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ABSTRACT BOOK

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New Diagnostic and Therapeutic Tools against Multidrug Resistant Tumours

UNIVERSITÀ DEGLI STUDI DI TORINO

Functional diagnostics as a new concept for the improvement of personalized targeted therapy

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Abstract:

Although advances in sequencing technology and target identification enabled the implementation of a personalized therapy approach, unfortunately, only 3-9% of cancer patients who receive the targeted therapy show an adequate response. On the other side, there are exceptional responders to targeted therapy among cancer patients without common genetic alterations. Therefore, current patient classifications relying only on sequencing are not sufficient to determine optimal treatment. Our intention is to start in the opposite direction to conventional diagnostics by performing pharmacological screening on patient-derived cancer cells *ex vivo* because testing of multiple drugs is not possible in clinical trials. An incomplete understanding of how tumour genotype reflects on tumour phenotype limits the efficacy of DNA and mRNA sequencing for personalized therapy. Functional diagnostics using patient-derived cancer cells is recently implicated to overcome this limitation and it is clinically available for haematological malignancies. We plan to perform the immunofluorescence-based drug-screening assay to determine non-small cell lung carcinoma (NSCLC) patients' cancer cells' response to targeted therapeutics, particularly tyrosine kinase inhibitors (TKIs) within the time frame necessary to influence patient care. The usage of the functional diagnostics approach should be an addition to clinical trials and complement DNA and mRNA sequencing.

In contrast to similar research efforts [1], we will shorten the cultivation of NSCLC patient-derived cells to 1-2 weeks because we intend to test drugs on a mixture of cancer and stromal cells (fibroblasts). It is well-known that the sensitivity of cancer cells depends on their interaction with the microenvironment including neighbouring cells. In addition, we will examine the changes in the expression level of ATP Binding Cassette transporters (ABCB1, ABCC1, and ABCG2) in both cancer and stromal cells that may occur during TKIs and chemotherapy treatment. In such way, we will gain knowledge about (i) which TKI or chemotherapeutic induces multidrug-resistant (MDR) phenotype in our NSCLC patients' cohort, (ii) whether the induction of MDR depends on the ratio between cancer and stromal cells, (iii) whether the induction of MDR is prevalent in cancer cells, and (iv) whether MDR induction depends on individual patient's characteristics (comparison with Whole Exome Sequencing results).

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References:

1- Kodack DP, Farago AF, Dastur A, et al. Primary Patient-Derived Cancer Cells and Their Potential for Personalized Cancer Patient Care. Cell Rep. 2017; 21(11):3298-3309. doi:10.1016/j.celrep.2017.11.051

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