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Self-hydrolysing polymers as potential mRNA vaccine vectors

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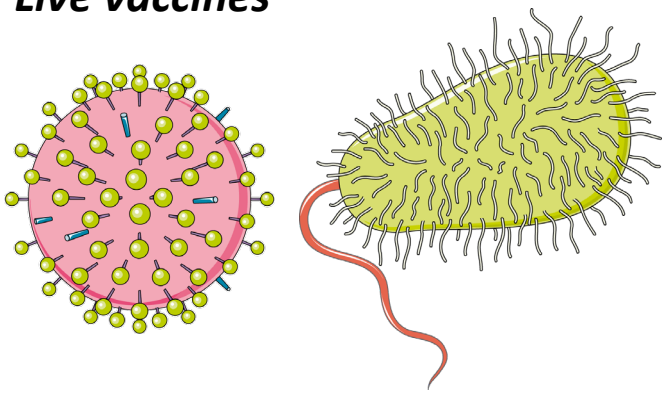
APS Pharmsci 2019

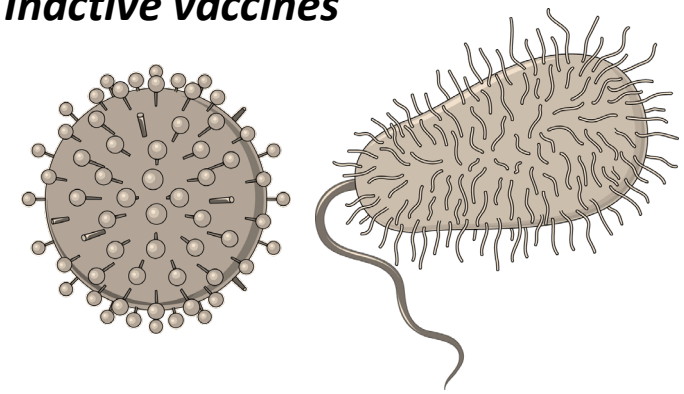
Current vaccines

Live vaccines



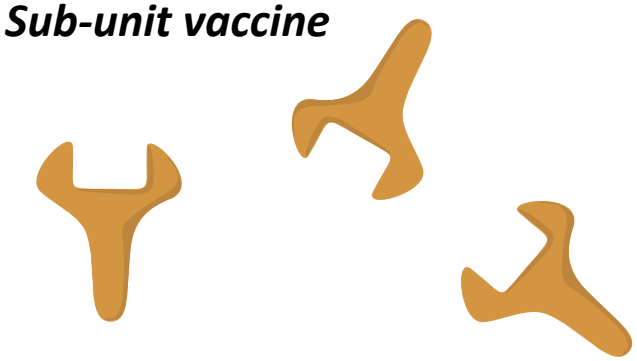
- *Severely weakened form of pathogen.*
- *Antigen display triggers immune response and memory.*

Inactive vaccines



- *Dead pathogens used to avoid infection risk*
- *Weaker immune response therefore boosters and immunological adjuvants required such as aluminium salts*

Sub-unit vaccine



- *Purification of select antigens*
- *Removal of components for infection and replication.*

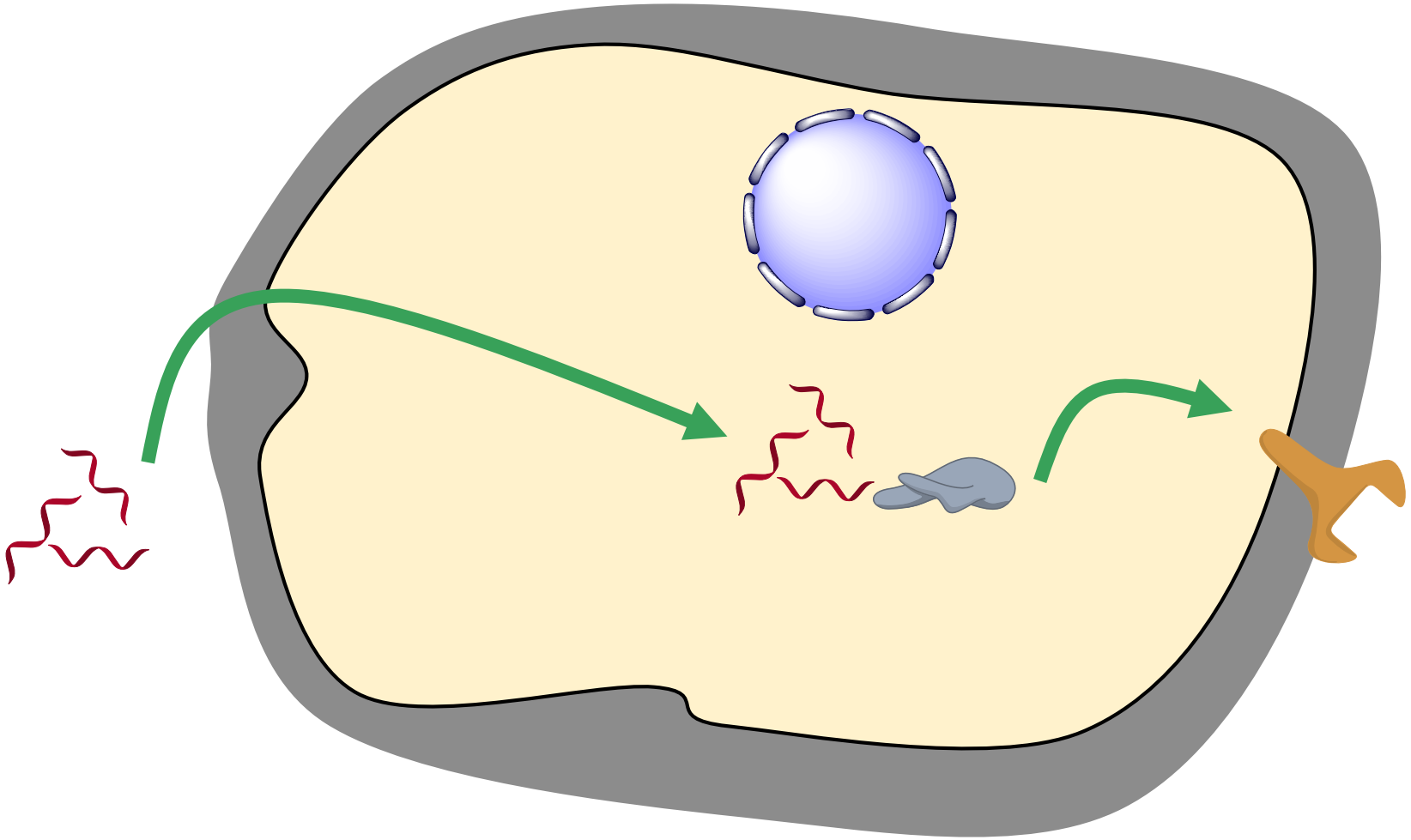
Manufacture, storage, transport risks remain

Nucleic acid vaccines – making cells do the hard work

Future of vaccines:

RNA vaccines

- *Genetic material encoding for antigen is administered*
- *Can be manufactured rapidly in outbreak scenarios*
- *mRNA as a material does not change depending on disease, only the code does*
- *Versatile formulation platform potentially removing cold chain limitations*



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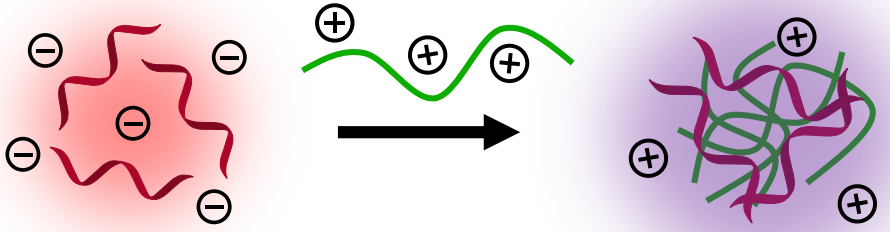
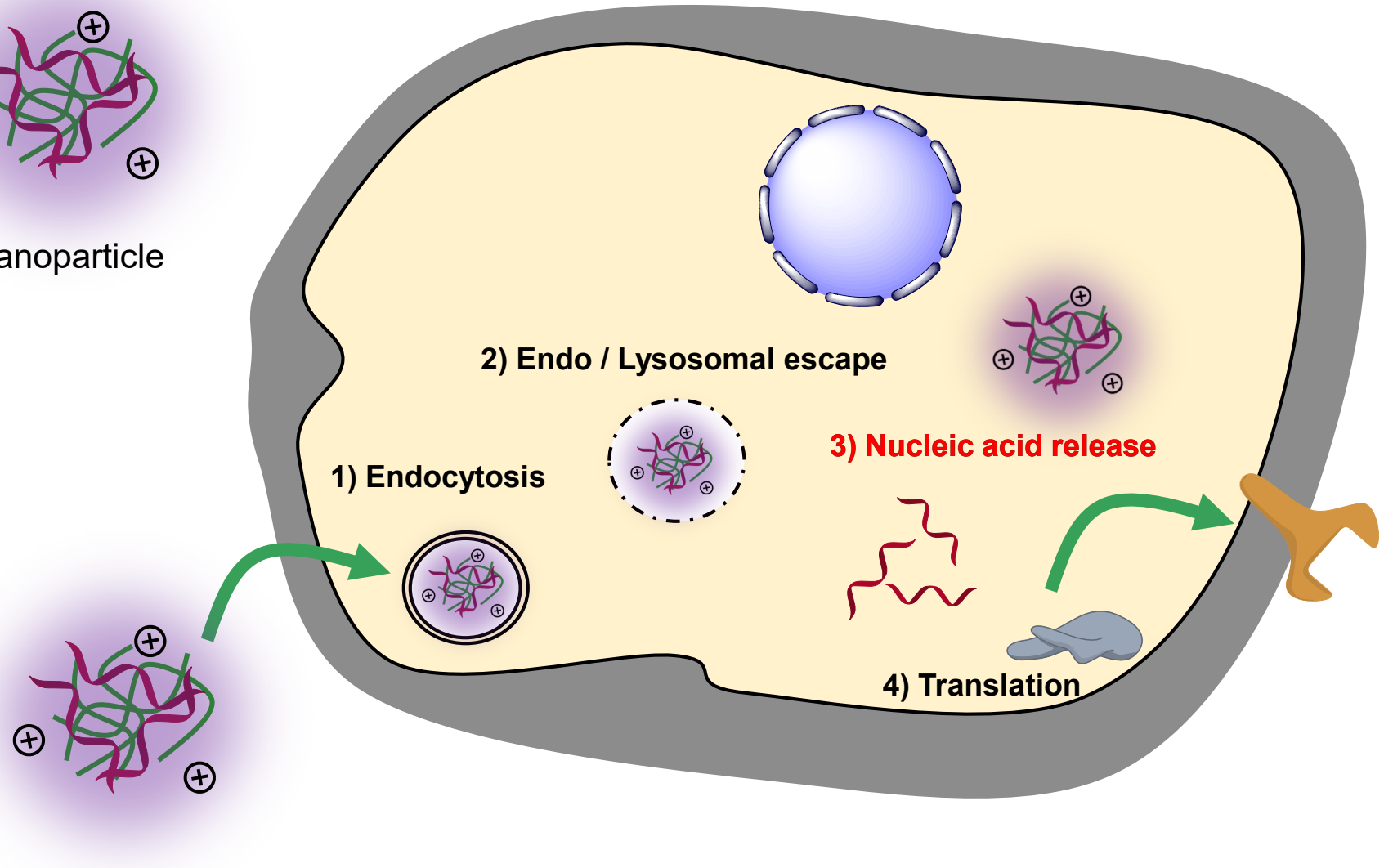
Cellular barriers for nucleic acid vaccines



Nucleic acids spontaneously form nanoparticle sizes ionic complexes - **polyplexes**



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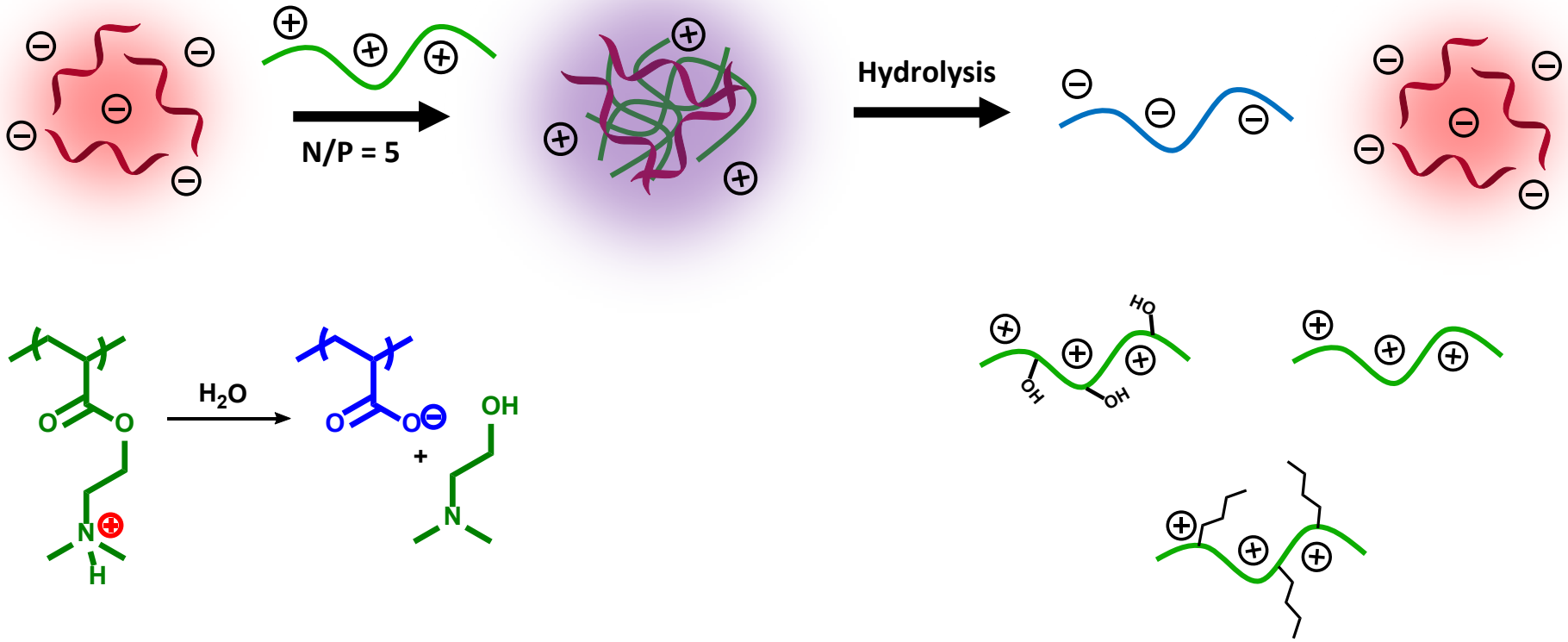
Self-hydrolysing charge reversible polymer - pDMAEA



What happens to the self-hydrolysing properties and transfection efficiency by changing lipophilicity of comonomer?

N. Truong, Z. Jia, M. Burgess, L. Payne, N. McMillan, and M. Monteiro, *Biomacromolecules*, 2011, **12**, 3540–3548

A. Cook, R. Peltier, M. Hartlieb, R. Whitfield, G. Moriceau, J. Burns, D. Haddleton, and S. Perrier, *Polymer Chemistry*, 2018, **9**, 4025–4035.

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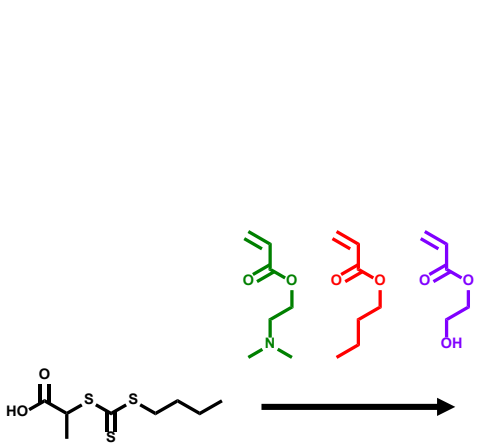
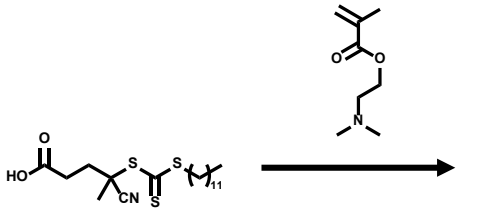
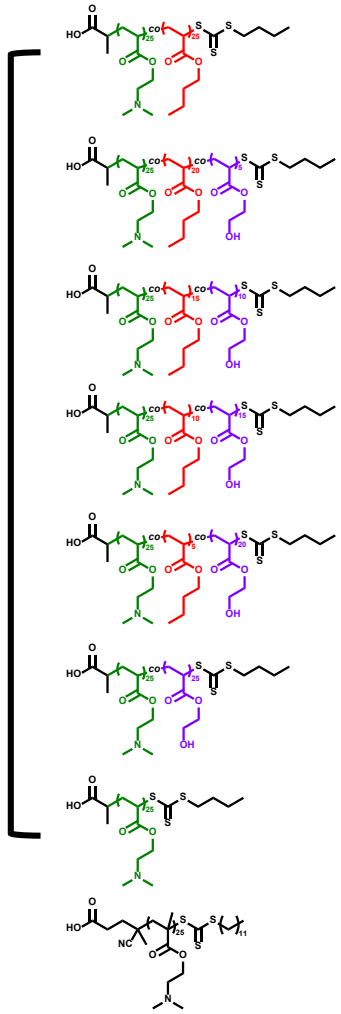
Polymer library







P1

P2

P3

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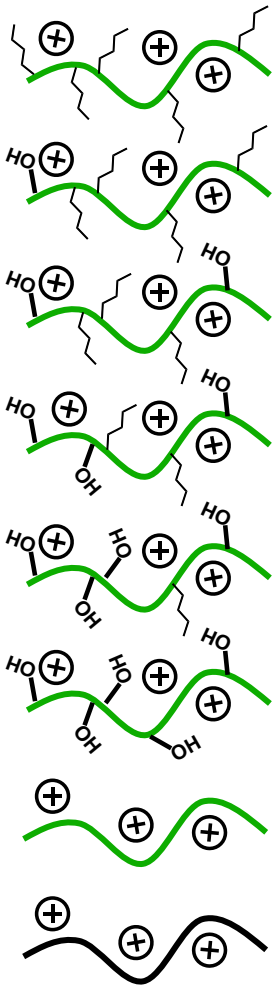
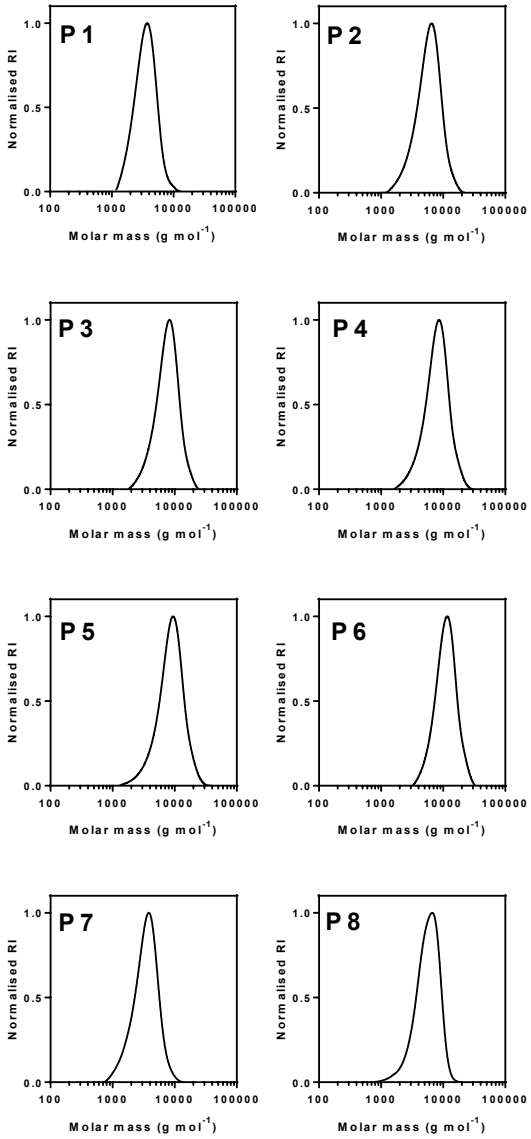


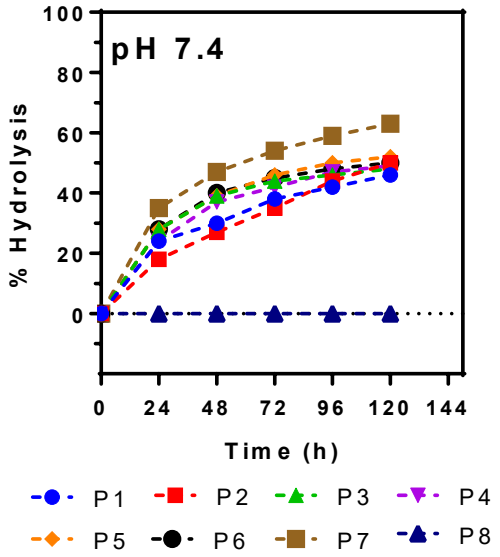
Fully hydrolysing

Non-hydrolysing

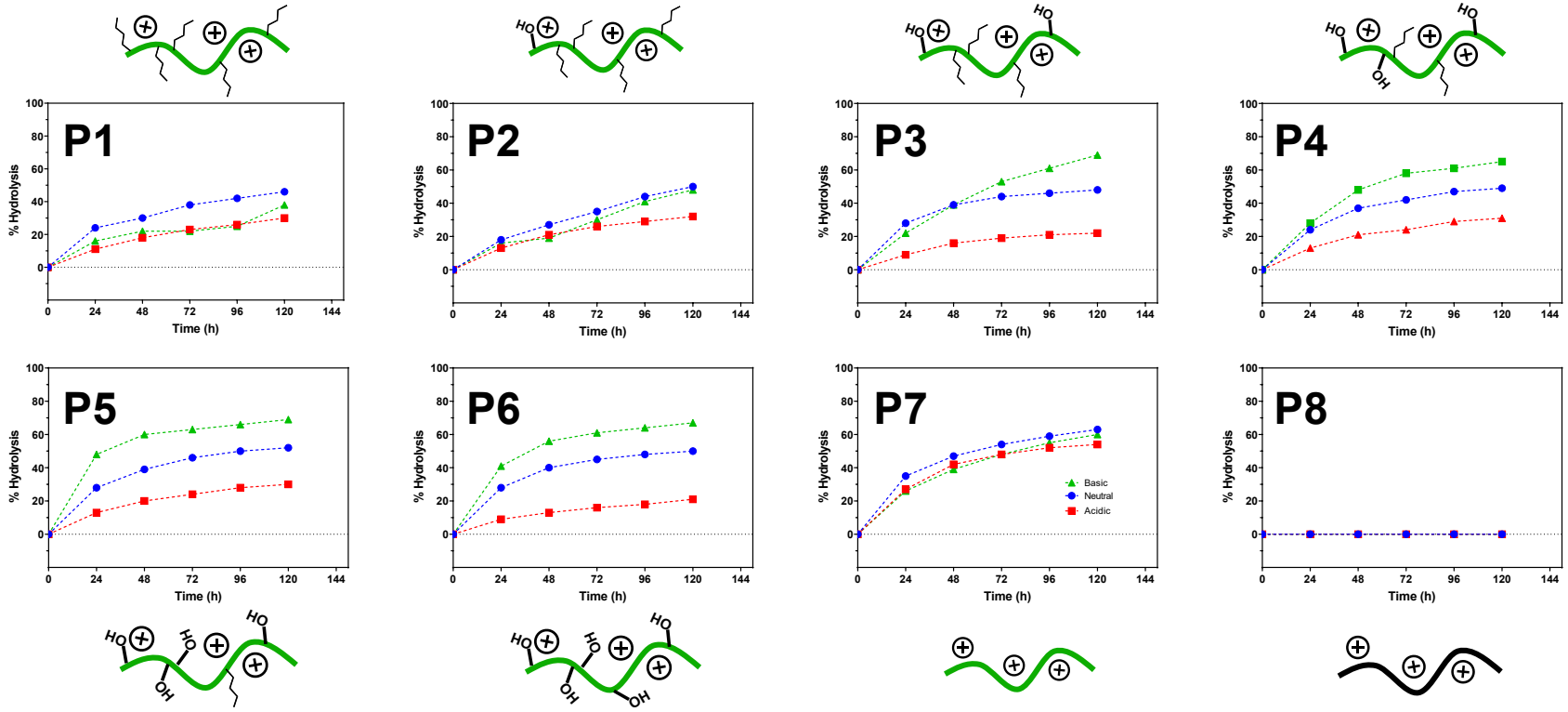
Increasing hydrophilicity



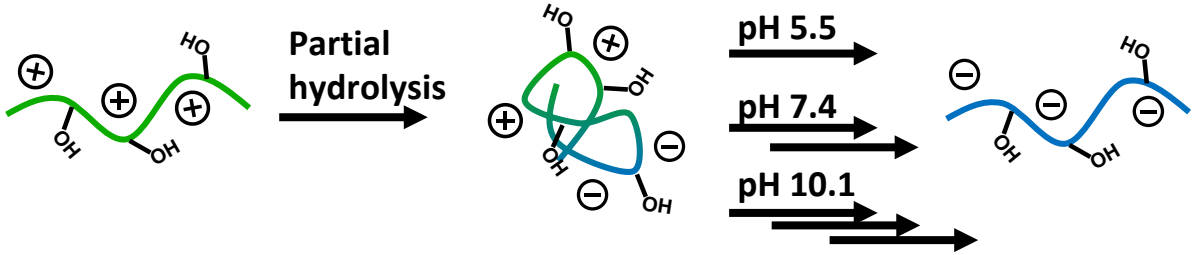
^{1}H NMR hydrolysis study



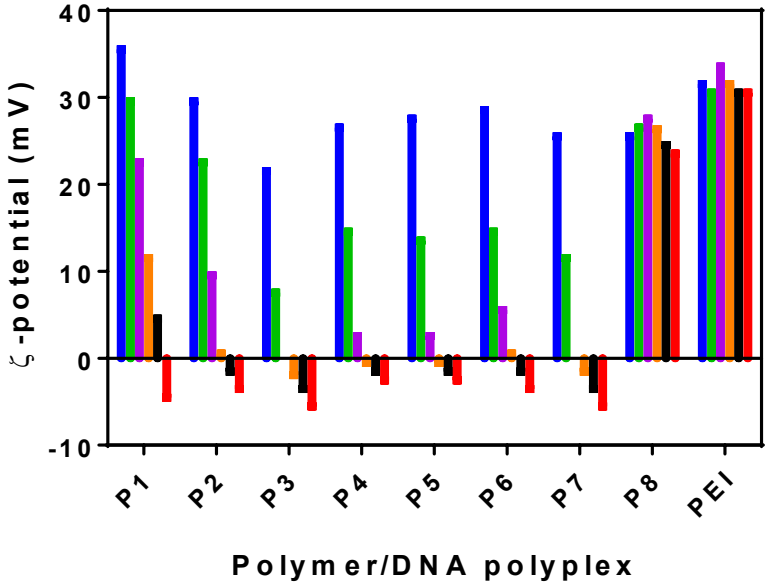
- Some small variation in hydrolysis rate, however altering hydrophobicity does not significantly affect hydrolysis at pH 7.4

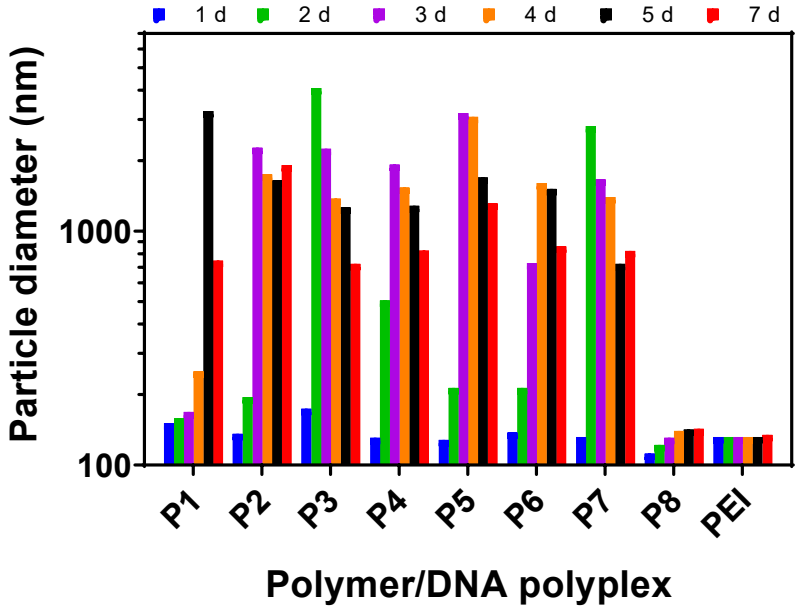


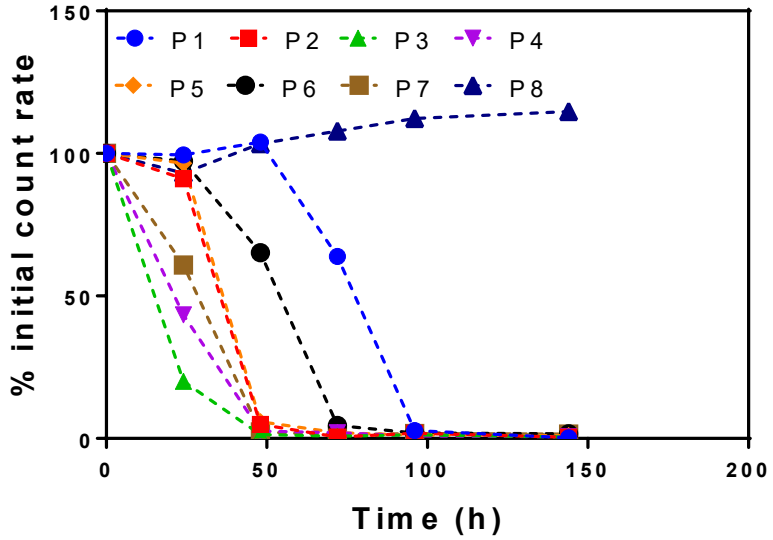
- By increasing hydrophilic co-monomer content, greater variation in hydrolysis rate depending on pH.

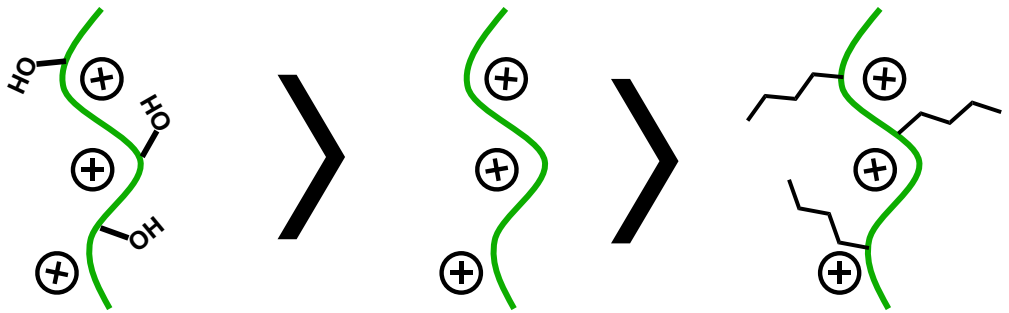


Polyplex hydrolysis



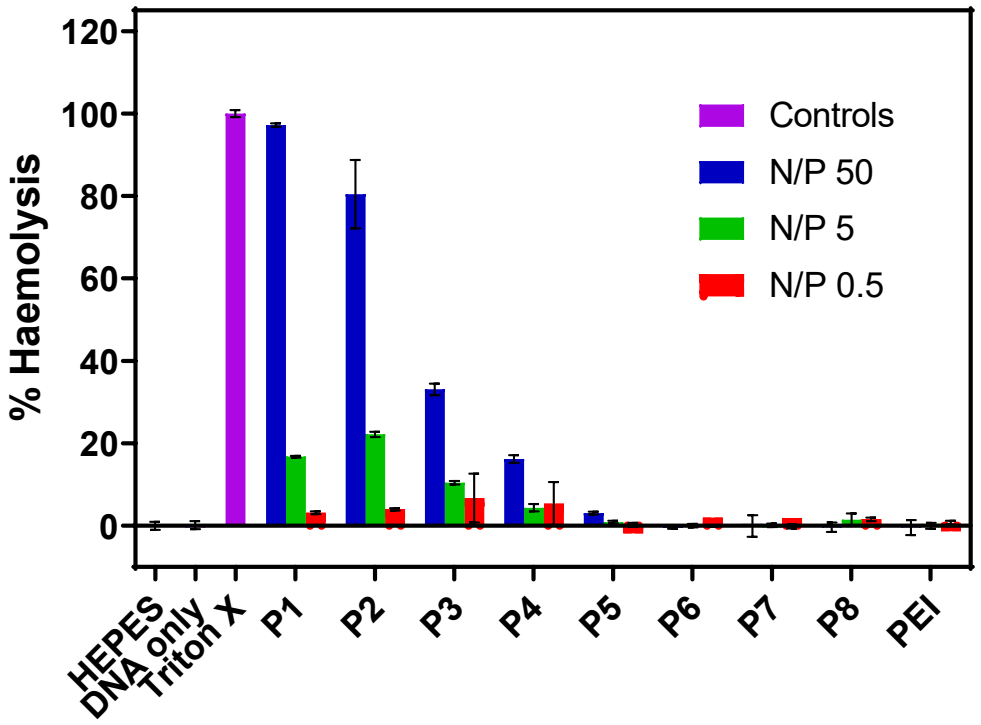


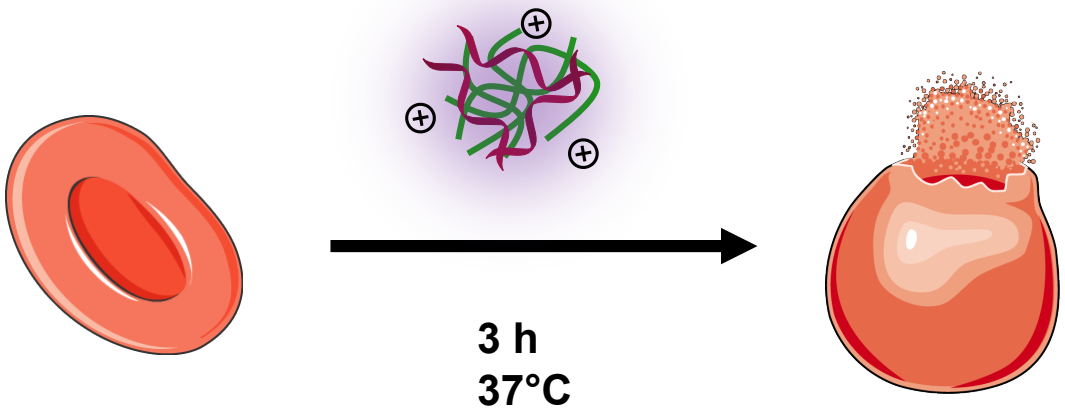




In general more hydrophilic are faster hydrolysing

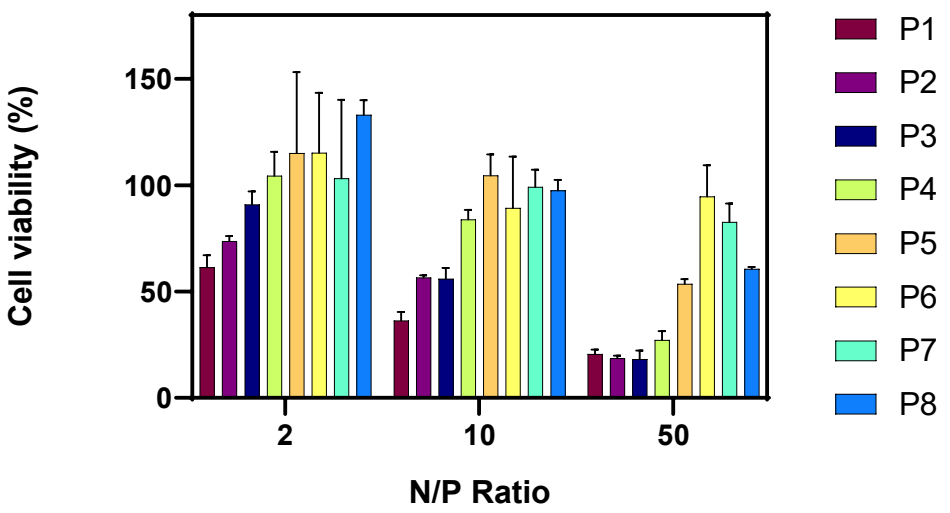
Membrane activity



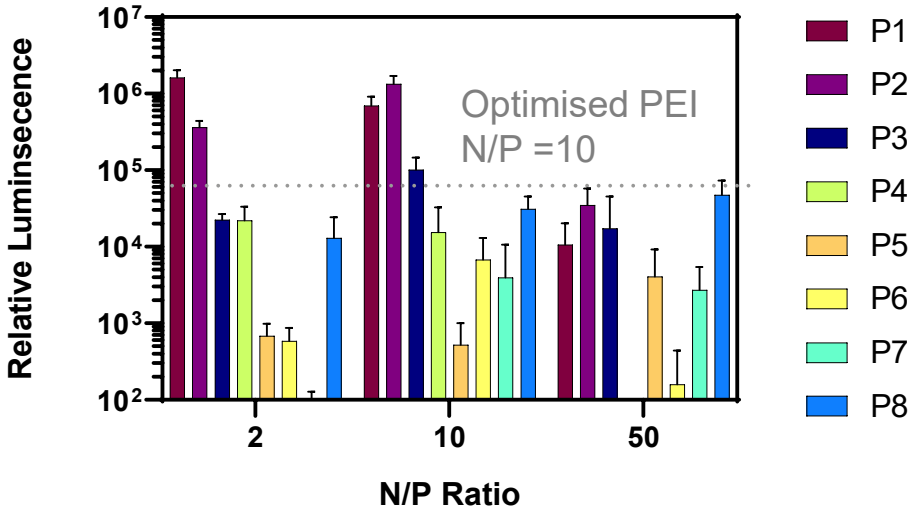


More hydrophobic polyplexes cause significantly higher haemolysis. Could be an indication of greater endosomolytic activity translating to higher transfection efficiency.

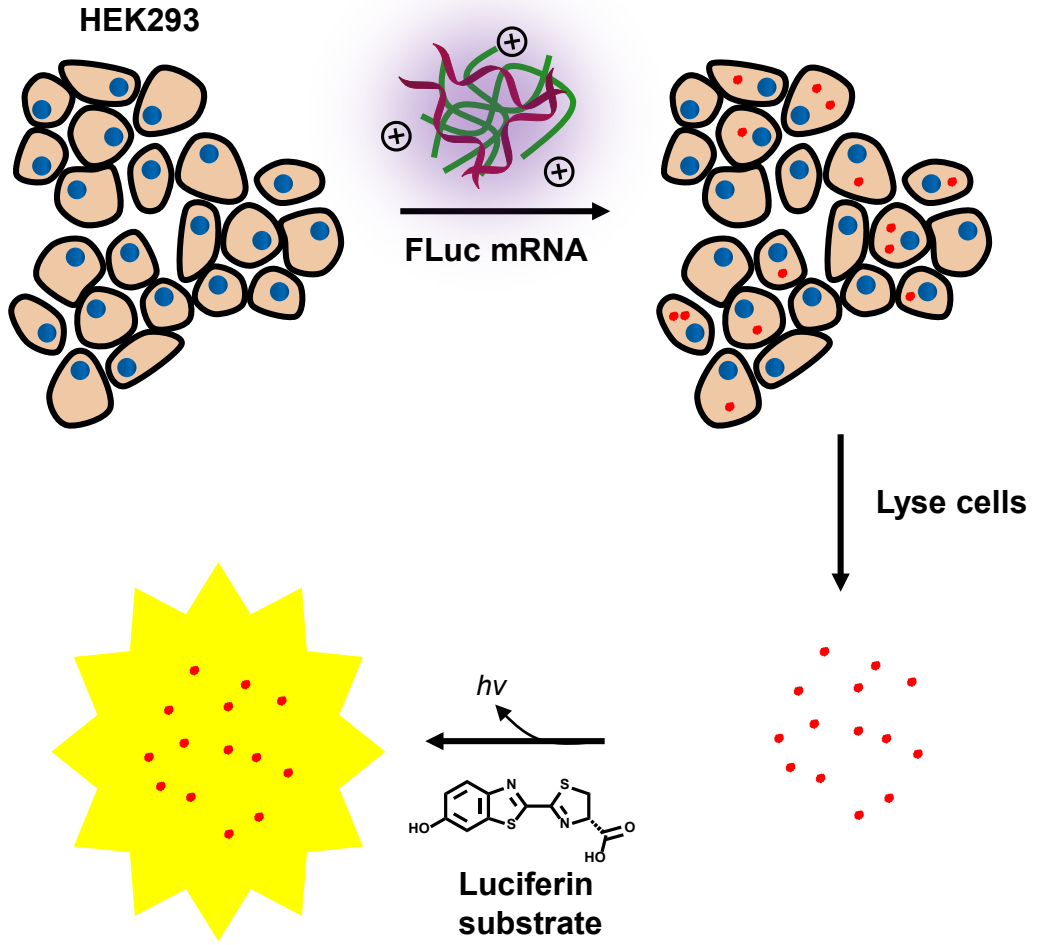
Transfection efficiency vs cytotoxicity



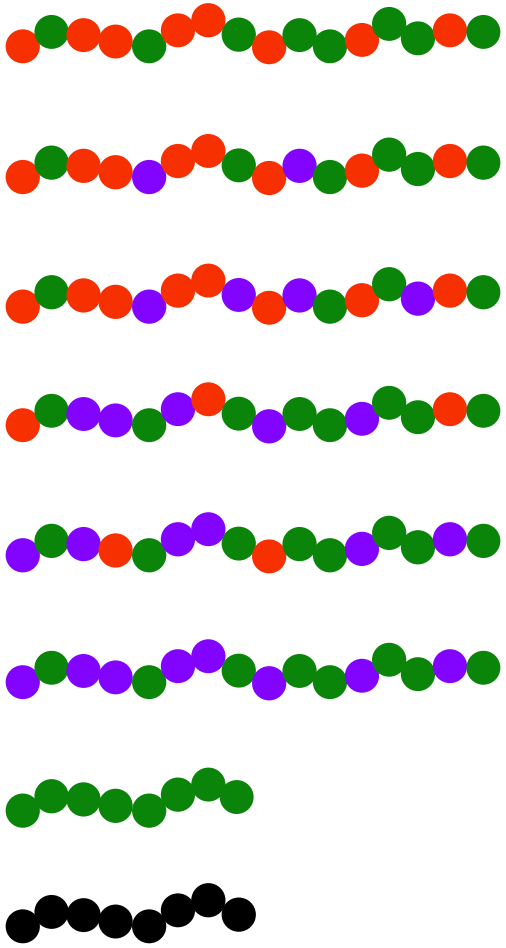
Cytotoxicity could be beneficial for immunogenic effects



Transfection with model mRNA



Conclusions and perspective



Comonomer lipophilicity strongly affects rate of side chain hydrolysis, and therefore polyplex disassembly rates.

However likely that membrane interactions govern the transfection efficiency.

Self-hydrolysing polyplexes could therefore be useful for clearance.

Next steps:

- Currently doing an *in vivo study* and *ex vivo* skin study
- Investigate with vaccine encoding mRNA

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Acknowledgements

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