A nanotechnology approach to evaluate drug promiscuity in cancer
Teresa Valero\textsuperscript{1,2}, Victoria Cano-Cortés\textsuperscript{2}, Asier Unciti-Broceta\textsuperscript{1} and Rosario Sánchez-Martín\textsuperscript{2}

\textsuperscript{1}Edinburgh Cancer Research UK Centre (MRC Institute of Genetics and Molecular Medicine), University of Edinburgh, Edinburgh EH4 2XR, UK.
\textsuperscript{2}Pfizer - Universidad de Granada - Junta de Andalucía Centre for Genomics and Oncological Research (GENYO), Parque Tecnológico de Ciencias de la Salud (PTS), Avenida de la Ilustración 114, 18016 Granada, Spain.
teresa.valero@genyo.es

Abstract

Cancer remains an important public health problem in Europe. Among currently available treatments for cancer, the use of kinase inhibitors has gained unprecedented popularity during the last decade, in part motivated by the success of Imatinib in the treatment of Chronic Myeloid Leukemia [1]. However, the appearance of resistance episodes led to the development of other tyrosine kinase inhibitors (TKI) with a broader target spectrum such as Dasatinib [2-3]. This promiscuous kinase inhibitor targets Bcr-Abl, Src family, receptor tyrosine kinases and TEC family kinases [4]. Therefore, it is difficult to elucidate which target/s of Dasatinib is/are responsible for the phenotypic effect observed in each cancer type. Inhibitor’s promiscuity may be advantageous or a major drawback depending on the result of the inhibition, if it circumvents resistance mechanisms or if it leads to severe side effects. Therefore it is of crucial importance to discover all the targeted kinases and which of the kinases produce each effect in each cancer type, in order to develop personalized highly selective therapies [5].

Our research team has developed the synthesis, multifunctionalization and a variety of biological applications of polymeric micro/nanospheres as cellular delivery and tracking devices capable of introducing a range biological and chemical modalities into a vast majority of both primary and cell lines, including embryonic stem cells [6-9]. Importantly, and due to their cross-link nature, these synthetic nanoparticles allows multistep solid-phase chemistry, allowing covalent binding of small molecules and macromolecules onto them, as well as the possibility to label them with different trackers, such as fluorophores and metals, thus creating multifunctional micro/nanospheres, an unique feature for this type of nanodevices. These nanodevices have been also fully proven to be biocompatible and have been used to sort out cells for subsequent downstream analysis. Up-to-date, cargoes delivered into eukaryotic cells include metals (palladium nanoparticles) [10], proteins (such as Enhanced Green Fluorescent Protein (EGFP) and β-Galactosidase) [11], oligonucleotides (DNA, siRNA) [12-13]. Of special importance has been the development of sensors for measuring intracellular pH and calcium ions[14-15], and fluorogenic peptides to assess in situ caspase activity [16]. All of these applications require the internalization of these nanodevices inside cells. Recently, we have developed a quick method to quantify the number of nanoparticles per sample using a standard spectrophotometry approach [17].

Based on this expertise, the central objective of this project is to develop an in situ and cost-efficient method based on nanotechnology to detect protein kinases which are targeted by promiscuous kinase inhibitors and to prove its functionality on living systems. This nanotechnology approach has been developed by conjugation of kinases inhibitors to fluorescently labelled nanoparticles. Dasatinib conjugation was used as proof of concept. Our recent results in the development of this nanotechnology will be presented.
References


