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A FLIM study of live HeLa cells reveals mechanistic insight into drug delivery of doxorubicin by means of a theranostic macromolecular prodrug

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A FLIM study of live HeLa cells reveals mechanistic insight into drug delivery of doxorubicin by means of a theranostic macromolecular prodrug

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Purpose: In the context of theranostic macromolecular prodrugs (TMPs), special attention is given to theranostic tumor agents, reducing systemic adverse effects through the inactive prodrug form. To understand kinetics and release profiles of such drug-nanocarrier systems, spatiotemporal information is mandatory. Here, we investigated the intracellular release kinetics of the cytostatic agent doxorubicin (Dox) from a TMP.

Methods: FLIM (fluorescence lifetime imaging microscopy)

Results: The TMP at hand is a polymeric nanocarrier composed of a dendritic polyglycerol and a FRET pair consisting of indodicarbocyanine (IDCC) and the fluorescent drug Dox [1]**.** Dox is bound using a pH-sensitive hydrazone, which should readily cleave in the acidic compartments of the cell. We followed the cellular uptake of TMP and Dox by consecutive FLIM measurements of live HeLa cells and evaluated the data using our multivariate Cluster-FLIM analysis [2].

Conclusion: Cluster-FLIM allowed us to quantify each of the interactions of TMP or Dox in the different cellular compartments of the cancer cell line by their unique fluorescence lifetime. This spatiotemporal sequence of TMP's cellular fate was not elucidated before, and thus provides a clear rationale for the mode of action of nanocarrier-delivered Dox. The ability of Cluster-FLIM [2] to discriminate target fluorescence from e.g. autofluorescence by the unique fluorescence lifetime signature enables not only monolayer experiments of cancer cells but can be used also for living tissue studies.

Quotes:

1 Krueger, H. R. et al.; J Control Release 2014; 194, 189-196.
2 Alexiev, U. et al.: Eur J Pharm Biopharm 2017; 116, 111-124.