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Use of 3D spheroid cultures to screen for drugs targeting cancer stem cells

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The cancer stem cell (CSC) concept has important implications not only for our understanding of carcinogenesis, but also for the development of cancer therapeutics. There is a growing body of preclinical evidence showing that cancer stem cells contribute to chemotherapy and radiation resistance in breast cancer. The use of drugs that interfere with stem cell self-renewal represents the strategy of choice for novel effective anti-cancer treatments, but also a great challenge because cancer stem cells and their normal counterparts share many pathways. The biology of cancer stem cells has proven complex and difficult to translate into effective therapeutic strategies. The question arises as: how do we test compounds for anti-cancer stem cell activity? The answer is: phenotypic screening. There are indeed several functional assays well validated in the scientific literature that have been used for years associated to the ability of cancer cells to demonstrate stem cell behavior. The most relevant is the 3D tumor spheroid assay. This assay has been used to uncover and culture stem cells from many tissues as well as from tumors. There are multiple reports now, that show that spheroid derived cells are enriched in tumor initiating or cancer stem cells, derived from cell lines and from natural fresh tumors as well. Here, we describe the use of 3D spheroid models to profile compound activity against cancer stem cells. Furthermore, a case of compounds preventing hypoxia-inducible transcription factor (HIFs) activity is presented. Recently, HIF transcription factor biology has been linked to pathways that regulate stem cell self-renewal and pluripotency, suggesting a new mechanism whereby HIF proteins may drive tumor growth, through the generation of tumour-initiating cells or cancer stem cells. Therefore, targeting the HIF pathway may provide a novel therapeutic avenue to target cancer stem cells. We demonstrate that interfering with HIF pathway activation prevents mammosphere formation, validated through independent confirmation through Sox2 promoter activation, Aldefluor® assay and *in vivo* proof-of concept experiments targeting tumor initiation.

Biography

Ines Prieto Remon is currently Senior Researcher at StemTek Therapeutics, a biopharmaceutical company located in the Basque Country, Spain. She earned her Bachelor of Biochemistry at the University of the Basque Country, Spain, in 2006, and her PhD in Molecular Biology and Biomedicine from the University of Cantabria, Spain, in 2013, working with Dr Carlos Pipaon Gonzalez and Dr Marian Ros. In her thesis work she studied signaling pathways in Fanconi anemia patients samples, regarding their aberrant acute sensitivity to chemotherapeutic agents. She also studied microphthalmia with Fancd2-/- mouse model. After her PhD, Ines accepted a postdoctoral position at the Laboratory for Experimental Hematology & DNA Repair, at Herman B Wells Center in Indianapolis, IN, US. There, she worked with Dr. Helmut Hanenberg in a project which aimed to study the protective effect of compounds in order to reduce/remove side effects of chemotherapy.

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