Workshop 1

The importance of biomarker validation to increase success in cancer drug development and approval

Background

Nucleolin is a multifunctional phosphoprotein ubiquitously distributed in the nucleolus, nucleus and cytoplasm of the cell.

Nucleolin has a bipartite nuclear localization signal sequence and is conserved in animals, plants and yeast. Its levels are correlated with the rate of functional activity of the nucleolus in exponentially growing cells.

Numerous reports have implicated the involvement of nucleolin either directly or indirectly in the regulation of cell proliferation and growth, cytokinesis, replication, embryogenesis, and nucleogenesis. Nucleolin, an RNA binding protein, is also an autoantigen, a transcriptional repressor, and a switch region targeting factor. In addition, nucleolin exhibits autodegradation, DNA and RNA helicase activities, and DNA-dependent ATPase activity.

Nucleolin is fundamental to the survival and proliferation of cells.

Nucleolin also functions as a cell surface receptor, where it acts as a shuttling protein between cytoplasm and nucleus, and thus can even provide a mechanism for extracellular regulation of nuclear events.

Exploration of the regulation of this multifaceted protein in a remarkable number of diverse functions is challenging.

Cell surface nucleolin has been described as overexpressed in cancer cells as well as a tumor angiogenic marker.

Nucleolin-specific therapeutic tools capable of simultaneous debulk multiple cellular compartments of the tumor microenvironment may pave the way towards a specific treatment for cancer.

PEGASEMP® is a platform conceived for delivering a cytostatic agent specifically to the tumor microenvironment, targeting two distinct cell populations: the cancer cell and the endothelial cells from the tumor blood vessels.

These nanoparticles act as nanocarriers for the targeted and specific delivery of drugs to both cancer cells and endothelial cells in the tumors overexpressing nucleolin.

The use of nucleolin as a biomarker for lymphangiogenesis in cancer prognosis and therapy was patented by Yongzhang Luo, Wei Zhuo, Yan Fu, Guodong Chang.

Advances in antibody and aptamer technology have enabled researchers to design those molecules to bind specifically to cancer cells, and deliver drugs that alter specific cellular processes.

The nucleolin aptamer targeted cancer cells by binding to membrane-associated nucleolin.

Nucleolin, as already mentioned, a conserved protein found in all eukaryotes, shuttles from the nucleus, through the cytoplasm to the cell membrane. Cancer cells express a far greater amount of membrane-associated nucleolin than somatic cells, making nucleolin an ideal cancer biomarker.

The shuttling, and oligonucleotide binding attributes of the protein enable it to deliver aptamer chimeras from the cell surface to the nucleus. Therefore the nucleolin aptamer has unique access to the nuclei of cancer cells, and can deliver therapeutic oligonucleotide cargoes through nucleolin binding. The nucleolin aptamer can also deliver therapeutic aptamers.

What needs to be done so that PEGASEMP® can help treat patients?

Objectives of the workshop 1:

. To create awareness about the importance of predictive biomarkers in cancer drug development

. To learn the opportunities and threats in biomarker development in pre-clinical and clinical phases

Research teams / partners:

1 – João Nuno Moreira (TreatU)
Why might Pegasemp® be useful in the treatment of malignant tumors that express nucleolin?
Preclinical studies with Pegasemp®, what were the results?
3 – Dylan Ferreira (IPO Porto)
Expression of Nucleolin in normal and tumor tissues: quantification and definition of criteria as possible biomarker for future clinical development.
5 – Beatriz Silva Lima (Faculty of Pharmacy – Lisbon University)
Regulatory issues in biomarker and drug development

Christian Blank (National Cancer Institute, Netherlands)
Comments and advice:
Expert insights in biomarker validation – pre-clinical and clinical issues and success examples.

Discussion

Chairs: Luis Almeida (Blueclinical) e Julio Oliveira (IPO Porto)

Organization:

Júlio Oliveira (IPO Porto), Lúcio Lara Santos (IPO Porto), André Albergaria (IPATIMUP)