

# THE FINE BALANCE BETWEEN STABILITY AND ENZYMATIC DEGRADABILITY OF POLYMERIC CARRIERS – THE IMPORTANCE OF MOLECULAR PRECISION

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Deep understanding of the factors that define the stability and degradability of polymeric assemblies is crucial for the development of biodegradable materials for biomedical applications ranging from drug delivery systems to tissue engineering. The poor accessibility of lipophilic substrates that may be hidden inside hydrophobic domains to the degrading enzymes seems to be one of the key parameters that determine enzymatic degradability. In the past several years, we designed and synthesized well defined amphiphilic PEG-dendron hybrids with enzymatically cleavable hydrophobic end-groups. The high molecular precision of the hydrophobic dendritic block, enabled us to observe how precise minor changes of the hydrophobic blocks significantly affect the stability and degradation rates of polymeric assemblies [1]. Furthermore, we demonstrated that the micellar stability in serum may result in different internalization mechanism of the polymeric assemblies into living cells [2].

Our results strongly imply that the enzymatic degradation of polymeric amphiphiles occurs at their monomeric state outside of the micelle through the micelle-monomer exchange. This equilibrium-based mechanism may explain the poor degradability that is often reported for many polymeric assemblies. Based on our molecular understanding, we recently started to design novel multi-responsive polymeric assemblies that can overcome the challenge of designing stable and yet enzymatically degradable polymeric assemblies [3].

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[1] Segal, M.; Avinery, R.; Buzhor, M.; Shaharabani, R.; Harnoy, A. J.; Tirosh, E.; Beck, R.; Amir, R. J.\* *Journal of the American Chemical Society* **2017**, 139, 803-810.

[2] Feiner-Gracia, N.; Buzhor, M.; Fuentes, E.; Pujals, S.; Amir, R.J.\*; Albertazzi, L.\*, *Journal of the American Chemical Society* **2017**, 139, 16677-16687.

[3] Rosenbaum, I.; Avinery, R.; Harnoy, A. J.; Slor, G.; Tirosh, E.; Hananel, U.; Beck, R.; Amir, R. J.\* *Biomacromolecules* **2017**, 18, 3457-3468.