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Emerging approaches to study cell-cell interactions

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Citation

Poulcharidis, D. (2020, June 3). *Emerging approaches to study cell-cell interactions*. Retrieved from <https://hdl.handle.net/1887/92370>

Version: Publisher's Version

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Issue Date: 2020-06-03

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Aim and outline of this thesis

The aim of this thesis is to study cell-cell interactions and the development of an assay to explore and quantify the exchange of membrane compounds. In the first part the rate of lipid exchange was studied, during both natural cell-cell contacts and prolonged enforced contacts. In the second part lipidated coiled-coil peptides were used to study the behaviour and potential fusogenic behaviour of these compounds on cell-wall-deficient bacteria.

Chapter 2 provides a comprehensive overview of membrane component exchange in cells, as well as chemical approaches to enhance cell-cell contacts. Examples of mechanisms of intercellular transfer, biological effects of intercellular membrane component transfer and chemical strategies to enhance cell-cell contacts are described, and their strengths and limitations discussed.

Chapter 3 explores a method to quantify the amount of exchange of cholesterol and sialic acid containing compounds between cells using flow cytometry in combination with bioorthogonal and fluorescent labelling techniques. This chapter demonstrates that direct cell–cell contact is the likely mechanism of sterol exchange. Furthermore, it shows that by manipulating the contact time between cells using complementary coiled-coil peptides results in an enhanced exchange rate of membrane components between cells.

Chapter 4 provides future implications for and directions towards quantification and identification of membrane lipid exchange between immune cells. This chapter presents an adaptable strategy based on trogocytosis assays in which fluorescent and clickable lipids were used to determine the membrane component exchange between antigen-presenting cells and T cells in co-culture. A range of sterols and aliphatic acids were screened and their effect on trogocytosis was determined.

Chapter 5 presents evidence – for the first time – of surface modification of living L-form cells (cell-wall-deficient bacteria) as a first step towards L-form fusion, using cell-compatible coiled-coil peptides. These L-form variants were generated from actinomycetes, by inhibiting crucial steps in the biosynthesis pathway of the cell wall. L-form morphology is adaptable and allows cells to surpass environmental difficulties; for example, hyperosmotic stress conditions or treatment with antibiotics. Also, in this chapter L-form surface modification and viability as well as potential membrane fusion is presented using confocal microscopy and flow cytometry assays.

Chapter 6 describes the synthesis of a fluorescent alkyl phospholipid ether analogue as well as preliminary results of the *in vitro* and *in vivo* imaging testing in a zebrafish cancer model. Alkyl phospholipid ether analogues were developed for diagnostic methods due to their accumulation in cancer cells.

