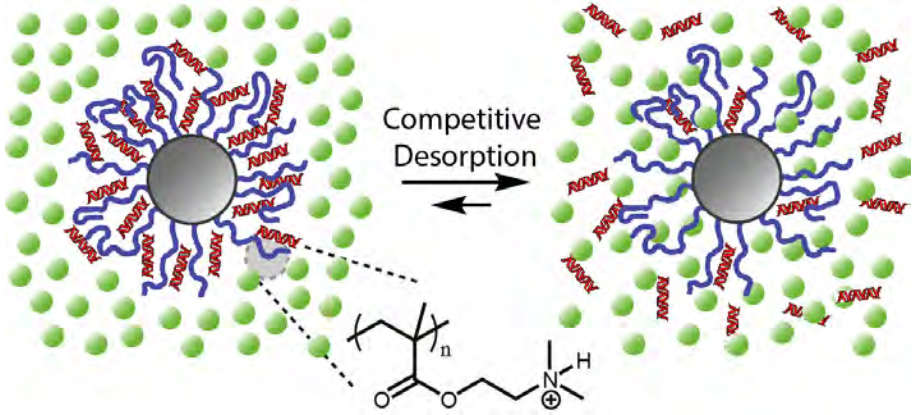
6. Is Molecular Crowding Regulating RNA desorption?



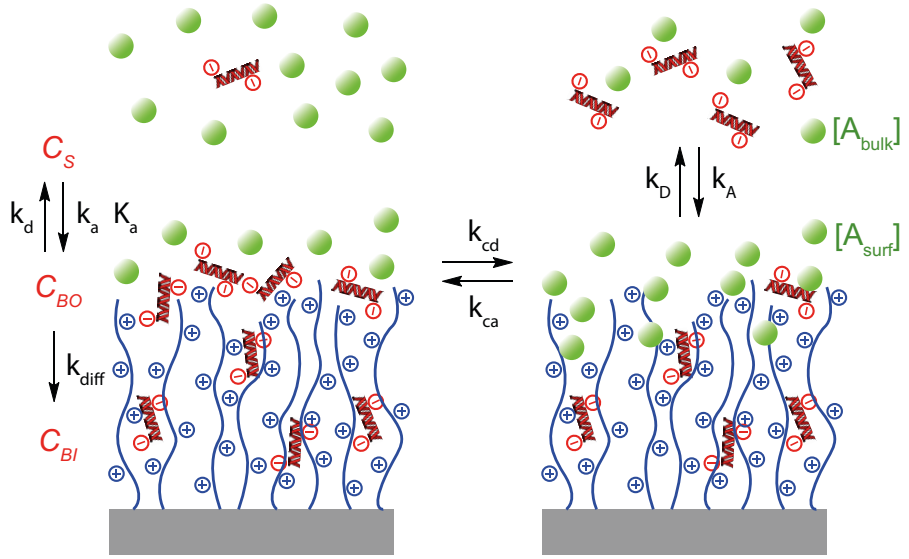


- Does competitive binding regulate RNA desorption from vectors upon cytosolic entry?

- Potentially also alters translational activity and underlies off-target effects?

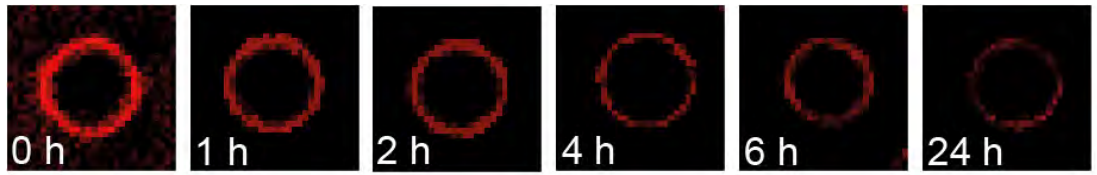


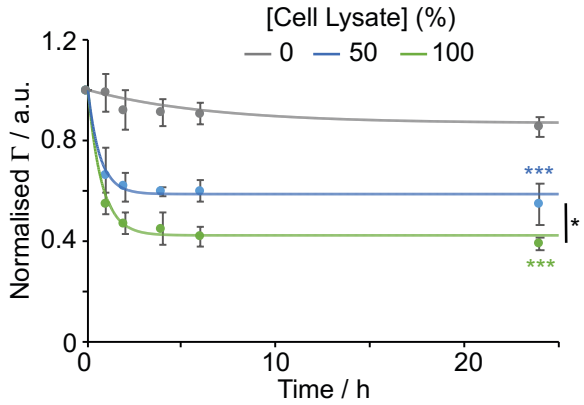
6. Model of Competitive Desorption of Oligonucleotides

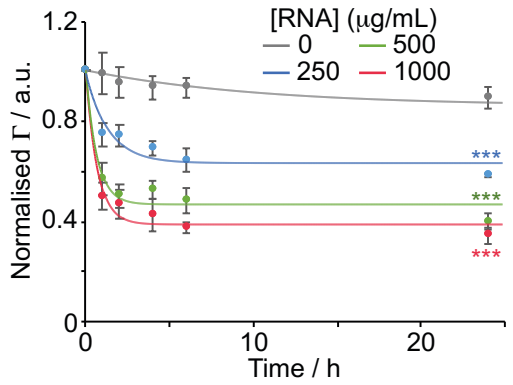


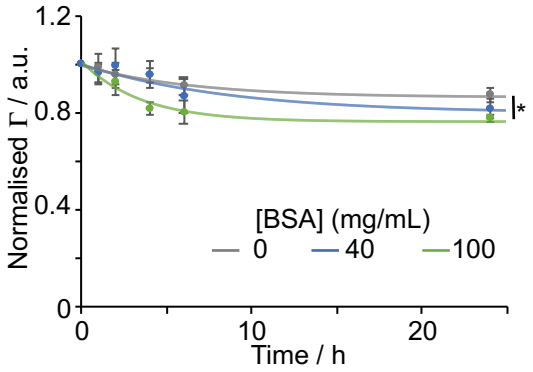
Raynold; Li et al. *Nat. Commun.* 2021 (12) 6445

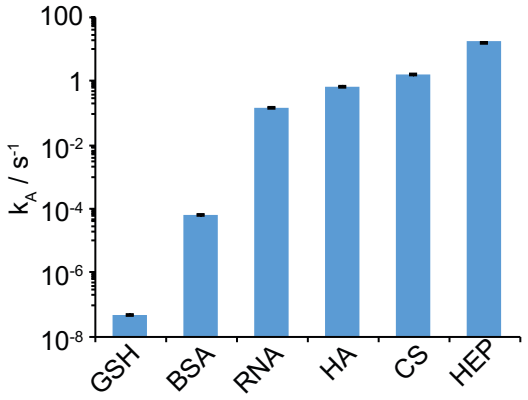
- Kinetics model of oligonucleotide desorption based on competitive interactions.
- Physiological cytoplasmic [RNA] clearly sufficient to displace oligonucleotides.
- But GAGs and proteoglycans should play important role.











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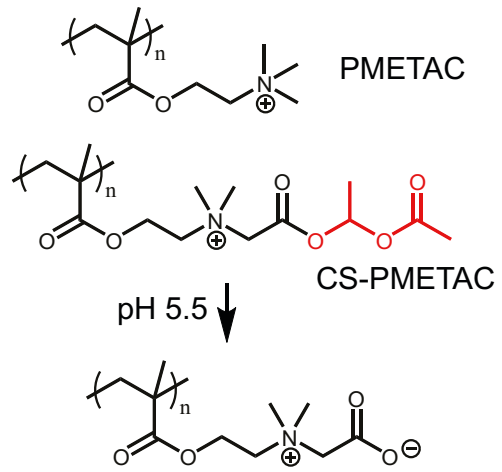
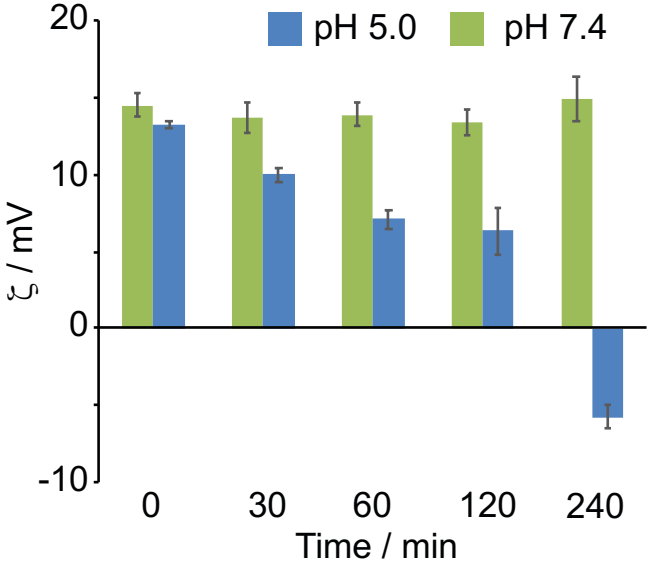
6. Regulation of Oligonucleotide Release



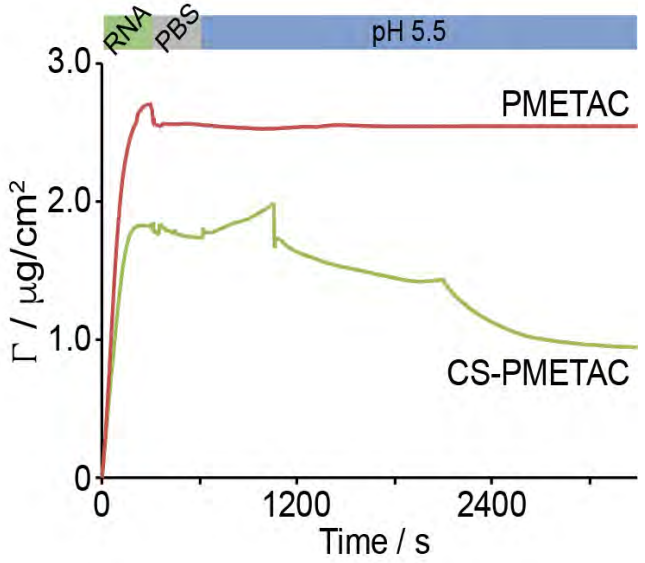
- Charge-shifting group in CS-PMETAC to allow cleavage and release of oligonucleotides to initiate in the endosome.
- PMETAC displays stronger interactions with oligonucleotides and better retains them upon cytosolic entry.

Raynold; Li et al. *Nat. Commun.* 2021 (12) 6445

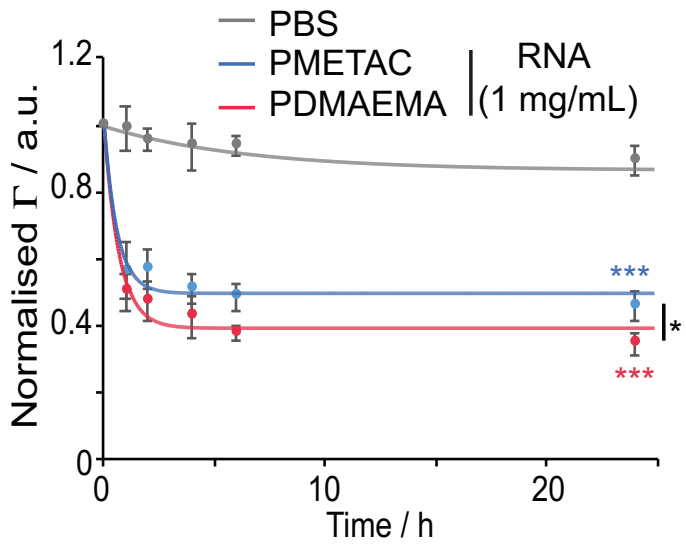
ζ-Potential Change - PMETAC



SPR – Release from CS-PMETAC



Cytosolic Release



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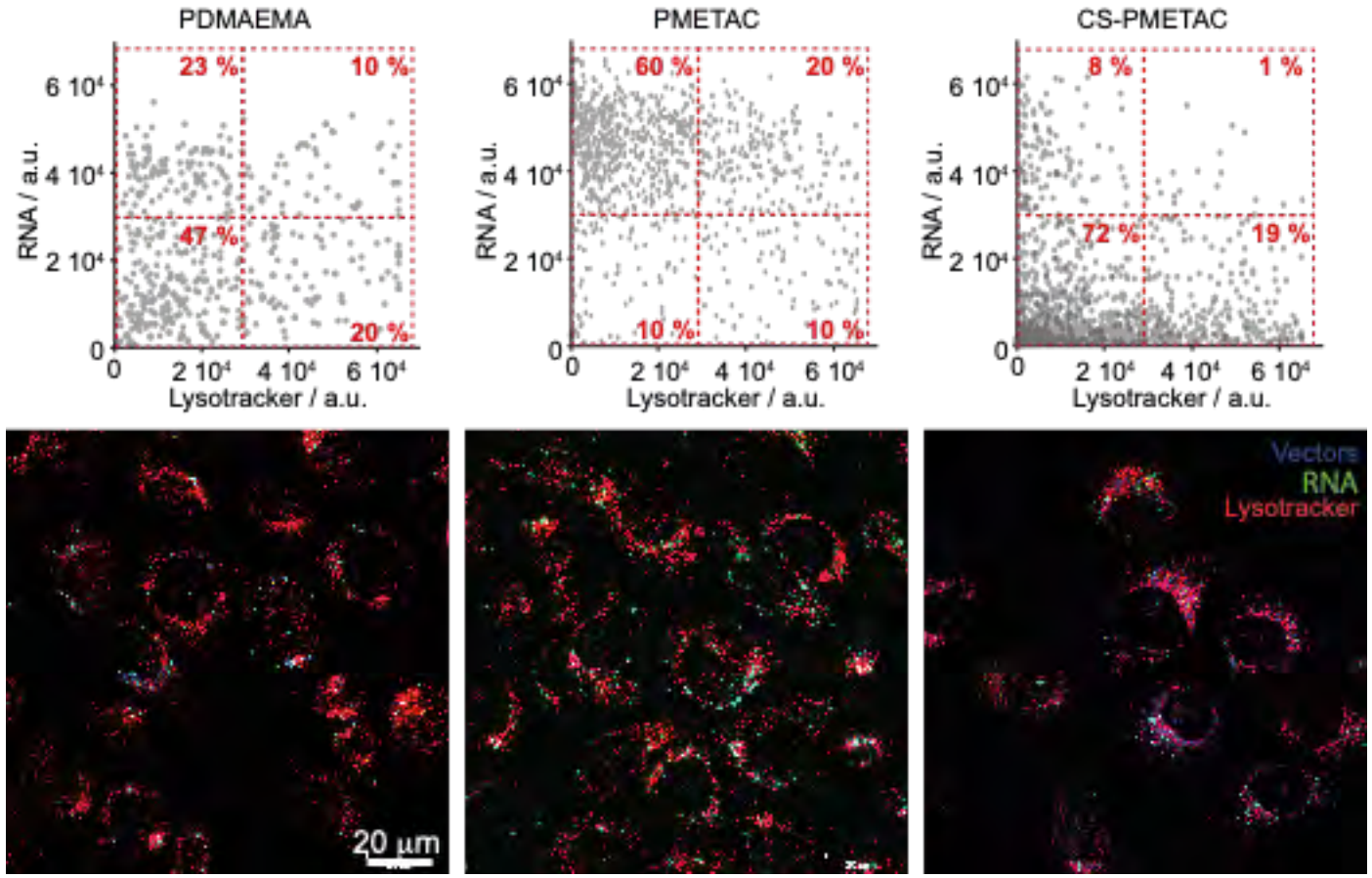
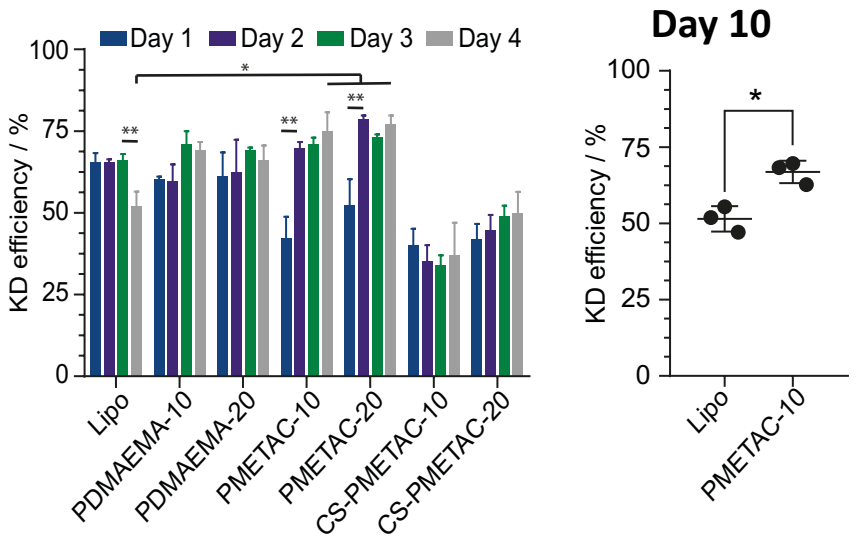
6. Regulation of Oligonucleotide Release

Controlled Cytosolic Retention



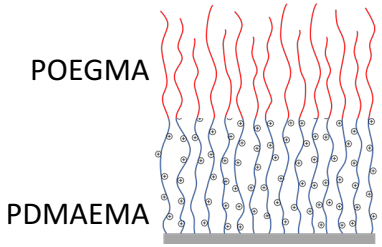
Raynold; Li et al. *Nat. Commun.* 2021 (12) 6445

Long-Term Knock Down

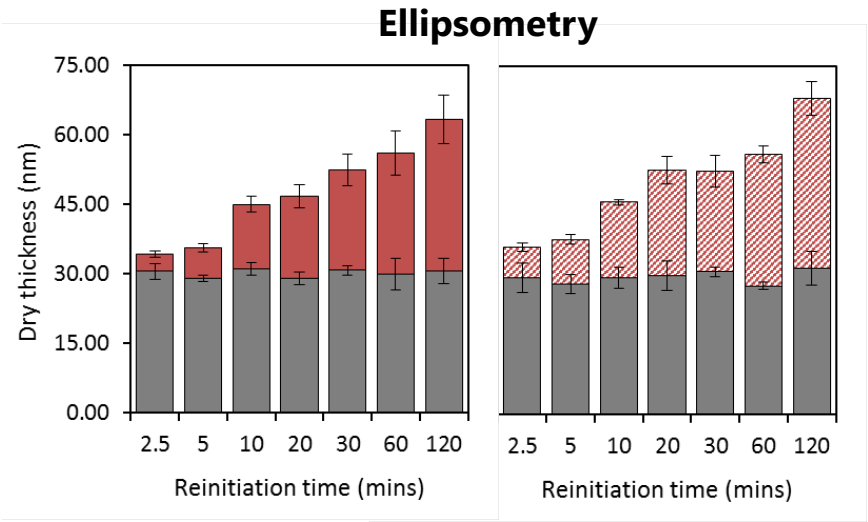


- Rapid release in cytoplasm in CS-PMETAC.
- PDMAEMA and PMETAC display improved retention of oligonucleotide upon cytoplasmic entry.
- Release data correlates with long term knock down efficiency observed for PMETAC brushes.

6. Design of Block Copolymer Brushes for siRNA Delivery

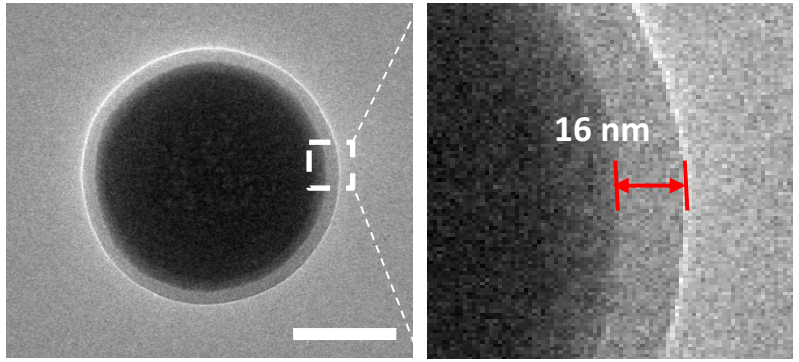


Li et al. *Biomacromolecules* 2018, 606



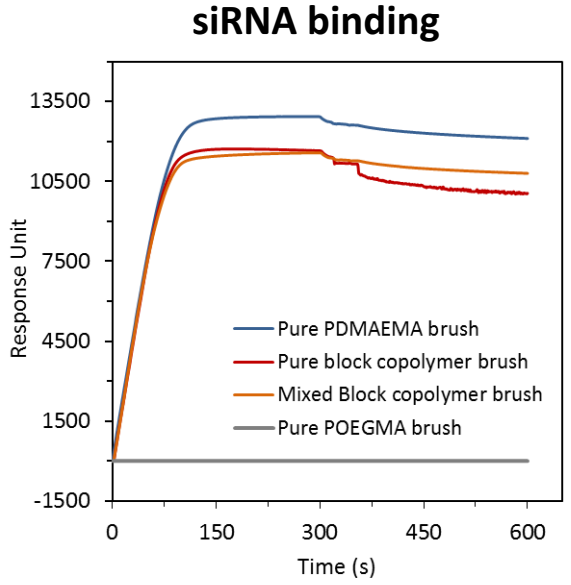
Pure block copolymer brush growth kinetics on silicon wafers (Left) and gold substrates (right)

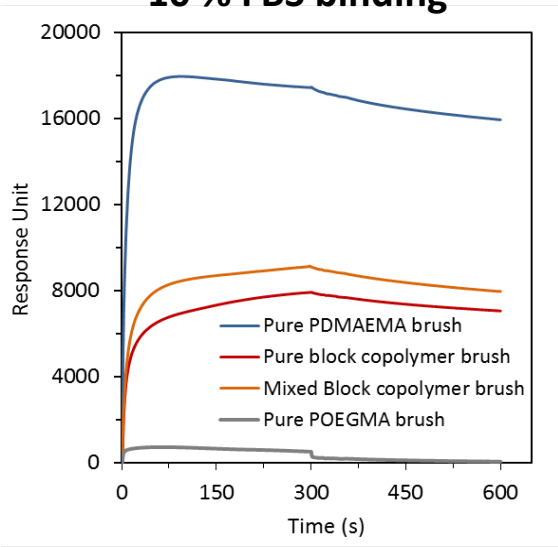
TEM images of SiO_2-BC



Scale bar: 100 nm

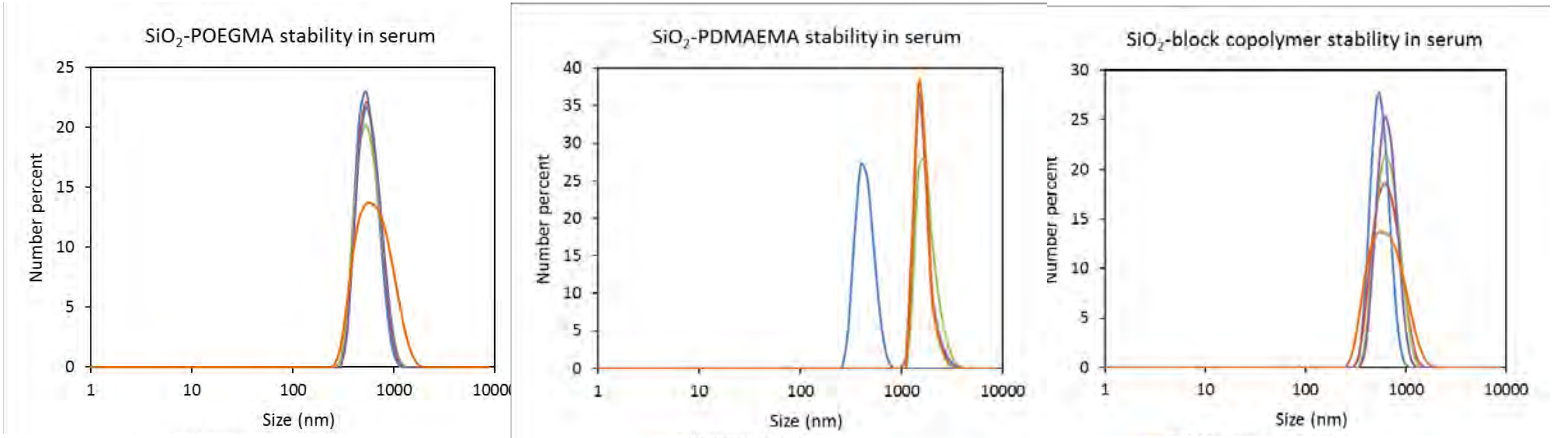
- Control of polymer brush re-initiation.
- Block copolymers retain the ability to bind RNA efficiently.
- Protein adsorption from serum is restricted.



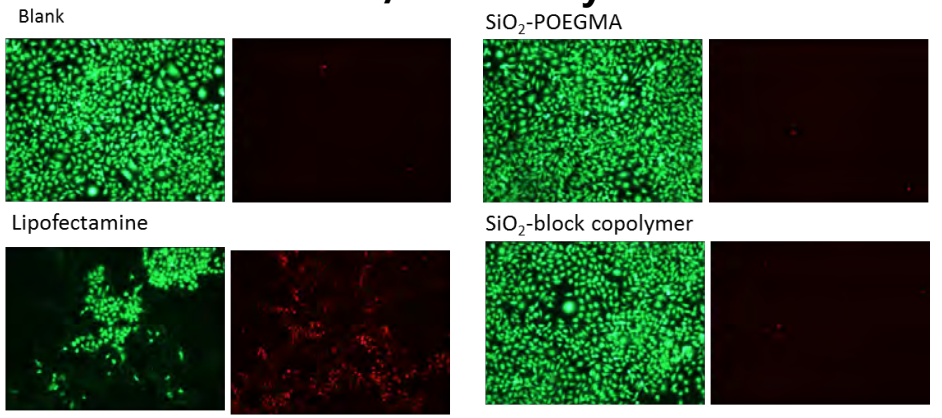


6. Stability of Block Copolymer Brush-Nanoparticles and Cytotoxicity

Light Scattering – Particles Stability



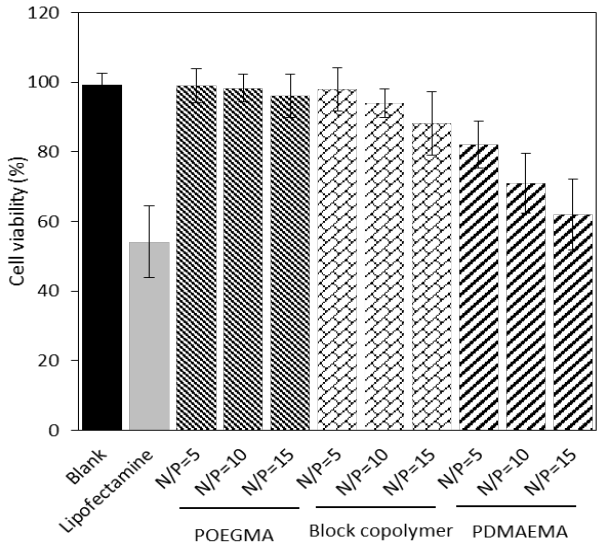
Live/Dead Assay



Li et al. *Biomacromolecules* 2018, 606

Images were at N/P=10
Green: live cells
Red: dead cells

- Excellent stability in serum.
- Low cytotoxicity resulting from screening of positive charges.



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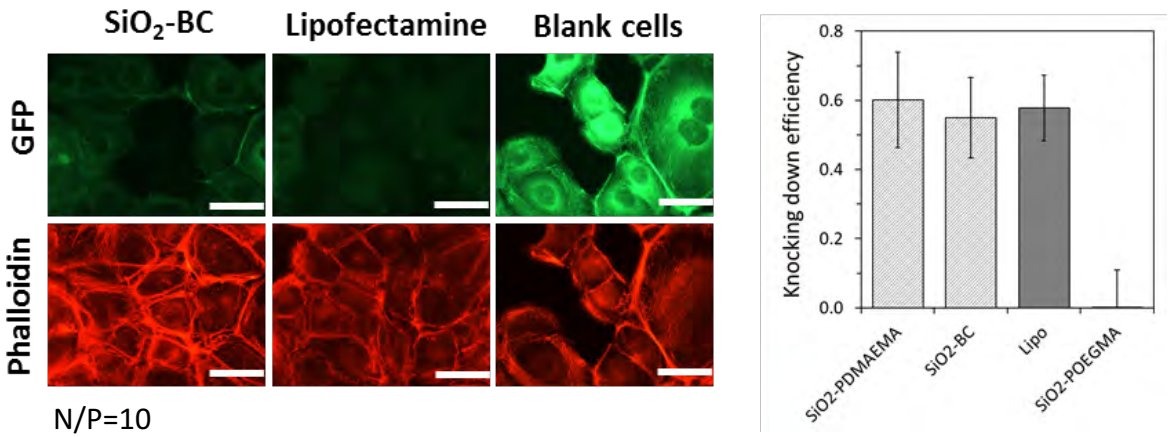
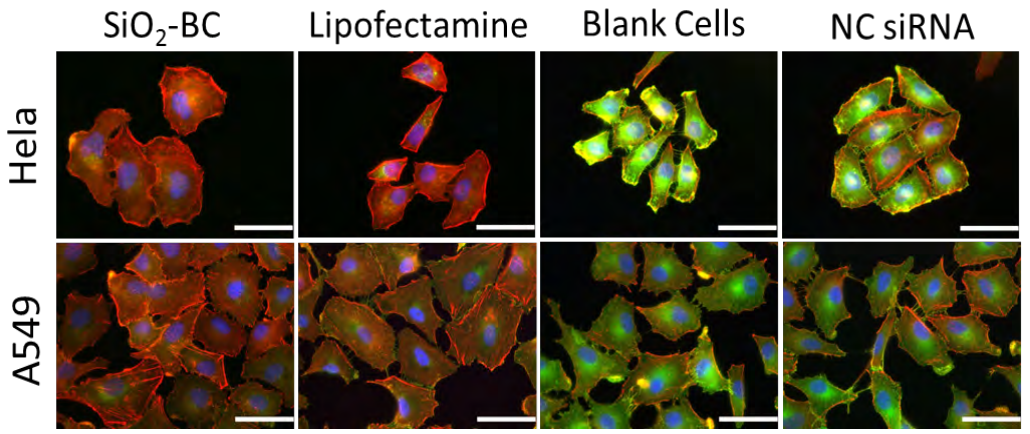
6. Knock Down Efficiency with Block Copolymer Brushes

Efficient Knockdown of GFP

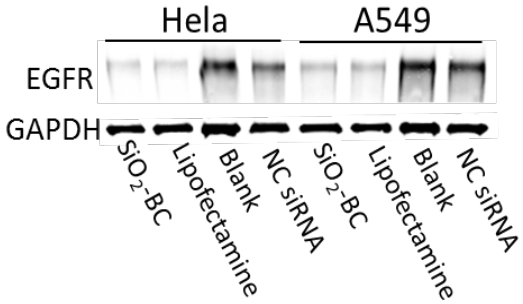


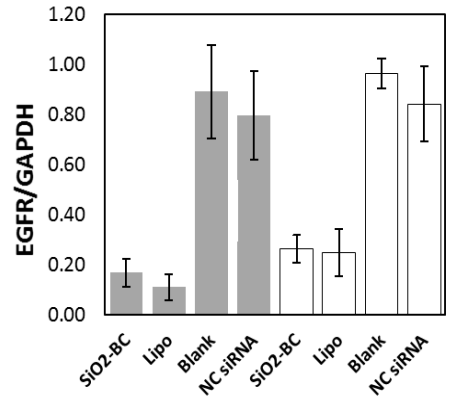
Li et al. *Biomacromolecules* 2018, 606

EGFR Knockdown in Cancer Cells



- Excellent knock down efficiency for GFP in engineered HaCaT cells and EGFR in cancer cell lines.
- Retain high viability and serum stability, potentially for long term delivery in complex physiological fluids.





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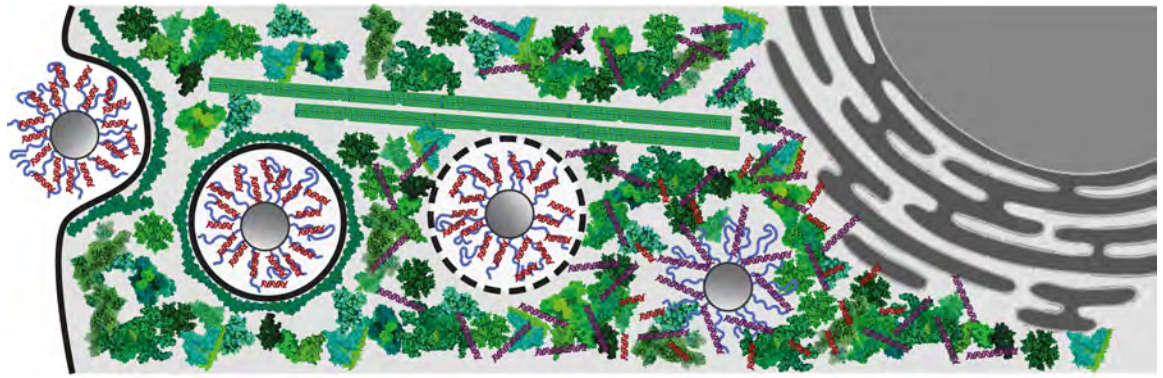
Conclusions

- Polymer brushes allow the precise control of surface chemistry, morphology and patterning.
- They enable tailoring interactions with biomacromolecules, whether proteins or oligonucleotides.
- Their rational design and biofunctionalisation can be applied to a broad range of biomedical applications.
- Dense brushes are particularly effective at stabilising high densities of oligonucleotides and controlling their release upon internalisation and cytosolic entry.



Thank You

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