Combinatorial Approach toward Programmed Decomposition of Bioconjugate Transporters for Drug Solubilisation and Controlled Release

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Motivations
Common problem for active compounds, especially in pharmaceutical research (e.g. high-throughput screening or structure based design), that drug candidates are hydrophobic
- poor solubility in water
- hampers application and medical approval

Polymer-peptide conjugates
- act as non-covalent solubilizers for small molecules
  - Peptide binds non-covalently to the drug
  - PEO polymer brings water solubility and biocompatibility

Water insoluble drug:
m-tetra(hydroxyphenyl)chlorin (mTHPC)
- Generates cytotoxic species upon light irradiation
- Approved drug for photodynamic cancer therapy
- But hydrophobic → water insoluble
  - application via formulation additives
- Toxic to healthy tissue
  - importance of controlled release

Aims
- Solubilise mTHPC using PEO-peptide conjugates and achieve controlled release by incorporating a linker (based on a disulfide bond) cleavable upon triggering

Library synthesis
- Repeated split-and-mix cycles
  - one-bead-one-compound library
    (each bead carries multiple copies of the same amino acid sequence)
- Based on Fmoc-protected solid phase supported synthesis
  - \( 7^1 \times 823543 \) different peptides

Screening for drug-binding peptides
Finding peptides which are good binders to mTHPC

Stop

Conclusion
- Use of a combinatorial library on solid support allows for screening of peptides with good binding affinity to a small molecule of interest
- Polymer-peptide conjugates incorporating a disulfide linker are solubilising mTHPC
- Payload capacity and release profile depend on amino acid sequence
- Cleavage of the linker can induce change in the release profile

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