# Virus-Like Signaling platforms for Regenerative Medicine Applications

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Stem cells reside within complex microenvironments called “niches” from which they integrate biochemical and mechanical signals that engage and instruct stem cells to proliferate, migrate, and differentiate. A very challenging goal is to mimic specific stem cell niches in order to control their behavior, physiology and fate. Recent findings show that it is essential to combine different bioactive factors at specific stoichiometries and densities to obtain the best bioactivity. As the activity of native proteins often lies within small bioactive domains, it is possible to use only fragments of the full-length protein, which can be easily synthesized or produced through recombinant technologies. However, it can be difficult to maintain their solubility and control their spatial distribution or orientation. Well-designed presenting scaffolds can help to resolve these problems.

In the recent years, scientists have been hijacking the capsid proteins from various viruses (Virus-Like Particles, VLPs) or creating de novo well-organized nano-scale molecular self-assemblies with improved stability and solubility [1]. In this project, we propose to use VLPs to create versatile signaling platforms for the control of cell behavior and stem cell fate. We will create spherical nanoscale receptacles that can be conjugated through isopetidic bounds formation (SpyTag/SpyCatcher system) with a series of bioactive peptides known to control specific biological functions such as adhesion and differentiation (Fig. 1). By mixing different peptides, we will create multifunctional biomimetic hydrogels with adjustable stiffness [2] presenting combinations of bioactive peptides at high densities and specific stoichiometries, in order to control stem cell physiology. Material surface biofunctionalization has relevance for the improvement of implant biointegration. This project will open new avenues for the development of next-generation biomaterials and biomimetic microenvironments.

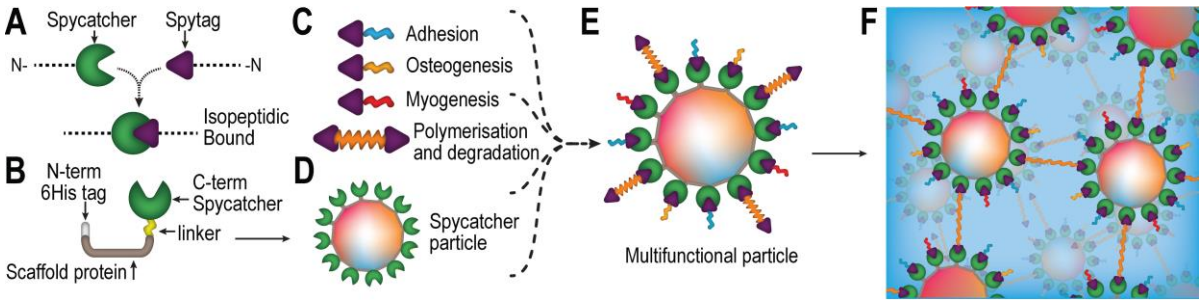


Figure 1: The Spytag/spycatcher system is a technology for irreversible conjugation of recombinant proteins by the formation of an isopeptidic bound between the two moieties (A). The Spytag moiety has been fused to various bioactive peptides influencing cell adhesion, osteogenesis and myogenesis, as well as polymerization proteins (C). We have fused the Spycatcher moiety to the scaffold protein of the VLP (B) to self-assemble Spycatcher particles (D). These particles will be combined to the fusions described in (C) to obtain a multifunctional particle (E) enabling the formation of a hydrogel displaying functional peptides for the control of cell morphology, behavior and fate (F).

[1] X. Ding, D. Liu, G. Booth, W. Gao, and Y. Lu. Biotechnol J. 13(5):e1700324. Review (2018). https://doi.org/10.1002/biot.201700324.
[2] Yang L , Liu A , de Ruiter MV , et al. Nanoscale. 10(8):4123-4129 (2018). http://doi.org/10.1039/c7nr07718a.